THE ROLE OF LIPIDS AND LIPOPROTEINS IN ATHEROSCLEROSIS

MacRae F. Linton, MD, Stephen and Mary Schillig Professor of Medicine, Professor of Pharmacology, Director, Vanderbilt Lipid Clinic & Laboratory, Director, Atherosclerosis Research Unit, Cardiovascular Medicine, Vanderbilt University School of Medicine, 2220 Pierce Ave., 318 Preston Research Building, Nashville, TN 37232-6300

Patricia G. Yancey, PhD, Research Assistant Professor, Cardiovascular Medicine Division, Department of Medicine
Vanderbilt University School of Medicine, 2220 Pierce Ave., 312B Preston Research Building, Nashville, TN 37232-6300

Sean S. Davies, PhD, Assistant Professor of Pharmacology, Division of Clinical Pharmacology, Vanderbilt Institute of Chemical Biology, Vanderbilt University, 2220 Pierce Ave., Room 506A Robinson Research Building, Nashville, TN 37232-6602

W. Gray (Jay) Jerome, PhD, Associate Professor Department of Pathology, Microbiology and Immunology, Director, Graduate Program in Cellular and Molecular Pathology, Vanderbilt University School of Medicine, U-2206 MCN, 1161 21st Ave, South Nashville, TN 37232-2561

Edward F. Linton, MD, Department of Ophthalmology, Vanderbilt University Medical Center, 2311 Pierce Avenue, Nashville, TN 37212

Wenliang L. Song, MD, Cardiovascular Medicine, Vanderbilt University School of Medicine, 2220 Pierce Ave.,
383 Preston Research Building, Nashville, TN 37232-6300

Amanda C. Doran, PhD, MD, Assistant Professor of Medicine, Cardiovascular Medicine, Vanderbilt University School of Medicine, 2220 Pierce Ave., 383 Preston Research Building, Nashville, TN 37232-6300

Kasey C. Vickers, PhD, Assistant Professor of Medicine and Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, 2220 Pierce Ave., 312B Preston Research Building, Nashville, TN 37232-6300

Updated January 2, 2019

ABSTRACT

Atherosclerosis is the underlying cause of heart attack and stroke. Early observations that cholesterol is a key component of arterial plaques gave rise to the cholesterol hypothesis for the pathogenesis of atherosclerosis. Population studies have demonstrated that elevated levels of LDL cholesterol and apolipoprotein B (apoB) 100, the main structural protein of LDL, are directly associated with risk for atherosclerotic cardiovascular events (ASCVE). Indeed, infiltration and retention of apoB containing lipoproteins in the artery wall is a critical initiating event that sparks an inflammatory response and promotes the development of atherosclerosis. Arterial injury causes endothelial dysfunction promoting modification of apoB containing lipoproteins and infiltration of monocytes into the subendothelial space. Internalization of the apoB containing lipoproteins by macrophages promotes foam cell formation, which is the hallmark of the fatty streak phase of atherosclerosis. Macrophage inflammation results in enhanced oxidative stress and cytokine/chemokine secretion, causing more LDL/remnant oxidation, endothelial cell

activation, monocyte recruitment, and foam cell formation. HDL, apoA-I, and endogenous apoE prevent inflammation and oxidative stress and promote cholesterol efflux to reduce lesion formation. Macrophage inflammatory chemoattractants stimulate infiltration and proliferation of smooth muscle cells. Smooth muscle cells produce the extracellular matrix providing a stable fibrous barrier between plaque prothrombotic factors and platelets. Unresolved inflammation results in formation of vulnerable plaques characterized by enhanced macrophage apoptosis and defective efferocytosis of apoptotic cells resulting in necrotic cell death leading to increased smooth muscle cell death, decreased extracellular matrix production, and collagen degradation by macrophage proteases. Rupture of the thinning fibrous cap promotes thrombus formation resulting in clinical ischemic ASCVE. Surprisingly, native LDL is not taken up by macrophages in vitro but has to be modified to promote foam cell formation. Oxidative modification converts LDL into atherogenic particles that initiate inflammatory responses. Uptake and accumulation of oxidatively modified LDL (oxLDL) by macrophages initiates a wide range of bioactivities that may drive development of atherosclerotic lesions. Lowering LDL-cholesterol with statins reduces risk for cardiovascular events, providing ultimate proof of the cholesterol hypothesis. All of the apoB containing lipoproteins are atherogenic, and both triglyceride rich remnant lipoproteins and Lp(a) promote atherothrombosis. Non-HDL cholesterol levels capture all of the apoB containing lipoproteins in one number and are useful in assessing risk in the setting of hypertriglyceridemia. Measures of apoB and LDL-P are superior at predicting risk for ASCVE, when levels of LDL-C and LDL-P are discordant. Here, we also describe the current landscape of HDL metabolism. Epidemiological studies have consistently shown that HDL-C levels are inversely related to ASCVE. We highlight recent clinical trials aimed at raising HDL-C that failed to reduce CVE and the shifting clinical targets of HDL-C, HDL particle numbers, and HDL function (e.g. cholesterol efflux capacity). Furthermore, we describe many beneficial properties of HDL that antagonize atherosclerosis and how HDL dysfunction may promote cardiometabolic disease.

PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

Atherosclerosis in Cardiovascular Disease

As the underlying cause of heart attack, stroke, and peripheral vascular disease, atherosclerosis is the major cause of death and morbidity in the United States and the industrial world (1). The discovery by Virchow more than 100 years ago that atheroma contained a yellow fatty substance, later identified as cholesterol by Windaus, suggested a role for lipids in the pathogenesis of atherosclerosis (2). Indeed, the goal of this chapter is to focus on the role of lipids and lipoproteins in the pathogenesis of atherosclerosis as well as their critical roles in risk assessment and as targets of therapy. The recognition that atherosclerosis is an inflammatory disease has led to tremendous progress in our understanding of the pathogenesis of atherosclerosis (3). First, we provide brief description of the cellular and molecular events in the key stages of atherosclerosis.

Initiation and Fatty Streak Phase of Atherosclerotic Lesions

The endothelial lining of arteries responds to mechanical and molecular stimuli to regulate tone, (4) hemostasis, (5) and inflammation (6) throughout the circulation. Endothelial cell dysfunction is an initial step in atherosclerotic lesion formation and is more likely to occur at arterial curves and branches that are subjected to low shear stress and disturbed blood flow (atherosclerosis prone areas) (7,8). These mechanical stimuli activate signaling pathways leading to a dysfunctional endothelium lining that is barrier compromised, prothrombotic, and proinflammatory (9). In atherosclerosis susceptible regions, the endothelial cells have cuboidal morphology, a thin glycocalyx layer, and a disordered alignment (8,10,11). In addition, these regions have increased endothelial cell senescence and apoptosis as evidenced by ER stress markers (12-14). In contrast, less atherosclerosis prone endothelium is exposed to laminar shear stress causing activation of signaling pathways that maintain endothelial cell coaxial alignment, proliferation, (13,14) glycocalyx layer, (15) and survival (12,16). In atherosclerosis resistant regions, the transcription factors, Kruppel-like factors (KLF) 2 and 4, are activated via MEK5/ERK5/MEF2 signaling which enhances expression of endothelial nitric oxide synthase (eNOS) (17-19). The increased nitric oxide (NO) production promotes endothelial cell migration and survival thereby maintaining an effective barrier (20). In addition, the expression of superoxide dismutase (SOD) is increased to reduce cellular oxidative stress (18). In atherosclerosis susceptible regions, reduced expression of eNOS and SOD leads to compromised endothelial barrier integrity (Figure 1), leading to increased accumulation and retention of subendothelial atherogenic apolipoprotein B (apoB)-containing lipoproteins (low-density lipoproteins (LDL)) and remnants of very low-density lipoproteins (VLDL) and chylomicrons) (21,22). KLF2, KLF4, and NO production inhibit activation of the nuclear factor kappa B (NF-κB) pathway. Increased NF-κB activation in atherosclerosis susceptible areas leads to endothelial cell activation (Figure 1), as evidenced by increased expression of monocyte adherence proteins (VCAM-1, ICAM-1, and P-selectin) and proinflammatory receptors (toll-like receptor 2, TLR2) and cytokines (MCP-1 and IL-8) (19,23,24). In addition, endothelial cell activation leads to increased production of reactive oxygen species (25) that can cause oxidative modification of apoB-containing lipoproteins (26). Besides mechanical stimuli, endothelial cell activation is increased by various molecular stimuli, including oxidized LDL, cytokines, advanced glycosylation end products, and pathogen-associated molecules (27-30). In contrast, an atheroprotective function of HDL is to prevent endothelial activation and enhance NO production to maintain barrier integrity (see details below) (31).

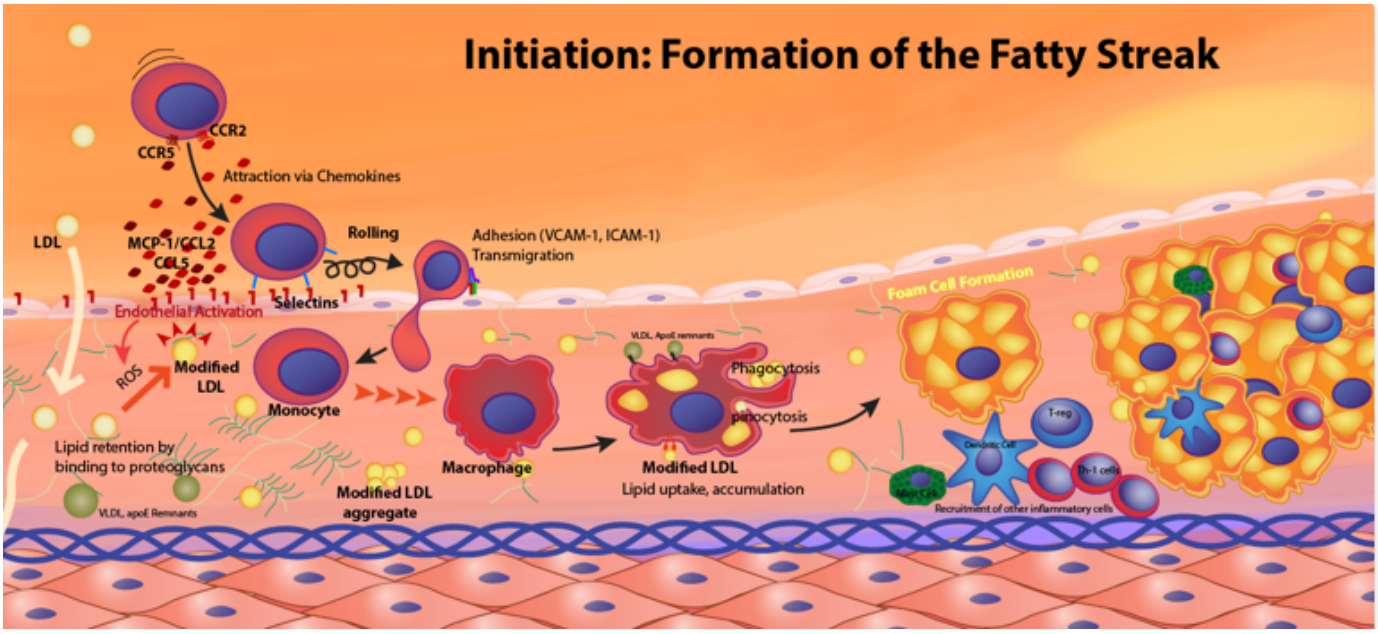

Figure 1. Initiation of the atherosclerotic lesion. The fatty streak phase of atherosclerosis begins with dysfunctional endothelial cells and the retention of apoB-containing lipoproteins (LDL, VLDL, and apoE remnants) in the subendothelial space. Retained lipoproteins are modified (oxidation, glycation, enzymatic), which, along with other atherogenic factors, promotes activation of endothelial cells. Activated endothelial cells have increased expression of monocyte interaction/adhesion molecules (selectins, VCAM-1) and chemoattractants (MCP-1) leading to attachment and transmigration of monocytes into the intimal space. Activated endothelial cells also promote the recruitment of other immune cells including dendritic cells, mast cells, regulatory T (T-reg) cells, and T helper 1 (Th-1) cells. The monocytes differentiate into macrophages and express receptors that mediate the internalization of VLDL, apoE remnants, and modified LDL to become foam cells. In addition, inflammatory signaling pathways are activated in macrophage foam cells leading to more cell recruitment and LDL modification.

Immune Cell Recruitment and Foam Cell Formation

Activation of endothelial cells causes a monocyte recruitment cascade involving rolling, adhesion, activation and transendothelial migration (Figure 1). Selectins, especially P-selectin, mediate the initial rolling interaction of monocytes with the endothelium (32). Monocyte adherence is then promoted by endothelial cell immunoglobulin-G proteins including VCAM-1 and ICAM-1 (32). Potent chemoattractant factors such as MCP-1 and IL-8 then induce migration of monocytes into the subendothelial space (33-35). $Ly6^{hi}$ monocytes, versus $Ly6^{lo}$, preferentially migrate into the subendothelial space to convert to proinflammatory macrophages in mice (36-38). The enhanced migration of $Ly6^{hi}$ versus $Ly6^{lo}$ monocytes likely results from increased expression of functional P-selectin glycoprotein ligand-1 (39). In addition, the number of blood monocytes originating from the bone marrow and spleen, especially $Ly6^{hi}$ cells, increases in response to hypercholesterolemia (36). Furthermore, hypercholesterolemia and atherosclerosis increase monocytosis in humans (40,41). Importantly, increased numbers of

inflammatory $CD14^{++}CD16^{+}$ monocytes independently predicted cardiovascular death, myocardial infarction, and stroke in patients undergoing elective coronary angiography (42). Intimal macrophages also result from proliferation of monocyte/macrophages, especially in more advanced lesions (43). During the initial fatty streak phase of atherosclerosis (Figure 1), the monocyte-derived macrophages internalize the retained apoB-containing lipoproteins, which are degraded in lysosomes, where excess free cholesterol is trafficked to the endoplasmic reticulum (ER) to be esterified by acyl CoA:cholesterol acyltransferase (ACAT), and the resulting cholesteryl ester (CE) is packaged into cytoplasmic lipid droplets, which are characteristic of foam cells (42) (Figure 2) (44,45). Modification of apoB lipoproteins via oxidation and glycation enhances their uptake through a number of receptors not down-regulated by cholesterol including CD36, scavenger receptor A, and lectin-like receptor family (see details below) (Figure 2) (46,47). Enzyme-mediated aggregation of apoB lipoproteins enhances uptake via phagocytosis (Figure 2) (48,49). In addition, native remnant lipoproteins can induce foam cell formation via a number of apoE receptors (LRP1 and VLDLR) (Figure 2) (50,51). Uptake of native LDL by fluid phase pinocytosis may also contribute to foam cell formation (Figure 2) (52,53).

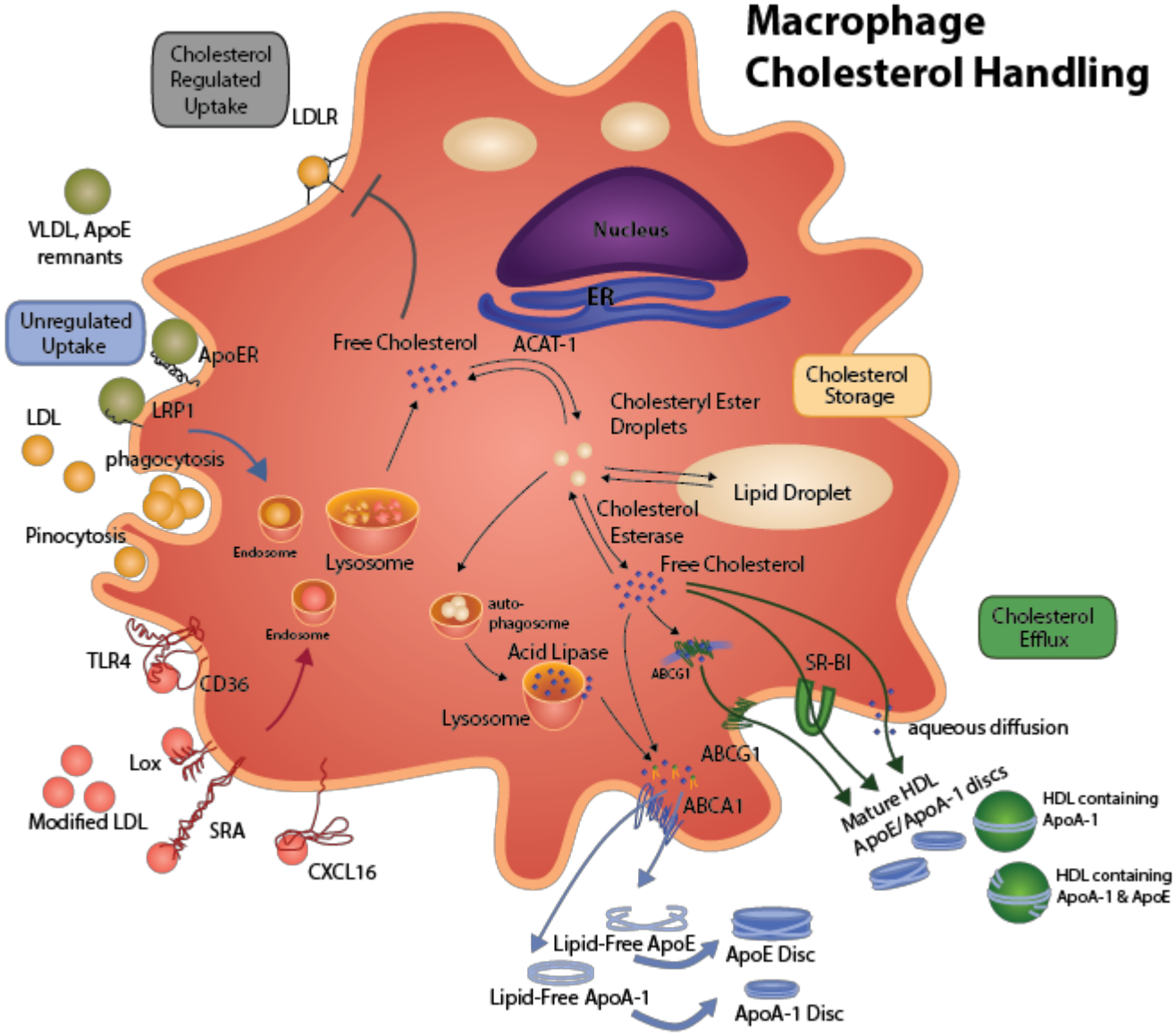

Figure 2. Macrophage Cholesterol Metabolism. Native LDL is recognized by the LDL receptor (LDLR). The LDL is endocytosed and trafficked to lysosomes, where the cholesteryl ester (CE) is hydrolyzed to free cholesterol (FC) by the acid lipase. The FC is transported to the endoplasmic reticulum (ER) to be esterified by acyl CoA:cholesterol acyltransferase (ACAT). Increased FC in an ER regulatory pool initiates a signaling cascade resulting in down-regulation of the LDL receptor. Cholesterol regulation of the LDLR prevents foam cell formation via this receptor in the setting of hypercholesterolemia. ApoB containing lipoproteins that also contain apoE (apoE remnants, VLDL) can cause cholesterol accumulation via interaction of apoE with apoE receptors including the LRP1 and the VLDL receptor, which are not regulated by cellular cholesterol. Uptake of native LDL by fluid phase pinocytosis may also contribute to foam cell formation. Modifications of apoB containing lipoproteins induce significant cholesterol accumulation via a number of mechanisms. Enzyme-mediated aggregation of

apoB lipoproteins enhances uptake via phagocytosis. Oxidation and/or glycation enhances internalization via a number of receptors that are not regulated by cholesterol, including CD36, scavenger receptor A (SRA), lectin-like receptors (LOX), and toll-like receptors (TLR4). The CE generated by ACAT is stored in cytoplasmic lipid droplets, where there is a continual cycle of hydrolysis to FC by neutral cholesterol esterase and re-esterification by ACAT. Cytoplasmic CE is cleared by two main pathways. In one pathway, removal of FC from the plasma membrane stimulates transport of FC that has been generated by neutral cholesterol esterase away from ACAT to the plasma membrane. Alternatively, cytoplasmic CE is packaged into autophagosomes, which are transported to fuse with lysosomes, where the CE is hydrolyzed by acid lipase and the resulting FC is then transported to the plasma membrane. The efflux of FC to lipid-poor apolipoproteins or HDL occurs by a number of mechanisms to reduce foam cell formation. Exogenous lipid-free apoA-I or endogenous apoE that is produced by the macrophages interacts with ABCA1 to stimulate the efflux of phospholipid and FC to form nascent HDL particles (e.g. apoA-I or apoE containing phospholipid discs). ApoE produces the most buoyant, FC-enriched particles. ABCA1 plays a major role in the clearance of cytoplasmic CE via autophagy. The apoA-I/apoE discs as well as mature HDL containing apoA-I and/or ApoE stimulate FC efflux via three major mechanisms including ABCG1, SR-BI, and aqueous diffusion. ABCG1 may also play a role in the intracellular trafficking of cholesterol.

The triggering of macrophage inflammatory pathways is also a critical event in lesion development. Inflammatory M1 phenotype macrophages exhibit increased oxidative stress, impaired cholesterol efflux and enhanced cytokine/chemokine secretion, leading to more LDL/remnant oxidation, endothelial cell activation, monocyte recruitment, and foam cell formation (54-59). Oxidative stress, modified lipoproteins, and other lesion factors (bioactive lipids, pattern recognition molecules, cytokines) are capable of inducing inflammation via receptors (54,55,60). In addition, plasma membrane cholesterol in macrophage foam cells enhances signaling via inflammatory receptors (61,62). Recently, inflammasome activation of IL-1β and IL-18 has been implicated in atherogenesis (63,64). Indeed, a recent clinical trial showed that subjects treated with the IL-1β monoclonal antibody, canakinumab, had a significantly lower rate of recurrent cardiovascular events which were independent of cholesterol lowering (65). Macrophage foam cell formation and cholesterol dependent inflammatory receptor signaling can be reduced by the removal of cholesterol by atheroprotective HDL and apoA-I via a number of mechanisms including ABCA1, ABCG1, SR-BI, and aqueous diffusion (Figure 2) (61,66-68) (see details below). Lipid-poor apoA-I stimulates efflux via ABCA1, whereas lipidated apoA-I or mature HDL are the main drivers of efflux via ABCA1, ABCG1, SR-BI, and aqueous diffusion (Figure 2) (61,69-71). Cytoplasmic CE is cleared by two major pathways. One route involves the hydrolysis of cytoplasmic CE by neutral cholesterol esterase and the resulting free cholesterol is mobilized away from the ACAT pool (72,73) and made available for efflux via ABCA1, ABCG1, SR-BI, and aqueous diffusion (Figure 2). Alternatively, cytoplasmic CE is packaged into autophagosomes, which are trafficked to lysosomes, where the CE is hydrolyzed by acid lipase(73,74), generating free cholesterol that is made available for efflux mainly via ABCA1(Figure 2) (73,74). Furthermore, HDL and apoA-I protect against

atherosclerosis by reducing inflammation via mechanisms independent of cholesterol efflux (31,75) (see details below). In addition, small non-coding RNAs have been found to impact atherosclerosis development by regulating inflammation and/or cholesterol homeostasis in different cell types in lesions (76,77). MiR-33a and MiR-33b promote atherosclerosis by impairing cholesterol efflux and promoting inflammatory M1 macrophage conversion (78-80).Other microRNAs including MiR-223 and MiR-93 exhibit atheroprotective effects by increasing cholesterol efflux and conversion to the anti-inflammatory M2 macrophage phenotype (76,81-83). HDL carry small non-coding RNAs (77), which can also reduce or promote atherosclerosis development depending upon composition of individual non-coding RNAs (see details below).

Although macrophages are the main infiltrating cells, other cells contribute to the development of lesions including dendritic cells (84,85), mast cells, T cells, and B cells (Figure 1) (86,87). Dendritic cells promote the priming of reactive T cell clones and secrete cytokines, functioning in a largely pro-inflammatory capacity(88). They also take up lipid, which leads to inflammasome activation and increased pro-inflammatory cytokine secretion (89). Mast cells produce interferon-γ (IFNγ) and IL-6 and appear to promote lesion development (90). Atherosclerotic plaques also contain a significant number of adaptive immune cells, including T and B lymphocytes. The role of T cells is subset-dependent and atherosclerotic plaques have been shown to contain $CD4^+$ and $CD8^+$ effector T cells as well as T helper 1 (Th-1), Th-2, Th-17, and regulatory T (T-reg) cells. Antigen-specific Th-1 cells produce IFNγ that converts macrophages to a proinflammatory M1 phenotype. Th-17 cells have also been identified in atherosclerotic plaques and have been shown to produce IFNγ. However, their specific role in atherosclerosis has not yet been elucidated (91). Classical T-reg cells produce anti-inflammatory cytokines (TGF-β and IL-10) and inhibit activation of Th-1 cells, leading to more anti-inflammatory M2 macrophages. As atherosclerosis progresses, T effector cell numbers increase or remain constant, while T-reg numbers decline. This reduction in T-regs is due in part to their heightened susceptibility to cell death as well as their impaired trafficking into lesions (91). Further, T-regs may appear fewer in number because they undergo phenotypic switching into other T-reg subtypes. Several subclasses of these ‘former’ T-regs have been identified in the atherosclerotic lesions of mice, including Th1-Tregs ($CD4^+CCR5^+IFN\text{-}\gamma^+FoxP3^+T\text{-}bet^+$) and T follicular helper cells ($CXCR5^+PD1^+Bcl6^+CD62L^{lo}CD44^{hi}CD4^+Foxp3^-$), and these have been shown to have both impaired regulatory and enhanced inflammatory function, therefore contributing to atheroprogression (91,92). B cells preferentially reside in the adventitial layer of arteries neighboring sites of plaque, in regions known as tertiary lymphoid organs (TLOs). The function of B lymphocytes is also subset dependent, with B-1 cells being atheroprotective and B-2 cells being atherogenic. B-1 cells undergo limited or no affinity maturation and produce natural antibodies (NAbs) that have broad specificity and low binding affinity. Among these are NAbs, found within atherosclerotic plaques, that can bind to oxidation motifs in LDL and block the uptake of oxLDL by macrophages (93). Mice engineered to overexpress a single-chain variable fragment of E06, an IgM NAb directed against oxidized phospholipids (oxPL), were found to have reduced atherosclerosis and features consistent with greater overall plaque stability, confirming the atheroprotective nature of these B-1 cell-derived antibodies (94). B-2 cells produce high-affinity IgA, IgE and IgG antibodies. While the role of IgA in atherosclerosis

remains controversial, IgG and IgE are atherogenic. IgG forms immune complexes with oxLDL and promotes an inflammatory macrophage phenotype while IgE also stimulates macrophages and mast cells to produce proatherogenic cytokines (95).

ApoE in Atherosclerosis

In addition to apoA-I and HDL, the endogenous production of apoE by macrophages is critical in preventing atherosclerotic lesion formation. The majority of apoE in plasma is produced by the liver, but macrophages are responsible for producing 5 -10% of apoE in plasma (96). ApoE serves as the ligand for clearance of all of the apoB containing lipoproteins from the blood by the liver except for LDL. Gene knockout of apoE in mice results in hypercholesterolemia and spontaneous atherosclerotic lesion development (97,98). Hence, ApoE deficient mice have been used widely to study mechanisms of atherosclerotic lesion development. Bone marrow transplantation studies were used to examine the role of macrophage apoE in lipoprotein metabolism. Transplantation of *Apoe*$^{-/-}$ mice with wildtype bone marrow, resulted in normalization of plasma cholesterol levels and protection from atherosclerosis (99), demonstrating the ability of macrophage apoE to exchange between lipoproteins and to serve as a vehicle for cellular gene therapy of atherosclerosis. Furthermore, reconstitution of wildtype (100) or LDL receptor deficient mice(*Ldlr*$^{-/-}$) (101) with *Apoe*$^{-/-}$ bone marrow accelerates atherosclerotic lesion development without affecting plasma cholesterol levels, demonstrating an atheroprotective role for macrophage apoE. Interestingly, ApoE protects against atherosclerosis via several mechanisms. Expression of apoE by hematopoietic stem cells reduces monocyte proliferation and infiltration into the intima (102). In addition, apoE on apoB lipoproteins reduces the lysosomal accumulation of cholesterol by enhancing the expression of acid lipase (103). Importantly, secretion of apoE by macrophages stimulates efflux in the absence and presence of exogenous acceptors, including HDL and lipid-free apoA-I (Figure 2) (104-107). Recent studies demonstrated that macrophage apoE facilitates reverse cholesterol transport *in vivo* (108). Macrophage apoE stimulates phospholipid and cholesterol efflux via ABCA1, and the apoE particles formed then promote cholesterol efflux through ABCG1, SR-BI, and aqueous diffusion (104,109-111). Endogenous apoE is required for efficient formation of the most buoyant, cholesterol-enriched particles by macrophages (Figure 2) (104,112-116). In addition to cholesterol efflux, macrophage apoE prevents inflammation (117-120) and oxidative stress (121-124). The local production of apoE is likely a critical atheroprotective mechanism considering that areas of atherosclerotic lesions have limited accessibility to plasma apoA-1 and HDL (100,101,125). Humans express three common apoE polymorphisms that predict CAD rates independently from plasma cholesterol levels (126). ApoE3 (C112, R158) is the most common isoform and is functionally similar to mouse apoE. Compared to apoE3 and apoE2 (C112, C158), apoE4 (R112, R158) are impaired in stimulating cholesterol efflux (127-130) and in preventing inflammation and oxidation (117,124,131). Consistent with the compromised function of apoE4, human carriers exhibit increased risk of CAD compared to humans expressing apoE3 or apoE2 (heterozygous) (126,132,133).

Progression to Advanced Atherosclerotic Lesions

Fatty streaks do not result in clinical complications and can even undergo regression. However, once smooth muscle cells infiltrate, and the lesions become more advanced, regression is less likely to occur (134,135). Small populations of vascular smooth muscle cells (VSMCs) already present in the intima proliferate in response to growth factors produced by inflammatory macrophages (136). In addition, macrophage-derived chemoattractants cause tunica media smooth muscle cells to migrate into the intima and proliferate (Figure 3). Critical smooth muscle cell chemoattractants and growth factors include PDGF isoforms, (137) matrix metalloproteinases, (138) fibroblast growth factors, (139) and heparin-binding epidermal growth factor (Figure 3) (140). HDL prevents smooth muscle cell chemokine production and proliferation. The accumulating VSMCs produce a complex extracellular matrix composed of collagen, proteoglycans, and elastin to form a fibrous cap over a core comprised of foam cells (Figure 4) (141). A vital component of the fibrous cap is collagen, and macrophage-derived TGF-β stimulates its production (Figure 4) (142). In addition, HDL maintains plaque stability by inhibiting degradation of the fibrous cap extracellular matrix through its anti-elastase activity (143). A subset of VSMCs accumulates CE and resides in the lesion core (Figures 3 and 4). This smooth muscle cell phenotype produces less α-actin and expresses macrophage markers, including CD68, F4/80 and Mac2 (144-146). While studies have shown that VSMCs express the VLDL receptor and various scavenger receptors, (145,147,148) data showing that these cells robustly load with CE, (147) similar to macrophages via these mechanisms is lacking. As lesions advance, substantial extracellular lipid accumulates in the core, in part due to large CE-rich particles arising from dead macrophage foam cells (149,150). Earlier *in vitro* studies showed that these CE-rich particles effectively cholesterol load VSMCs (151,152). Regardless of the mechanisms of cholesterol enrichment, VSMCs compared to macrophages are inefficient at lysosomal processing and trafficking of cholesterol (152,153) and express much less ABCA1(154), which all contribute to impaired cholesterol efflux (155). However, macrophages in more advanced plaques also have reduced lysosome function and trapping of free and esterified cholesterol within their lysosomes contributes to the overall sterol accumulation in the lesion (156-158). The reduced lysosome function appears multifactorial but includes direct and indirect inhibition of lysosomal acid lipase, the enzyme responsible for hydrolysis of cholesteryl esters in lysosomes, and a reduced capacity for transferring cholesterol from lysosomes (159-162). In cell culture models of human macrophage foam cells, the inability to clear cholesterol from macrophages with compromised lysosome function continues even in the presence of compounds that stimulate efflux (161,163). Proteomic analysis of foam cells shows that changes in a number of lysosome proteases are related to macrophage sterol accumulation (164). Thus, at least in the advanced stages of atherosclerosis, lysosome dysfunction contributes to the overall lesion severity. As the intimal volume enlarges due to accumulating cells, there is vascular remodeling to lessen protrusion of the lesion into the lumen (Figure 4), thereby decreasing occlusion and the appearance of clinical symptoms for much of the life of the lesion (165-167).

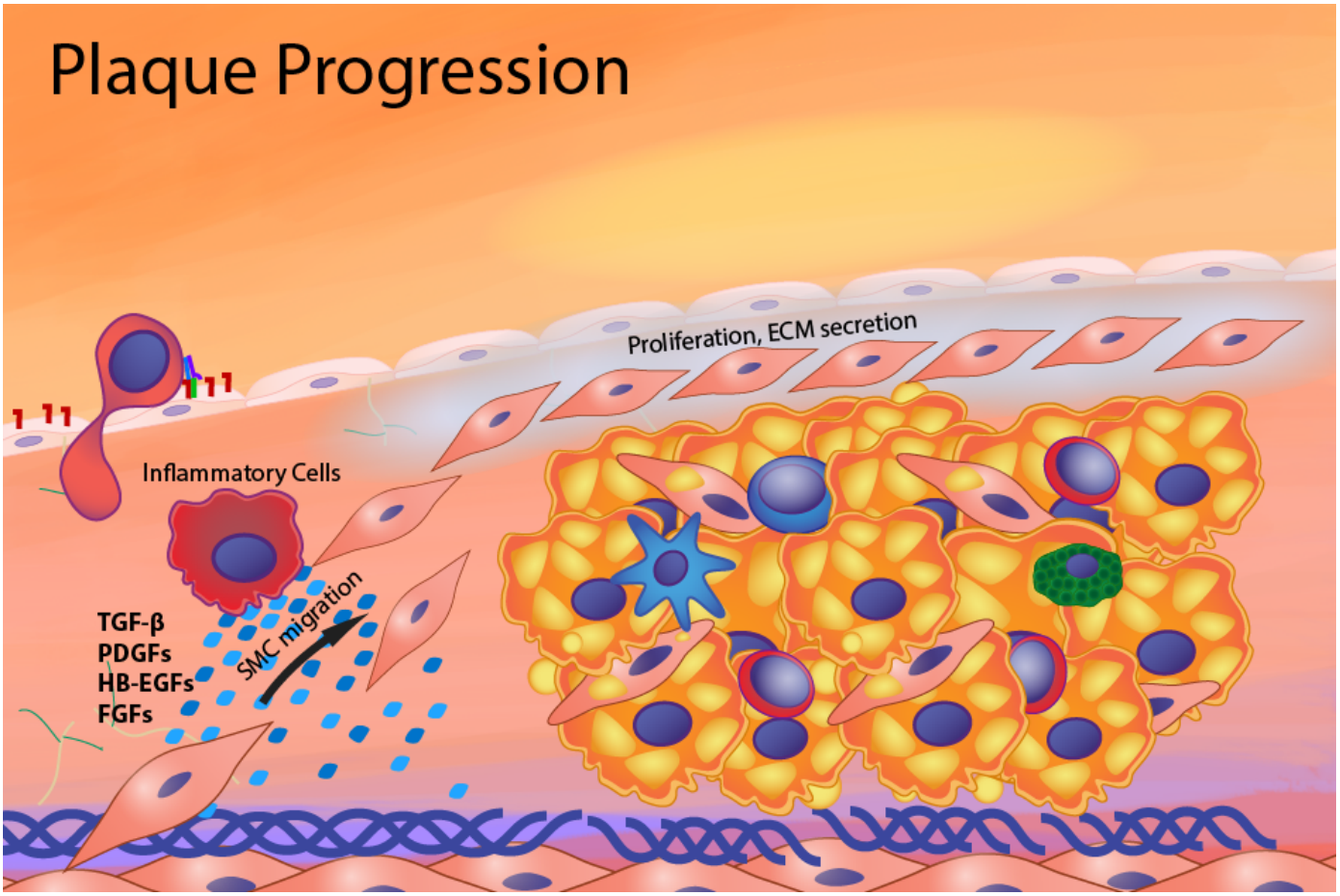

Figure 3. Progression of the atherosclerotic plaque. Macrophage foam cell and endothelial cell inflammatory signaling continues to promote the recruitment of more monocytes and immune cells into the subendothelial space. Transition from a fatty streak to a fibrous fatty lesion occurs with the infiltration and proliferation of tunica media smooth muscle cells. Macrophage foam cells and other inflammatory cells produce a number of chemoattractant and proliferation factors, including transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF) isoforms, matrix metalloproteinases, fibroblast growth factors (FGF), and heparin-binding epidermal growth factor (HB-EGF). Smooth muscle cells are recruited to the luminal side of the lesion to proliferate and generate an extracellular matrix network to form a barrier between lesional prothrombotic factors and blood platelets and procoagulant factors. A subset of smooth muscle cells express macrophage receptors and internalize lipoproteins to become foam cells. Fibrous fatty lesions are less likely to regress than fatty streaks.

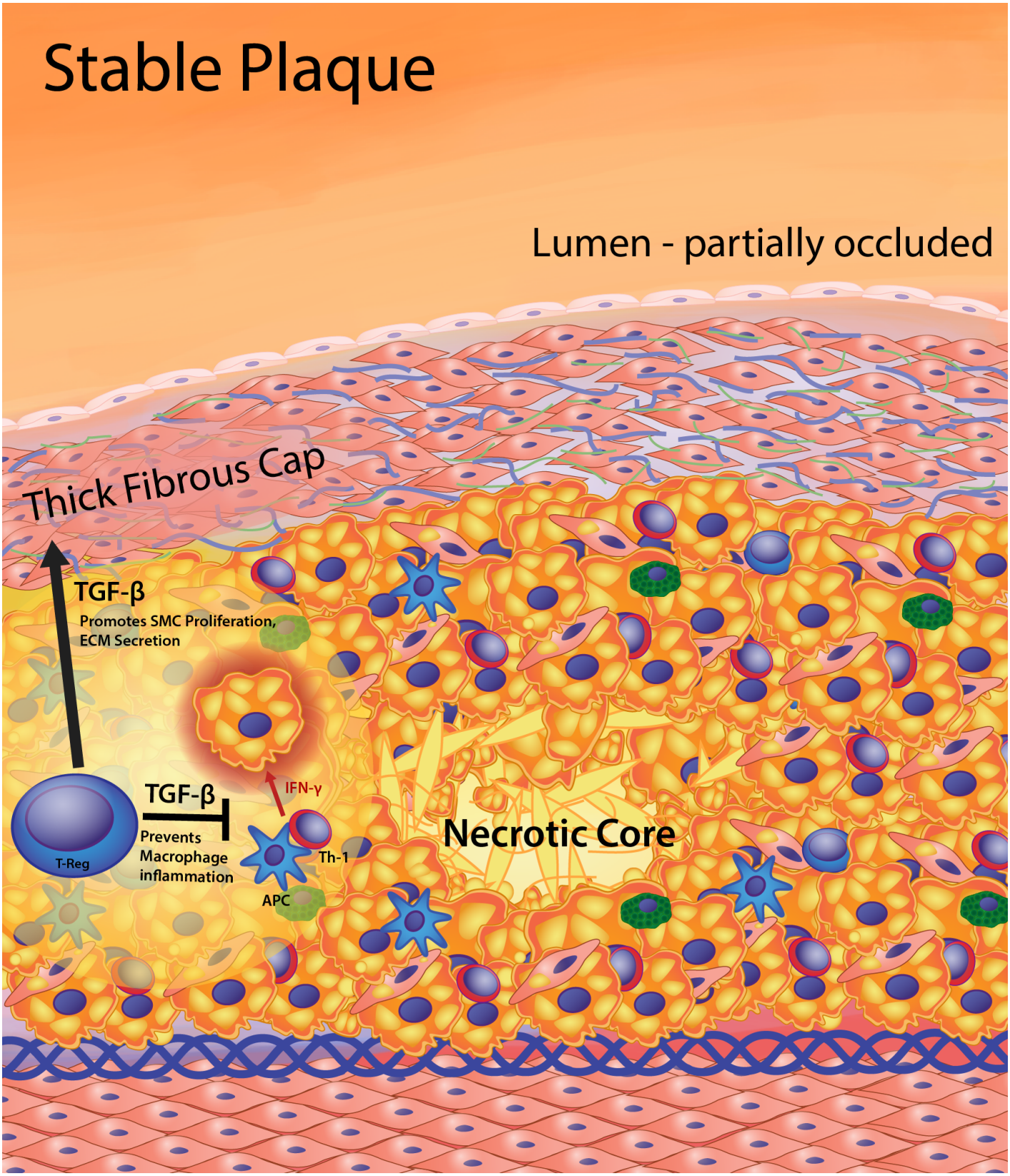

Figure 4. Features of the stable fibrous plaque. As the cell volume of the intima increases, there is vascular remodeling so that the lumen is only partially occluded,

substantially lessening clinical events resulting from occlusion. The stable plaque contains a generous fibrous cap composed of layers of smooth muscle cells ensconced in a substantial extracellular matrix network of collagen, proteoglycans, and elastin. The thick fibrous cap of the stable plaque provides an effective barrier preventing plaque rupture and exposure of lesion prothrombotic factors to blood, thereby limiting thrombus formation and clinical events. Maintenance of a thick fibrous cap is enabled by regulation of the inflammatory status of the foam cell core of the lesion. Regulatory T (T-reg) cells produce transforming growth factor-β (TGF-β) and IL-10. In addition, T-reg cells inhibit antigen-specific activation of T helper 1 (Th-1) cell to produce interferon gamma (IFNg). Increased TGF-β and IL-10 and decreased IFNg reduce the proinflammatory macrophage phenotype leading to reduced cell death, effective efferocytosis (phagocytosis of dead cells), and anti-inflammatory cytokine production (i.e. TGF-β, IL-10). Thus, stable plaques have small necrotic cores containing macrophage debris and extracellular lipid resulting from secondary necrosis of noninternalized apoptotic macrophage foam cells. The production of TGF-β by T-reg cells and macrophages maintains fibrous cap quality by being a potent stimulator of collagen production in smooth muscle cells.

Vulnerable Plaque Formation and Rupture

The advanced atherosclerotic lesion is essentially a nonresolving inflammatory condition leading to formation of the vulnerable plaque, increasing the risk of plaque rupture. The vulnerable plaque is characterized by two fundamental morphological changes: 1) Formation of a necrotic core and 2) Thinning of the fibrous cap. Sections of the atheroma with a deteriorated fibrous cap are subject to rupture (Figures 4 and 5) (168,169). A recent lipidomics study showed that stable versus unstable plaques have different lipid subspecies profiles (170). Compared to plasma and control arteries, stable plaques have increased CE containing polyunsaturated fatty acids (170), which have increased susceptibility to oxidation. The CE containing polyunsaturated fatty acids are decreased in unstable plaques compared to stable plaques of the same subjects (170). In addition, 18:0 containing lysophosphatidylcholine is increased in unstable plaques indicating enhanced oxidation (170). Plaque rupture leads to acute exposure of procoagulant and prothrombotic factors from the necrotic core of the lesion to platelets and procoagulant factors in the lumen, thereby causing thrombus formation (Figure 5) (168,169). Thrombus formation at sites of plaque rupture accounts for the majority of clinical events with acute occlusive luminal thrombosis causing myocardial infarction, unstable angina, sudden cardiac death, and stroke (168,169).

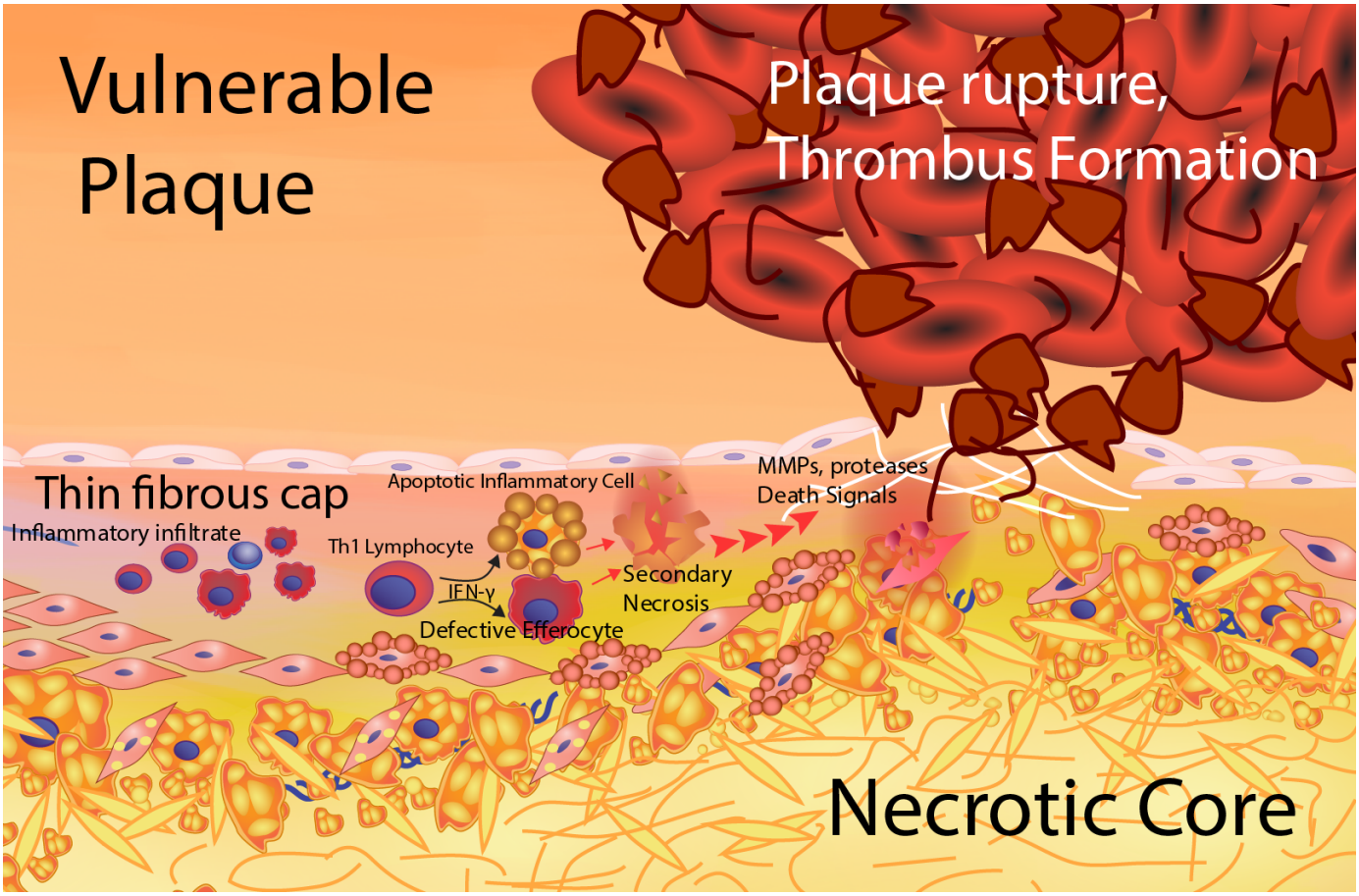

Figure 5. Formation of the vulnerable plaque. The vulnerable plaque results from a heightened, unresolved inflammatory status of the lesion foam cell core. Antigen-specific activation of T helper 1 (Th-1) cells produces interferon gamma (IFNg) resulting in a proinflammatory macrophage phenotype. The proinflammatory macrophage foam cells exhibit enhanced inflammatory cytokine secretion and apoptosis susceptibility. There is less secretion of the anti-inflammatory cytokines, TGF-β and IL-10. In addition, proinflammatory macrophages have impaired atheroprotective functions including cholesterol efflux and efferocytosis. The defective efferocytosis of inflammatory apoptotic macrophages results in secondary necrosis leading to an enlarged necrotic core composed of leaked oxidative and inflammatory components. This unresolved inflammation causes thinning of the fibrous cap resulting from increased smooth muscle cell death, enhanced extracellular matrix degradation and decreased extracellular matrix production. Areas of thin fibrous cap are prone to rupture exposing prothrombotic components to platelets and procoagulation factors leading to thrombus formation and clinical events.

Macrophage Cell Death and Efferocytosis Influence Plaque Stability

The necrotic core results from a combination of accelerated macrophage death and impaired efferocytosis (receptor-mediated phagocytosis of apoptotic cells) (Figure 5) (171,172). As apoptotic cells accumulate and fail to be internalized by phagocytes, they undergo secondary

necrotic death leading to the leakage of intracellular oxidative and inflammatory components, which then propagate more inflammation, oxidative stress, and death in neighboring cells (Figure 5) (173). Multiple triggers likely occur in lesions to accelerate macrophage death, including oxidative stress, death receptor activation, and nutrient deprivation (174). Prolonged ER stress and activation of the unfolded protein response (UPR) contribute to macrophage apoptosis as substantiated by studies showing that apoptosis and the UPR effector, CHOP, increase with each stage of atherosclerosis in humans, but the largest increase is observed in the vulnerable plaque (175). In diabetes and obesity, accelerated formation of an enlarged necrotic core is likely instigated by defective macrophage insulin signaling (176) and saturated fatty acids (177,178), which are potent inducers of ER stress. In addition, other triggers act in tandem with ER stress to accelerate apoptosis. In particular, activation of toll-like receptors (TLR) (TLR2 and TLR4) and scavenger receptors (CD36 and SR-A) by oxidized phospholipids induces apoptotic signaling (178-181). Death is also accelerated by simultaneous suppression of survival pathways such as pAkt and NF-κB via these same receptors. Accelerated apoptotic macrophage death is not sufficient to promote necrosis. Apoptotic cells undergo secondary necrotic death if they are not internalized by phagocyte efferocytosis receptors. Necrotic death leads to the leakage of intracellular oxidative and inflammatory components, which then propagate more inflammation, oxidative stress, and death in neighboring cells (Figure 5) (173). The presence of necrotic tissue together with apoptosis is consistent with defective efferocytosis in human plaques. Studies have shown that the majority of apoptotic cells are free in advanced human lesions, whereas in tonsils apoptotic cells are macrophage-associated (182). Efferocytosis also becomes defective in advanced atherosclerosis through several different mechanisms. First, accumulating evidence has shown that the expression and function of key efferocytosis receptors, MerTK (183), LRP1 (184), and SR-BI (185) are impaired in advanced atherosclerosis. These receptors recognize apoptotic cell ligands such as phosphatidylserine (185,186). and efferocytosis efficiency is enhanced by bridging molecules such as apoE and MFG-E8 that interact with efferocytosis receptors to enhance their efficiency and also have reduced expression in advanced lesions (186-190). Compared to apoE3, apoE4 is defective at facilitating efferocytosis of apoptotic cells (191). Efferocytosis via LRP1 (187) and SR-BI (185) also stimulates signaling pathways leading to pAkt production to promote phagocyte survival. In addition, anti-inflammatory signaling (185,192) is activated so that phagocytes secrete TGF-β and IL-10 (Figures 4 and 5). In addition, efferocytosis may be limited by competition for apoptotic cell binding. For example, oxPLs bind efferocytosis receptors and effectively compete for apoptotic cell recognition. In addition, lesional autoantibodies to oxPL and oxLDL are able to bind to ligands on the apoptotic cell themselves in order to prevent their binding and ingestion. Finally, apoptotic cells in advanced lesions appear to become poor substrates for efferocytosis. CD47, which typically acts as a “don’t eat me” signal expressed by live cells, is upregulated by apoptotic cells within human and murine atherosclerotic plaques, allowing them to evade uptake by phagocytes. When given to atheroprone *Apoe*$^{-/-}$ mice, a CD47-blocking antibody enhanced lesional efferocytosis and resulted in smaller necrotic cores (193). Similarly, mice that express low levels of the “eat me” signal, calreticulin, have increased necrotic cores compared to control mice and apoptotic cells from these mice demonstrate resistance to uptake by phagocytes (194).

Components of the necrotic core promote thinning of the fibrous cap. Loss of extracellular matrix is in part due to death of fibrous cap smooth muscle cells, resulting from macrophage-derived Fas receptor ligand (195), inflammatory cytokines (196), and oxidation products (Figure 5) (197,198). Smooth muscle cells are inefficient at efferocytosis (199) relying on macrophages to internalize apoptotic smooth muscle cells. As such, the impaired efferocytosis by lesional macrophages likely leads to uncontrolled VSMC death (Figure 5). In addition, impaired production of TGF-β by phagocytes (185,200) reduces collagen production by healthy smooth muscle cells (Figures 4 and 5). The extracellular matrix components are degraded by macrophage-derived matrix metalloproteinases, (201-203) elastases, and cathepsins (Figure 5) (204). HDL can reduce VSMC apoptosis and elastin degradation induced by elastases (143,205).

Importantly, HDL can prevent efferocyte apoptosis via ER stress by its cholesterol efflux and anti-oxidant functions (179,206,207). Furthermore, HDL drives conversion to the anti-inflammatory M2 macrophages which have enhanced efferocytosis ability compared to inflammatory M1 macrophages (56,208) leading to increased plaque stability. Once plaque rupture occurs, critical HDL functions may also include prevention of platelet activation and thrombus formation. In addition to the role of HDL in stabilizing plaques, recent studies have focused on the lesional loss of specialized proresolving mediators (SPM) versus proinflammatory factors (i.e. leukotriene B_4) in promoting uncontrolled inflammation and formation of vulnerable plaques (209). Studies on human atherosclerotic lesions have shown that unstable versus stable plaques have decreased lipid-derived SPM including resolvin D1 and lipoxin A_4 (210). In addition, resolving D1 treatment of *Ldlr*$^{-/-}$ mice with established atherosclerosis increased lesional efferocytosis and collagen content and reduced the necrotic area and reactive oxygen species content (210). Similar results were observed in *Apoe*$^{-/-}$ mice treated with the phospholipase D derived proresolving lipid, palmitoylethanolamide (211). Other lipid derived resolving mediators which impact atherosclerotic plaques include maresin 1 and resolvin D2 (212). Protein SPM have also been identified including annexin 1 and IL-10 (209). Administration of lesion targeting nanoparticles containing the bioactive annexin 1 peptide, Ac2-26, to *Ldlr*$^{-/-}$ mice with atherosclerosis reduced both lesional oxidative stress and necrosis while increasing collagen content and fibrous cap thickness (213). Enhancing the lesional IL-10 content also improved atherosclerotic lesion stability (214). In addition, Treg cells likely control atherosclerotic lesion inflammation resolution as recent studies demonstrated that Treg cells regulate efferocytosis in atherosclerotic lesions by secreting IL-13 to stimulate macrophage production of IL-10 to induce Vav-1 activation of Rac1 and increased efferocytosis (215).

Summary

Atherosclerotic lesions initiate with endothelial cell dysfunction causing modification of apoB containing lipoproteins (LDL, VLDL, remnants) and infiltration of immune cells, particularly monocytes, into the subendothelial space (Figure 1). The macrophages internalize the retained apoB containing lipoproteins to become foam cells forming the fatty streak (Figure 1). Macrophage inflammatory pathways are also activated leading to increased oxidative stress and

enhanced cytokine/chemokine secretion, causing more LDL/remnant oxidation, endothelial cell activation, monocyte recruitment, and foam cell formation (Figure 1). HDL, apoA-I, and endogenous apoE reduce lesion formation by preventing endothelial cell activation, inflammation, and oxidative stress and also by promoting cholesterol efflux from foam cells. As the lesion progresses to fibrotic plaques as a result of continued inflammation, macrophage chemoattractants stimulate infiltration and proliferation of smooth muscle cells (Figure 3). Smooth muscle cells produce the extracellular matrix providing a stable fibrous barrier between plaque prothrombotic factors and platelets (Figure 4). Unresolved inflammation results in formation of vulnerable plaques, which have large necrotic cores and a thinning fibrous cap (Figure 5). Enhanced macrophage apoptosis and defective efferocytosis of apoptotic cells results in necrotic cell death causing heightened inflammation leading to increased smooth cell death, decreased extracellular matrix production, and collagen degradation by macrophage proteases. An imbalance between inflammatory factors and SPMs is prominent in facilitating formation of the vulnerable plaque. Rupture of the thinning fibrous cap promotes thrombus formation resulting in clinical ischemic cardiovascular events (Figure 5).

THE ROLE OF CHOLESTEROL AND LIPOPROTEINS IN ATHEROGENESIS

Metabolism of ApoB Containing Lipoproteins

Apolipoprotein B (apoB) occurs in two isoforms, apoB100 and apoB48. ApoB100 is the main structural apolipoprotein of low-density lipoproteins (LDL), and there is only one molecule of apoB100 per LDL particle (216). ApoB100 is produced mainly by the liver, where it is required for the synthesis and secretion of triglyceride-rich very low-density lipoprotein (VLDL) particles (Figure 6). In the circulation, VLDL is metabolized to the cholesteryl ester-enriched intermediate low-density lipoprotein (IDL) and LDL particles through the progressive hydrolysis of triglycerides by lipoprotein lipase (LPL) and hepatic lipase (Figure 6). In humans, apoB48 is produced exclusively in the intestine through an unique RNA editing mechanism by the apobec-1 enzyme complex (217). ApoB100 is the full-length protein, which contains 4536 amino acids, whereas apoB48 contains the first 48% of the amino terminal amino acids. ApoB48 is required for the synthesis and secretion of triglyceride-rich chylomicrons, which play a critical role in the intestinal absorption of dietary fats and fat-soluble vitamins. Similar to the metabolism of VLDL, chylomicrons are metabolized in the circulation through the hydrolysis of triglycerides by LPL and hepatic lipase to form cholesteryl ester-enriched chylomicron remnants, which release free fatty acids that can be used for energy by the tissues.

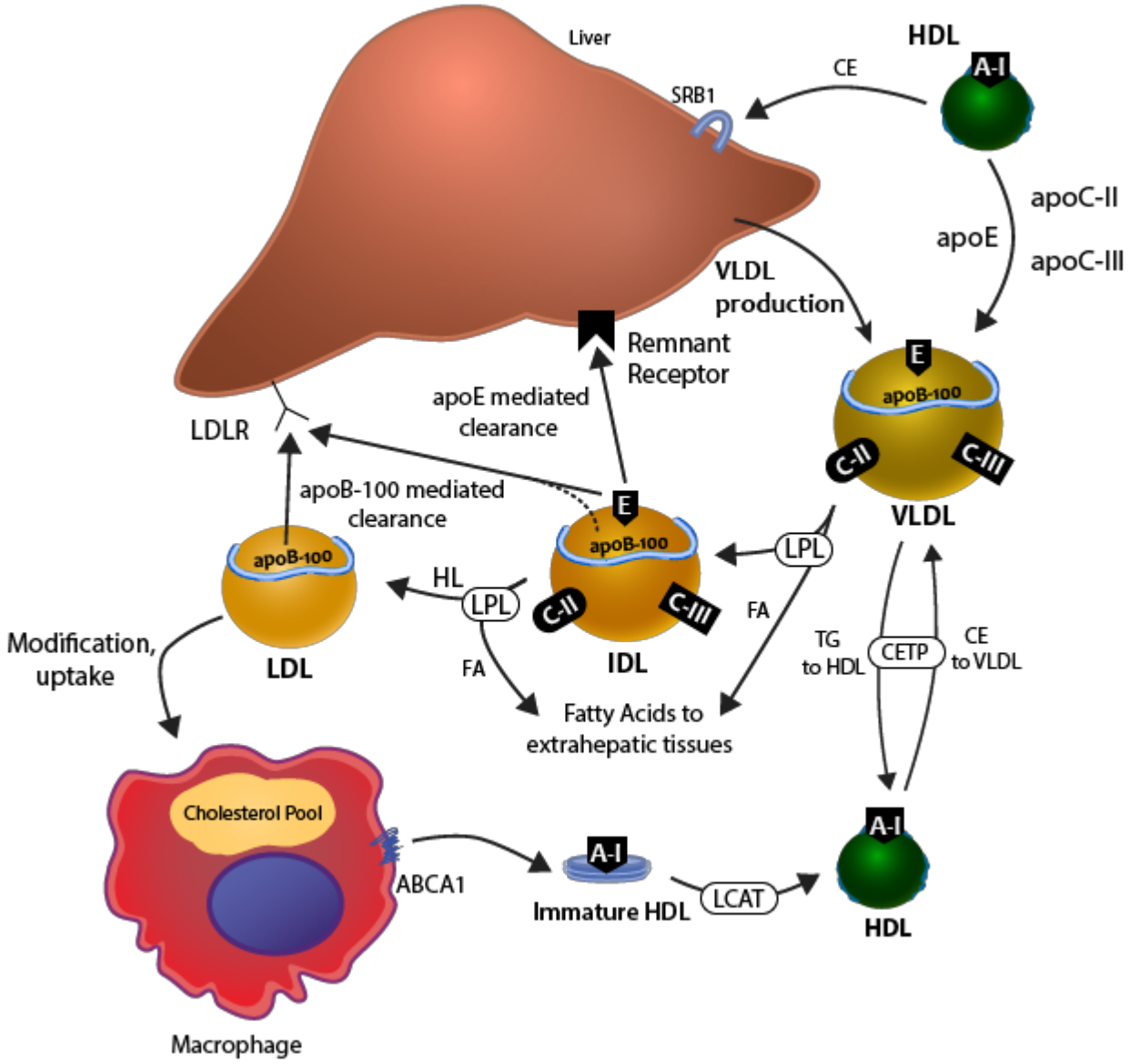

Figure 6. Metabolism of ApoB100 containing lipoproteins. ApoB100 is critical for the production and secretion of very low-density lipoprotein (VLDL) by the liver. Plasma VLDL is metabolized to cholesteryl ester-enriched intermediate low-density lipoprotein (IDL) and LDL particles via hydrolysis of triglycerides by lipoprotein lipase (LPL) and hepatic lipase (HL). In addition, cholesteryl ester transfer protein (CETP) transfers CE from HDL to VLDL in exchange for triglyceride (TG) to HDL. ApoCII and apoCIII are transferred from HDL to VLDL and act as an activator or inhibitor of LPL activity, respectively. ApoB100 is the ligand for hepatic LDL receptor-mediated clearance of LDL. VLDL acquires apoE from HDL, and apoE mediates the clearance of triglyceride-enriched remnants and IDL. In addition, HDL can directly transfer cholesterol to liver via interaction with SR-BI. VLDL and IDL remnants can induce foam cell formation by internalization via apoE receptors on macrophages. LDL, IDL, and VLDL can be modified (oxidation, glycation) and internalized by a number of macrophage receptors including

scavenger receptors and lectin-like receptors. HDL and lipid-poor apoA-I reduce foam cell formation by stimulating cholesterol efflux.

Static measurements of cholesterol in the LDL pool (LDL-C) represent the steady state of production of VLDL, its metabolism to LDL, and the receptor-mediated clearance of LDL by the LDL receptor (LDLR). Mutations in the *Ldlr* gene are the most common cause of familial hypercholesterolemia (FH), an autosomal dominant disorder associated with elevated levels of LDL-C and increased risk for premature cardiovascular disease (218). ApoB100 serves as the ligand for receptor-mediated clearance of LDL by the liver (Figure 6). In contrast, apoE mediates the clearance of triglyceride-rich remnants (IDL and chylomicron remnants) either through the LDLR or the remnant receptor pathway (Figure 6). The existence of the remnant receptor pathway was suggested by the fact that patients with homozygous FH, who completely lack LDLR function, have severely elevated levels of LDL-C but normal blood levels of triglycerides. The clearance of these remnant lipoproteins involves binding to heparin sulfate proteoglycans and the LDLR like protein -1 (LRP1) in the hepatic space of Disse, in a process called secretion capture that requires local enrichment by hepatic expression of apoE (96,219).

The Cholesterol Hypothesis

Studies by Anitschkow showing that feeding cholesterol in oil to rabbits caused the formation of atheroma, similar to those seen in humans, demonstrated a causal role of cholesterol in the pathogenesis of atherosclerosis in 1913 (220). In 1939, Muller described families with inherited high cholesterol and increased risk for cardiovascular disease (221). Yet it would take several decades before compelling evidence from epidemiological studies, such as Framingham (221) and MRFIT (222), demonstrated that elevated blood cholesterol levels were associated with increased risk of cardiovascular events (CVE). Subsequently, LDL-C levels were found to be directly associated with CVE (223); whereas HDL-C levels were shown to be inversely related to risk of CVE (224). The Seven Countries Studies by Ancel Keys showed that coronary heart disease (CHD) mortality rates were higher in countries with higher blood levels of cholesterol (e.g. Finland, Norway, and the USA) than in countries of southern Europe and Japan with lower blood levels of cholesterol (225). The high levels of cholesterol were proposed to be associated with the amount of saturated fat in the diet. As such, the cholesterol hypothesis was born, proposing that lowering LDL-C would reduce CVE (226).

Response to Retention Hypothesis for the Initiation of Atherosclerosis

The response to retention hypothesis holds that retention of atherogenic lipoproteins in the artery wall is a critical initiating event that sparks an inflammatory response and promotes the development of atherosclerosis (Figure 1). First articulated in 1995 by Williams and Tabas (227), the hypothesis was based on more than two decades of work demonstrating that apoB-containing lipoproteins are retained in the artery wall by interaction with proteoglycans (228,229). Proteoglycans consist of a protein core bound covalently to one or more glycosaminoglycans (GAGs). The most common proteoglycans in the artery wall are decorin,

biglycan, perlecan, versican, and syndecan-4 (230). There is ionic binding between the positively charged GAGs and negatively charged amino acids of apoB100 (229). Boren *et al.* identified the principal proteoglycan-binding site in LDL and showed that a single point mutation in apoB100 impaired binding to proteoglycans (231). The major proteoglycan binding site consists of residues 3359-3369 in apoB100 (site B), which is in the C-terminal half of apoB100. Furthermore, mutation of "site B" in mice resulted in reduced retention of apoB100 in the artery wall and reduced atherosclerosis, providing *in vivo* support for the response to retention hypothesis (232). Subsequently, proteoglycan binding sites were identified for apoB48 (233) and a second site (site A) on apoB100, which is exposed when LDL is modified by secreted phospholipase A2 (sPLA2), forming a small dense LDL particle (234).

Surprisingly, native LDL, despite the strong evidence for its critical role in promoting atherosclerosis, does not induce macrophage foam cell formation or much in the way of inflammation *in vitro*. These observations led to the hypothesis that LDL has to be modified to promote foam cell formation and induce inflammation. Binding of proteoglycans induces structural changes in LDL impacting both the configuration of apoB100 and the lipid composition (234). Hence, the binding of LDL to proteoglycans makes the LDL more susceptible to oxidation and aggregation, which promotes foam cell formation and a proinflammatory response, and the process is self-perpetuating. Oxidized LDL (oxLDL) can induce further production of proteoglycans by vascular smooth muscle cells, retaining more LDL in the arterial wall. Furthermore, macrophages express LPL, which can serve as bridging molecules, binding both lipoproteins and proteoglycans (235,236). Consistent with an important role for LPL in atherogenesis, the loss of macrophage LPL expression protects mice from atherosclerosis (237,238). In addition, macrophages secrete sphingomyelinase, which has been reported to act synergistically with LPL to promote binding of LDL and lipoprotein (a) (Lp(a)) to vascular smooth muscle cells (VSMC) and the extracellular matrix promoting their retention in the artery (239,240). Furthermore, sphingomyelinase induces aggregation and fusion of LDL particles, promoting increased binding to proteoglycans and induces foam cell formation (241). Thus, interfering with the retention of apoB-containing lipoproteins in the artery wall is a potential strategy for preventing atherosclerosis.

OXIDATION OF PHOSPHOLIPIDS AND PROTEINS IN LIPOPROTEINS AND THEIR ROLE IN ATHEROSCLEROSIS

Overview

The response to retention hypothesis for the initiation of atherosclerosis posits that retention of LDL in the artery wall leads to its modification into highly atherogenic particles that initiate inflammatory responses. A key overall point is that retention of LDL leads to oxidative modification of LDL, allowing this oxidized LDL (oxLDL) to be recognized by scavenger receptors on macrophages and other cells. Uptake of oxLDL by macrophages leads to marked accumulation of cholesterol, converting them to foam cells and initiating development of atherosclerotic lesions. In addition to serving as a substrate for cholesterol accumulation, oxLDL exerts a wide range of bioactivities that are consistent with it being critical for driving

atherogenesis (Table 1). In mouse models, loss of enzymes that modulate LDL oxidation increases atherosclerosis, and dietary antioxidants that reduce levels of oxLDL also inhibit atherosclerosis. Although human trials with dietary antioxidants have failed to reduce disease outcomes, it is important to recognize that these interventions are less efficacious in reducing oxLDL levels in humans than in rodent models. Additional studies are needed to determine optimal interventions for lowering oxLDL levels and whether such interventions will be effective for preventing or treating atherosclerosis.

Table 1-Potential Atherogenic Activities of Oxidized LDL (oxLDL)	
Macrophages	**Smooth muscle cells**
Serves as ligand for recognition by scavenger receptors [256, 257, 258]	Induces proliferation, migration, and transition to inflammatory phenotype [276, 277, 278, 279]
Serves as substrate for unregulated cholesterol uptake [262]	
Induces expression and secretion of inflammatory cytokines [280, 281, 282, 283]	**Lymphocytes**
Induces polarization to M1 (minimally oxidized LDL) or M2-phenotype (highly oxidized LDL) [284]	Serves as a neo-antigen [274]
Inhibits egress from atherosclerotic lesions [289]	Induces chemotaxis [275]
Induces macrophage apoptosis and rupture of atherosclerotic plaques [290, 291, 292]	Increases antibody production [275]
	Other cell types
Endothelial cells	Induces chemotaxis of monocytes, PMN, and eosinophils [285, 286, 287, 288]
Induces surface expression of adhesion molecules [266, 268, 269, 270]	Increases platelet aggregation [293, 294, 295, 296]
Induces inflammatory genes including cytokine release [271, 272]	Activates dendritic cells and induces their release of T cells stimulating cytokines [284]

Peroxidation of Polyunsaturated Fatty Acids Generates Oxidatively Modified Lipoproteins

The outer shell of lipoproteins is composed of phospholipids with polyunsaturated fatty acid (PUFA) side chains. These PUFAs (and to a lesser extent the PUFAs of cholesterol esters and triglycerides in the lipoprotein core) are highly vulnerable to oxidation by free radical species, particularly hydroxyl radicals ($^{\bullet}OH$). This vulnerability results from the relatively low energy required for free radicals to abstract hydrogen atoms located between two adjacent double bonds (bis-allelic hydrogens). Hydrogen abstraction by free radicals creates a lipid radical that reacts nearly instantaneously with any molecular oxygen present in the environment.

The resulting lipid peroxide radical ($LOO^{\bullet}$) can then propagate the radical reaction by abstracting hydrogens from neighboring phospholipids or can react with itself to create a large number of secondary peroxidation products (Figure 7). Secondary products that may be

relevant to atherogenesis can be thought of in two broad classes: oxidized lipids (primarily oxidized phospholipids but also oxidized cholesterol esters) and reactive lipid aldehydes that exert their effects by modifying proteins and other macromolecules. Oxidized phospholipids (oxPL) include chain shortened oxPL such as 1-palmitoyl-2-oxovaleroyl-sn-glycero-3-phosphorylcholine (POVPC)(242), 1-O-alkyl-2-azelaoyl-sn-glycero-3-phophorylcholine (azPAF) (243), and 1-(Palmitoyl)-2-(5-keto-6-octene-dioyl) phosphatidylcholine (KOdiA-PC) and cyclized oxPL such as 1-palmitoyl-2-(5,6)-epoxyisoprostane E2-sn-glycero-3-phosphocholine (PEIPC) (244) and 1-palmitoyl-2-F2-isoprostane-sn-glycero-3-phosphocholine (F2IsoP-PC) (245). Reactive lipid species include malondialdehyde (246), 4-hydroxynonenal (246), and isolevuglandins (247) that modify proteins associated with lipoprotein particles including ApoB100 (Figure 7).

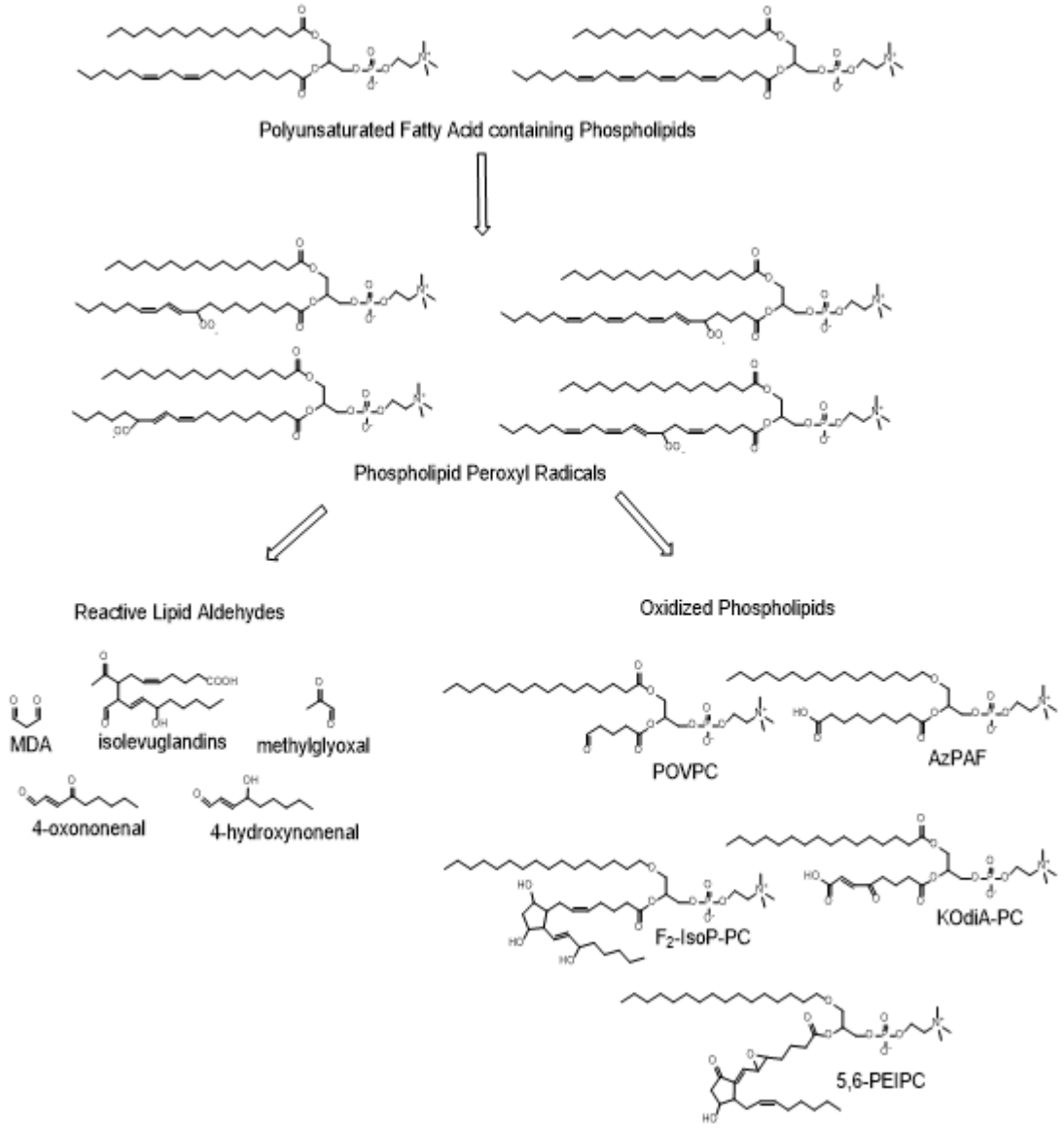

Figure 7. Oxidation of Phospholipid Polyunsaturated Fatty Acids. Oxidation of phospholipids containing polyunsaturated fatty acids present in plasma lipoproteins

results in formation of a variety of reactive lipid aldehydes and oxidized phospholipids that convert these lipoproteins to atherogenic particles. Reactive lipid species include malondialdehyde (MDA), isolevuglandins (IsoLG), methyglyoxal (MGO), 4-oxononenal (ONE), and 4-hydroxynonenal (HNE). Oxidized phospholipids include 1-palmitoyl-2-oxovaleroyl-sn-glycero-3-phosphorylcholine (POVPC), 1-O-alkyl-2-azelaoyl-sn-glycero-3-phophorylcholine (azPAF), 1-(Palmitoyl)-2-(5-keto-6-octene-dioyl) phosphatidylcholine (KOdiA-PC), 1-palmitoyl-2-F2-isoprostane-sn-glycero-3-phosphocholine (F2IsoP-PC), and 1-palmitoyl-2-(5,6)-epoxyisoprostane E2-sn-glycero-3-phosphocholine (PEIPC).

It is critical to keep in mind that oxidatively modified LDLs (oxLDLs) are in fact highly heterogeneous and complex particles, even though oxLDL is usually referred to as a discrete entity. Oxidation of LDL in vitro has been used extensively to study the biological activities of oxLDL, but, even here, the actual species present varies significantly based on the oxidation method (exposure to air, to copper, or to oxidases) and length of oxidation. Many of the methods commonly used to measure the concentration of oxLDL in vivo only measure general characteristics of oxLDL. For instance, because the reaction of reactive lipid species with lysine residues of ApoB100 converts LDL from a positively charged particle to a negatively charged particle, oxLDL is often detected by increased mobility during agarose gel electrophoresis. Alternatively, oxLDL in plasma and other tissues can be quantified by the immunoreactivity of the natural IgM autoantibody E06. However, while E06 recognizes a variety of oxidized phosphatidylcholines, it does not necessarily recognize all oxPL equally. Therefore, equivalent E06 immunoreactivity does not necessarily mean exposure to identical oxLDL particles. While modification of LDL with malondialdehyde (MDA-LDL) (248) is often used as a model of oxLDL for bioactivity assays, modification of LDL by other reactive lipid species can exert unique effects from MDA-LDL, and MDA-LDL does not include any of the various oxPL species. Therefore, it is important to keep in mind that in vivo oxLDL is a mixture of many different compounds and that the atherogenic activities of oxLDL represent the net cellular responses to the full range of compounds present.

While oxLDL has been studied in greatest detail, all lipoproteins are vulnerable to oxidation at least in vitro, and this oxidative modification alters their biological activities in ways that may be atherogenic. The species of plasma lipoprotein that has the highest content of oxidized phospholipids (oxPL) depends on the species of oxPL under consideration. This suggests that not all oxPL are formed in situ on the lipoprotein where they are found and might instead be transferred from other lipoproteins or tissues. Lp(a) is the major carrier in plasma of oxPLs that are detected by E06 immunoreactivity (249) and these oxPLs associate with Lp(a) in preference to native LDL particles in human plasma (250). E06 immunoreactive oxPL generated in chemically oxidized LDL can rapidly transfer to Lp(a) (249), so the high content of these lipids in Lp(a) isolated from human plasma may be due either to direct oxidation of Lp(a) or by transfer of the oxPL from oxLDL to Lp(a). In LDL and Lp(a) isolated from human plasma, levels of MDA-modified lysine (based on E014 immunoreactivity) are higher in LDL than Lp(a), while E06 immunoreactivity is much greater for Lp(a) than for LDL (249). Because MDA-modified proteins do not readily transfer between particles, these findings suggest that oxidation initially occurs in LDL with subsequent transfer of oxPL to Lp(a). Thus, a physiological role has been proposed for

Lp(a) in binding and transporting oxPL in the plasma (251). Unlike oxPL detected by E06 immunoreactivity that are highest in Lp(a), the F_2-IsoP-phospholipids forms of oxPL are highest in HDL (252). As with Lp(a), the high levels of these oxPLs in HDL may well be the result of transfer from other oxidized lipoproteins and tissues. Because oxidation is unlikely to occur in the circulation, the rate that oxPL are transferred from tissue to various plasma lipoproteins could potentially be an important determinant of the risk for atherosclerosis.

Significant correlations have been found between levels of oxLDL and extent of atherosclerosis in human patients. Measurement of oxLDL using E06 antibody showed that: 1) significant elevation of oxLDL in acute coronary syndromes (250), 2) treatment with a statin markedly reduced these levels (253), 3) oxLDL levels are higher in children with familial hypercholesterolemia compared to their siblings (254), and 4) oxLDL levels predict the presence and progression of atherosclerosis and symptomatic cardiovascular disease (255). Measurement of oxLDL using antibodies against MDA-LDL found that oxLDL were elevated in patients with coronary artery disease (CAD) (256), that elevated levels of oxLDL predicted future cardiac events in diabetic patients with CAD, that oxLDL were particularly elevated in patients with rheumatoid arthritis and CAD compared to either alone (257), and that treatment with fibrates decreased levels of oxLDL (258). Thus, there is a clear correlation between the presence of oxLDL and cardiovascular disease.

Mechanisms of Lipoprotein Oxidation In Vitro And In Vivo

The precise mechanisms that generate oxidized lipoproteins in vivo are still only partially understood. LDL circulating in the plasma appears to be protected from oxidation, both by dietary antioxidants such as vitamin E and C (259) and by protective enzymes including glutathione peroxidases (260,261), peroxiredoxins, PAF-acetylhydrolase (also known as lipoprotein-PLA2) (262,263), and paraoxonases (PON) (264,265). Penetration of LDL into the artery wall occurs at branch points in the aorta and other places with turbulent flow and shear stress. Retention of LDL in the intima, due to interactions with extracellular matrix such as chondroitin sulfate-rich proteoglycans, sequesters LDL away from the antioxidant environment of the plasma and exposes LDL to oxidation. A variety of oxidases and peroxidases generate strong oxidants that can readily oxidize LDL. These include myeloperoxidase (MPO) (266), xanthine oxidase (XO) (267), NADPH oxidases (NOXs) (268), and inducible nitric oxide synthase (iNOS) (269). Oxygenases such as lipoxygenases (LOX) have also been shown to oxidize LDL in vitro (270,271). The extent that each of these enzymes contributes to lipoprotein oxidation in vivo and thus to atherosclerosis remains to be fully elucidated, and there is much we do not understand about these individual processes. This is illustrated by studies on MPO and the 12/15-Lipoxygenase, the two enzymes most closely linked to lipoprotein oxidation.

MYELOPEROXIDASE (MPO)

MPO released from activated neutrophils (and to a lesser extent from monocytes/macrophages) can accumulate in the subintimal space of the artery wall(272), so neutrophil activation indirectly increases the chance for lipoprotein oxidation. Increased plasma levels of MPO correlate with

increased levels of oxLDL in hypercholesterolemic children (273). Increased MPO blood levels also associate with increased risk for atherosclerosis (274-277) and polymorphisms in the MPO gene that lower MPO activity reduce the risk for atherosclerosis (278,279).

Incubation of lipoproteins with MPO generates oxidized phospholipids that serve as ligands for CD36(280). A putative binding site for MPO with the apoB of LDL has been identified (281), although further verification is needed. Of interest, MPO also associates with HDL via binding to ApoAI and PON1 in a ternary complex (282), so that the binding of MPO to HDL and subsequent generation of reactive oxygen species may account for the high levels of oxidized lipids carried by HDL. Association of MPO with HDL leads to modification of tyrosine 71 of paraoxonase, reducing PON1 activity (282). It also generates reactive lipid dicarbonyls such as isolevuglandins that modify ApoAI (283) and phosphatidylethanolamine (284). In the presence of small molecules that scavenge lipid dicarbonyls, the ability of MPO to crosslink ApoAI is markedly reduced (283). Modification of HDL by lipid dicarbonyls such as isolevuglandins and MDA reduce its ability to drive cholesterol efflux from macrophages and protect against inflammatory stimuli such as LPS (283,285).

Mouse models have been used to directly examine the contribution of MPO to atherosclerosis, although these studies carry the caveat that mouse MPO levels are only 10-20% that of humans (286,287). Transplantation of bone marrow from genetically altered mice into atherosclerosis susceptible strains (e.g. *Ldlr*$^{-/-}$ and *Apoe*$^{-/-}$ mice) after lethal irradiation to ablate host hematopoietic cells is commonly used to study the effect of specific genes expressed by macrophages and other hematopoietic cells on atherogenesis (99). Reconstitution of *Ldlr*$^{-/-}$ mice with macrophages overexpressing MPO markedly increased their susceptibility to atherosclerosis (288). However, transplantation of MPO$^{-/-}$ macrophages into *Ldlr*$^{-/-}$ mice, also markedly increased atherosclerosis, and this was confirmed in MPO$^{-/-}$/ *Ldlr*$^{-/-}$ double knockout mice compared to MPO$^{+/+}$/ *Ldlr*$^{-/-}$ controls (289). The reasons for these paradoxical findings with both MPO overexpression and deletion remain unclear. Perhaps the complete lack of MPO activity is harmful because it allows overgrowth of specific microbes that incite atherosclerosis via alternative mechanisms. In contrast to effects of complete ablation, a recently developed selective MPO inhibitor (e.g. INV315) that only partially reduces MPO activity markedly reduced atherosclerosis in *Apoe*$^{-/-}$ mice (290). Thus, clinical studies with selective MPO inhibitors are needed to determine if this will be a meaningful therapeutic approach to the treatment of atherosclerosis in humans.

12/15-LIPOXYGENASES

Although the primary substrates for lipoxygenases are non-esterified fatty acids, exposure of LDL to 15-LOX also leads to oxidation of phospholipids and cholesterol esters (270,271). In mice, the gene analogous to the human 15-LOX encodes a lipoxygenase that converts arachidonyl chains to both 12-HPETE and 15-HPETE and is thus a 12/15-LOX. 12/15-LOX$^{-/-}$ mice on *Apoe*$^{-/-}$ background have reduced atherosclerosis compared to *Apoe*$^{-/-}$ mice (291). Importantly, they also have lower levels of autoantibodies against oxLDL and MDA-LDL (291). These results support the notion that 12/15-LOX can directly contribute to atherosclerosis via

LDL oxidation. Nevertheless, the role of 15-LOX in human atherogenesis is less clear-cut. While homozygotes of an Alox15 variant that almost completely ablates 15-LOX activity tended to have a reduced risk for coronary artery disease, heterozygotes paradoxically have increased risk of disease (292). Other polymorphisms in the Alox15 gene encoding 15-LOX increase risk for coronary artery calcification (293), yet others have no effect (294). Direct correlations between Alox15 polymorphisms and biochemical measurements of oxidized lipoproteins or oxPL and oxidized cholesterol esters have not been reported to date in humans, but are clearly needed.

Biological Activities of OxLDL And Receptors That Mediate These Activities

Perhaps the most important atherogenic effect of LDL oxidation is that this modification of LDL shifts recognition and internalization of the lipoprotein from the LDL receptor (LDLR) to scavenger receptors (295-297). While internalization of LDL by the LDLR in hepatocytes downregulates cholesterol synthesis to maintain cholesterol homeostasis, internalization of oxLDL by scavenger receptors fails to trigger this inhibition (298,299,300). Thus, cholesterol synthesis continues unabated despite the fact that peripheral cells are accumulating large amounts of cholesterol. In particular, macrophages express scavenger receptors and gluttonously take up large quantities oxLDL to form foam cells in the initial atherosclerotic lesion (301).

OxLDL also activates a number of cellular responses in macrophages, dendritic cells, endothelial cells, T cells, and smooth muscle cells that in aggregate promote inflammation, lesion formation, atherogenesis, and unstable atherosclerotic plaques (302-304). OxLDL induces surface expression of adhesion molecules and the release of chemokines from endothelial cells (305-311), all of which are important steps in recruitment of leukocytes to sites of lesions. Exposure to oxLDL activates dendritic cells so that they induce T-cell proliferation and production of IL-17 (312). OxLDL itself also serves as a neo-antigen (313). OxLDL also induces increased antibody generation by lymphocytes (314). OxLDL also promotes smooth muscle cell proliferation, migration, and transition to a proinflammatory phenotype (315-318). OxLDL induces secretion by macrophages of inflammatory cytokines (e.g. TNF□, IL-1, MCP-1, and IL-8) that activate other inflammatory cell types (319-322). OxLDL polarizes macrophages towards the M1-like phenotype or M2-like phenotype depending on its extent of oxidation (323). OxLDL promotes the chemotaxis of monocytes, neutrophils, eosinophils, and T cells (314,324-327), bringing them into the arterial wall. In contrast, oxLDL inhibits macrophage emigration out of atherosclerotic lesions, because it induces netrin-1 (328). OxLDL induces apoptosis of macrophages and development of unstable plaques prone to rupture (329-331). Thrombotic arterial occlusion in the aftermath of plaque rupture is a critical cause of mortality, therefore the fact that oxLDL increases platelet aggregation (332-335) suggests an additional mechanism whereby elevated circulating oxLDL may increase risk of mortality during acute coronary events (336). As discussed in detail below, identification of cognate receptors for various components of oxLDL and other oxidized lipoproteins has provided important insight into the mechanisms by which these oxidized lipoproteins exert their pathophysiological effects.

MACROPHAGE SCAVENGER RECEPTOR (SR-AI)

In 1979, Brown and Goldstein demonstrated that macrophages had specific binding sites for acetylated LDL (AcLDL) that allowed uptake of this modified LDL even in the presence of high cellular cholesterol levels (298). This was in contrast to LDL uptake by the LDLR, which is markedly downregulated when cellular cholesterol levels rise (Figure 2). Cholesterol synthesis is also downregulated by LDL uptake by LDLR (337). The lack of feedback inhibition during uptake of modified LDL by this unidentified receptor suggested a plausible mechanism for the massive accumulation of cholesterol in macrophages that generates foam cells. The putative receptor mediating this binding was named the macrophage scavenger receptor (MSR). Later, oxLDL (338) and MDA-LDL (248) were shown to compete with AcLDL for binding and uptake by macrophages, suggesting they were native ligands for MSR. In 1990, Kodama et al. purified and sequenced this scavenger receptor, allowing identification of the *MSR* gene (339). Through alternative gene splicing, this gene gives rise to Scavenger Receptor A–I (SR-AI), SRA-II, and SRA-III. Deletion of the *MSR* gene in C57BL6 mice fed butterfat diet substantially reduced atherosclerotic lesions and deletion of MSR in *Ldlr*$^{-/-}$ mice also reduced lesion formation (340).

CD36 AND OTHER SCAVENGER RECEPTORS

Subsequent work has shown that in addition to SR-AI, macrophages express a wide range of scavenger receptors that recognize oxidized lipoproteins including MARCO, scavenger receptor-B1, -B2, -B3 (CD36), and Lectin-like oxLDL Receptor-1 (LOX-1) (341). These scavenger receptors belong to a larger family of pattern recognition receptors, all of which are individually capable of binding to a wide spectrum of ligands. Quantitatively, SR-A1 and CD36 account for the vast majority of all oxLDL uptake by macrophages (342). The specific ligands of the two receptors on oxLDL appear to diverge (342). SR-AI appears to preferentially recognize more rigorously oxidized LDL and seems to primarily recognize modified lysine residues like MDA-lysines. In contrast, the primary ligands of CD36 on oxLDL appear to be oxidized phospholipids, in particular fragmented phosphatidylcholine including azPAF (243), POVPC (343) and KOdiA-PC (280). *Apoe*$^{-/-}$ mice lacking CD36 are more vulnerable to some bacterial infections (344) but also have less atherosclerosis when fed a high cholesterol diet (345).

Recent findings suggest that SR-AI and other scavenger receptors have both pro- and anti-atherosclerotic effects, depending on the context. For instance, deletion of the MSR gene actually increased lesion size in male *Apoe*$^{-/-}$ mice (346); however, deletion of both MSR and CD36 greatly reduces lesion complexity and vulnerable plaques, the most critical aspect of lesion development (347). The complex results of scavenger receptor deletion should not be surprising given that scavenger receptors have multiple ligands and that an important role of scavenger receptors expressed by macrophages is to allow these macrophages to remove bacteria and damaged cells from surrounding tissues. Under normal physiological conditions, uptake of oxLDL by macrophages is probably generally protective, because subsequent efflux of the cholesterol from the macrophages to HDL via reverse cholesterol transport as well as emigration of these macrophages from the arterial wall to lymph nodes serves to minimize the accumulation of cholesterol-laden macrophages in the arterial wall. However, under conditions

where reverse cholesterol transport capacity is reduced or where emigration of macrophages is inhibited, uptake of oxLDL by macrophages leads to its accumulation and initiation of pathophysiological processes.

TOLL-LIKE RECEPTORS AND OTHER TARGETS OF OXLDL

In addition to scavenger receptors, other pattern recognition receptors also recognize components of oxLDL. Perhaps most important among these are the Toll-like Receptors (TLR) including TLR-2 (348,349), TLR-4 (350), TLR-6 (351), TLR-7 (352), and TLR-9 (352). TLRs can interact with scavenger receptors, for instance, CD36 forms complexes with TLR4 and TLR6 that recognize oxLDL and activate NFkappaB (351). While bacterial components such as bacterial lipopolysaccharide (LPS) are full agonists for TLRs, oxLDL components like POVPC often appear to act functionally as partial agonists of TLRs, so that activation of macrophages and dendritic cells by full agonists like LPS is reduced in the presence of oxLDL (353,354).

In addition to TLRs, another important pattern recognition receptor for oxLDL is the receptor for advanced glycation end-products (RAGE) (355). Other factors of the innate immune response that bind oxidized phospholipids including C-reactive protein(CRP) (356,357) and natural IgM antibodies like E06 (358,359). While scavenger and pattern recognition receptors tend to recognize broad classes of compounds, a number of G-protein coupled receptors (GPCRs) recognize specific oxidized phospholipids. These include the receptor for platelet-activating factor (PAFR) (360-362), prostaglandin receptor EP2 (363,364), and sphingosine-1-phosphate receptor 1 (S1P1) (365). Intracellular receptors for oxidized phospholipids include nuclear hormone receptors PPAR alpha (366) and PPAR gamma (243). Non-receptor, intracellular targets for oxLDL include c-SRC (367) and NRF-2 (368,369).

Mechanisms Protecting Against LDL Oxidation In Vivo

Given the susceptibility of LDL to oxidation, it is perhaps not surprising that a number of mechanisms appear to exist in order to protect LDL from oxidation. These include small molecule antioxidants circulating in plasma and enzymes that catabolize oxidized lipids. How essential each of these mechanisms are to the control of oxLDL levels and preventing the development of atherosclerosis remains an area of active investigation. Obviously, a better understanding of the relationship between changes in protective mechanism and atherogenesis might allow identification of particularly vulnerable individuals and the development of novel therapeutic approaches.

SMALL MOLECUE ANTIOXIDANTS

Circulating small molecule antioxidants such as ascorbate (vitamin C), alpha-tocopherol (vitamin E), urate, and bilirubin serve as sacrificial targets reacting with free radicals and reactive oxygen species to prevent lipid and protein oxidation. Thus, even when strong oxidants are added to plasma ex vivo, there is relatively little generation of oxLDL until the oxidants have depleted these small molecule antioxidants, most specifically ascorbate (370). Depletion of vitamin C and

vitamin E increase atherosclerosis in *Apoe*$^{-/-}$mice (371). Importantly, plasma ascorbate levels inversely correlate with prevalence of cardiovascular disease in humans (372). Supplementation with vitamin C appears to play a role in preventing endothelial dysfunction in humans (373). However, it is not clear that supplementing dietary antioxidants beyond those typically obtained in a well-balanced diet endows any additional atheroprotective effects. Supplementation with dietary antioxidants inhibits development of atherosclerosis in susceptible mice (374-378). While a few human trials with dietary antioxidants have demonstrated reduced atherosclerosis and cardiovascular disease (379-382), most large-scale trials have failed to demonstrate any disease reduction (383-387). The reasons underlying these failures continue to be investigated and debated (388,389). Because it had not been fully appreciated that relatively high doses of these antioxidants were needed to markedly alter lipid peroxidation rates in humans (390), one possibility is that the doses used in most large scale prevention trials were simply insufficient (390,391) . However, the ability to use very high doses of small molecule antioxidants like vitamin E for extended periods of times may be limited by the toxicity of these high doses (392).

ANTIOXIDANT ENZYMES

Antioxidant enzymes appear to play a more critical role than dietary antioxidants in limiting lipoprotein oxidation. Two families of nonheme peroxidases, the glutathione peroxidases and the peroxiredoxins, appear to be the most critical. Glutathione peroxidases (Gpx) 1-4 are selenoproteins that convert glutathione to glutathione disulfide while reducing peroxides (including lipid peroxides) to water (393,394). Polymorphisms in glutathione peroxidase 1 (Gpx1) are associated with increased risk for atherosclerosis in various human populations (395-397). Furthermore, genetic deletion of Gpx1 markedly exacerbates atherosclerosis in *Apoe*$^{-/-}$ mice (398,399), while overexpression of Gpx4 in *Apoe*$^{-/-}$ mice inhibits atherogenesis (400). Peroxiredoxins (Prdx) are cysteine containing proteins where the cysteine is oxidized to sulfenic acid during reduction of peroxides (401). Deletion of either Prdx1 or Prdx2 increases atherosclerosis in *Apoe*$^{-/-}$ mice (402,403). Overexpression of Prdx4 inhibits atherosclerosis in *Apoe*$^{-/-}$ mice (404). In contrast, overexpression of Prdx6 failed to inhibit atherosclerosis in C57BL6 mice fed an atherogenic diet (405).

In general, studies looking for associations between risk for atherosclerosis and polymorphisms or deficiencies in other major antioxidant genes including catalase, SOD-1, -2, and -3, and glutathione S-transferase have been negative (406,407). In fact, SOD-1 overexpression may even increase fatty streak lesions in mice (408). However, SOD-1 does inhibit proliferation and migration of smooth muscle cells induced by oxLDL in vitro (315), and overexpression of both SOD-1 and catalase reduce atherosclerosis in *Apoe*$^{-/-}$ mice (409). *Sod2*$^{+/-}$ mice crossed with *Apoe*$^{-/-}$ mice have increased atherosclerosis compared to control *Apoe*$^{-/-}$ mice (410), but there is little effect on atherosclerosis of crossing *Sod3*$^{-/-}$ mice with *Apoe*$^{-/-}$ mice (411). Several studies have demonstrated an association between *SOD2* and hypertriglyceridemia (412,413).

ENZYMES THAT CATABOLIZE LIPIDS

In addition to anti-oxidant enzymes, several enzymes specifically catabolize oxidized phospholipids including secreted Platelet-Activating Factor Hydrolases (sPAF-AH) and Paraoxonases (PON). sPAF-AH, also known as lipoprotein associated PLA2 (LP-PLA2) is a calcium independent PLA_2 secreted by macrophages that primarily circulates on LDL and to a lesser extent on HDL (414,415). sPAF-AH does not hydrolyze phospholipids with the typical long-chain fatty acids, but efficiently cleaves phospholipids with oxidatively fragmented (e.g. azPAF and POVPC) (362,416,417) or oxidatively cyclized (e.g. F2-isoprostane-PC) sn-2 chains (418). Whether this effect results in a net gain of pro- or anti-inflammatory lipids is controversial, because only some of these oxPL are highly potent inflammatory mediators, while others are partial agonists that might therefore antagonize inflammatory responses to other mediators like LPS. Furthermore, this hydrolysis generates lysoPC and lysoPAF, which are proinflammatory at high concentrations. This ambivalent effect is also seen in vivo. While a large number of clinical studies have found that increased sPAF-AH predicts increased risk for atherosclerosis (419,420), whether increased sPAF-AH actually contributes to atherogenesis or simply reflects a compensatory increase in response to elevated oxLDL is unclear (421,422). Some gene polymorphisms in sPAF-AH that reduce its activity (i.e. Val279Phe) appear to increase the risk of myocardial infarction (423), yet another polymorphism (i.e. Ala379Val) appears to have little effect (424). The interpretation that increased sPAF-AH activity caused an increased risk of atherosclerotic cardiovascular disease (ASCVD) led to the development of selective sPAF-AH inhibitors and their clinical trials (425). However, two recently completed phase III trials with one such inhibitor, darapladib, found that while this drug significantly reduced circulating PAF-AH activity, it had no effect on ASCVD events (426,427).

Paraoxonases (PONs) were originally named for their ability to hydrolyze the neurotoxin paraoxon and this activity is still routinely used to assay paraoxonase activity in plasma. However, in terms of atherosclerosis, the most important physiological function of PONs appears to be their ability to protect against LDL oxidation (428). PON-1 and PON-3 circulate bound to HDL. HDL treated with specific inhibitors of PON fails to protect LDL from oxidation (429). Treatment of oxLDL with purified PON1 markedly decreases its ability to induce endothelial cell activation and monocyte binding (264). Genetic deletion of PON1 markedly increases atherosclerosis in C57BL6 mice(430) , and this is further exacerbated in *Apoe*$^{-/-}$ mice (431). Conversely, overexpression of PON-1 reduces atherosclerotic lesions in both wild-type mice fed high cholesterol diets and *Apoe*$^{-/-}$ mice (432). Adenovirus expression of PON-2 and PON-3 also inhibits atherosclerosis in *Apoe*$^{-/-}$ mice (433,434), indicating that all three PON enzymes have protective effects. However, transgenic *Apoe*$^{-/-}$ mice overexpressing the entire gene cluster of PON genes (PON-1, -2, -3) were not further protected compared to *Apoe*$^{-/-}$ mice with transgenic expression of PON-1 or PON-3 alone (435), suggesting these effects are redundant rather than additive. These mouse studies appear relevant to human disease, as a large number of studies have shown that polymorphisms in PON1 are associated with increased risk for atherosclerosis (265). It should be noted that PON activity varies greatly even in persons with the same polymorphism, suggesting that environmental factors leading to PON inactivation may also be important in determining disease risk.

Summary for Oxidized Lipoproteins

In summary, substantial evidence has accumulated over the past several decades for a causative role for oxidized lipoproteins in the initiation and progression of atherosclerosis and the need to reduce lipoprotein oxidation in order to reduce disease burden. Nevertheless, significant questions remain including which mechanisms are most important for driving lipoprotein oxidation, what treatment strategies can effectively reduce lipoprotein oxidation, and what are the key components of oxidized lipoproteins that drive atherogenesis?

ELEVATED LDL-C AND RISK FOR ASCVD

Genetic Causes of Elevated LDL-C

As described above, FH is an autosomal dominant inherited disorder associated with elevated levels of LDL-C and premature ASCVD, and provides some of the most compelling evidence for a causal role for LDL-C in atherosclerosis. Brown and Goldstein discovered the LDLR pathway and found that mutations in the *Ldlr* gene cause FH (300). Heterozygotes for loss-of-function mutations have cholesterol levels that are about twice normal, and these subjects are at increased risk of premature CVE. In contrast, individuals with homozygous FH have extremely high levels of LDL-C (> 500 mg/dL) and often develop severe coronary atherosclerosis and supravalvular aortic stenosis in early childhood. The prevalence of heterozygous FH is around 1/200-250 in the USA, whereas homozygous FH is extremely rare affecting only about 1/160,000 to 1/250,000 individuals (436). Nonetheless, about 20% of people having myocardial infarctions (MI) before 40 years of age have heterozygous FH. Thus, FH offers an important opportunity to target therapies to prevent atherosclerosis (437), but FH remains under recognized with recent evidence suggesting that only 1-10% of subjects with FH have been identified (438). Most individuals with significant hypercholesterolemia do not have classic monogenic autosomal dominant inherited dyslipidemias, but polygenic factors contributing to susceptibility to environmental factors underlie the observed increase in LDL-C levels. A recent study suggests that among individuals with LDL cholesterol ≥190 mg/dl, gene sequencing identified a monogenic FH mutation in only <2%of subjects (439). However, for any observed LDL cholesterol, FH mutation carriers are at substantially increased risk for CAD (439). Pathogenic variants in three genes (LDLR, APOB, and PCSK9) account for the majority of monogenic FH cases. Recent genome-wide association studies (GWAS) have identified more than 50 discrete genetic loci that are associated with an increased risk of CVE(440,441). Many of these genetic loci are associated with genes previously known to impact LDL-C levels and cardiovascular risk (e.g. *Ldlr*, *APOB*, *PCSK9*), but novel loci that impact both LDL-C levels and risk for MI have also been identified, e.g. sortilin-1 (*SORT1*) (442,443). Most importantly, inherited low levels of LDL-C due to loss-of-function mutations in the *PCSK9* gene have been shown to be associated with dramatic reductions in risk for ASCVD events in the Atherosclerosis Risk in Communities study (444). Hence, genetic disorders of lipoprotein metabolism provide strong evidence that the impact of LDL-C on the development of atherosclerosis is dose- and time-dependent (445), supporting a causal role for LDL-C in atherosclerosis.

Lowering LDL-C Reduces ASCVD

Large randomized outcomes trials of cholesterol lowering drugs have provided critical proof of the cholesterol hypothesis (446). The Coronary Drug Project, conducted between 1966 and 1975, found niacin treatment showed modest benefit in decreasing definite nonfatal recurrent myocardial infarction by 26% (10.2% for niacin group vs 13.8% for placebo group) (447). However, there was no benefit in primary endpoint, total mortality. Impressively, with a mean follow-up of 15 years, nearly 9 years after termination of the trial, all-cause mortality was 11%

lower in niacin group than in the placebo group (448). The Lipid Clinics Research trial was another early major outcomes trial to show that lowering cholesterol reduced cardiovascular events. Treatment with cholestyramine, a bile acid binding inhibitor, resulted in a 12% reduction in LDL-C levels and a 19% reduction in CHD events (449). The early lipid lowering cardiovascular outcomes trials were limited by a lack of highly effective approaches for lowering LDL-C levels, and several trials raised concerns that cholesterol lowering did not reduce total mortality and might increase the risk of cancer, accidental death and suicide (446). The advent of the statin drug class (HMG-CoA reductase inhibitors) provided a much more effective approach to lowering LDL-C and laid to rest the concerns raised by the earlier trials. The 4S trial was a landmark clinical trial of cholesterol lowering with simvastatin in patients with coronary artery disease (CAD) and severely elevated levels of LDL-C that was designed to look at total mortality as the primary endpoint (450). The 4S showed for the first time that lowering LDL-C levels by 35% with simvastatin resulted in a 30% reduction in total mortality with a 42% reduction in CHD deaths and a 34% reduction in the risk of Major Coronary Events (450). A large number of subsequent trials extended these results to populations with CHD with low levels of LDL-C and to subjects without known CAD (primary prevention) with high or low levels of LDL-C (451). It is important to note that the relationship between on-treatment LDL-C lowering and reduction in cardiovascular events in secondary prevention trials was similar for both statin and non-statin approaches to lowering LDL-C levels. A large meta-analysis of 26 statin trials involving over 170,000 subjects demonstrated that statin treatment for 5–years reduced the combined incidence of major coronary events, coronary revascularization, and stroke by 20% per every 1 mmol/l (38.7 mg/dL) reduction in LDL-C (452). These results have been extended by a recent large meta-analysis of 49 trials involving 9 different interventions to lower LDL that included more than 300,000 patients and approximately 40,000 major vascular events, each 1mmol/l (38.7mg/dl) reduction in LDL-C was associated with 23% relative reduction in the risk of major vascular events (453). This raised the question of whether further lipid lowering would be of additional benefit. With the recent development of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, dramatic additional LDL lowering up to 50 -70% is now possible. In the FOURIER trial, patients with prior stable CAD who received the PCSK9 inhibitor, evolocumab, in combination with statin therapy achieved median LDL-C levels of 30 mg/dl. This was associated with a 15% reduction in the composite endpoint of cardiovascular death, MI, stroke, hospitalization for unstable angina or coronary revascularization (454). Similarly, ODYSSEY demonstrated that administration of alirocumab to acute coronary syndrome patients already on maximally tolerated statin therapy led to LDL-C values <50 mg/dl and was associated with a 15% reduction in the composite endpoint of death from coronary heart disease, nonfatal MI, ischemic stroke or unstable angina requiring hospitalization, and this benefit approached 24% in the subgroup of patients with initial LDL-C values >100 mg/dL (455). Together, the results of these PCSK9 trials reinforce the “lower is better” hypothesis.

Although statins are very effective in preventing CVE, many patients on statins do still have CVE, a phenomenon referred to as residual risk (456). This residual risk is likely attributable at least in part to inflammation. Indeed, definitive support for this hypothesis recently came from the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), where

administration of an anti-IL1β antibody to patients with prior MI and elevated serum hsCRP successfully reduced recurrent CVE independent of lipid lowering (>90% of patients were receiving concurrent statin therapy) (457). A secondary analysis of the FOURIER trial also demonstrated that, while relative risk for the primary cardiovascular endpoint was consistent across groups, the absolute risk reduction with evolocumab was greatest in patients with elevated hsCRP (458). These results suggest that targeting both LDL and inflammation will provide the most robust strategy for lowering ASCVD risk.

Levels of LDL-C, ApoB-100, Non-HDL Cholesterol and LDL-P as Markers for ASCVD Risk.

Based on the strength of the direct association of LDL-C levels and risk for ASCVD, the guidelines for treatment of hypercholesterolemia have focused on LDL-C levels for risk assessment, stratification and treatment recommendations. Indeed, the terms LDL-C and LDL are often, though incorrectly, used interchangeably in practice. It is important to understand that LDL is a collection of particles defined by density (d = 1.019 – 1.063 g/ml) that are heterogeneous, consisting of a large variety of lipids and proteins (459). In addition, LDL particles vary in size and cholesterol content. The relationship between LDL-C levels and risk for ASCVD is “J-shaped”, and the predictive value of LDL-C levels is better at higher levels of LDL-C. Surprisingly, the majority of subjects presenting to the hospital with acute coronary artery syndrome do not have elevated levels of LDL-C, but tend to have low levels of HDL-C and elevated triglycerides (460). There has been tremendous interest in whether other measures of LDL, including subpopulations, apoB100, or particle number, might serve as a better predictors of CVE than quantifying LDL cholesterol content.

Groundbreaking studies by Krauss and co-workers (461) described two major patterns for LDL subpopulations based on size and density of the LDL particles. Pattern A is characterized by large buoyant LDL (lbLDL) particles, whereas Pattern B is associated with small dense LDL (sdLDL). Importantly, sdLDL is associated with increased triglyceride levels and low HDL-C, which is referred to as the lipid triad, a phenotype common in insulin resistance. Hence, Pattern B is commonly seen in subjects with obesity, metabolic syndrome and type 2 diabetes mellitus. A number of studies have reported that Pattern B is associated with an increased risk of CVE (462). Several different approaches have been used to characterize LDL phenotypes, including gradient gel electrophoresis, ultracentrifugation (sequential and vertical), ion mobility and nuclear magnetic resonance (NMR) (462,463). A number of mechanisms have been proposed to underlie the proatherogenic properties of sdLDL, including increased susceptibility of oxidation (464) and glycation (465), promoting arterial retention and increased macrophage foam cell formation. Cholesteryl ester transfer protein (CETP), which transfers CE from HDL to VLDL/LDL and triglycerides in the opposite direction, and hepatic lipase, which hydrolyses triglycerides, impacts the lipid composition and size of sdLDL. As such, increased levels of sdLDL have the potential to provide additional information regarding risk of CVE in individuals with normal LDL-C levels but elevated triglycerides and low HDL. Alternatively, it has been proposed that the real impact of sdLDL is due to increased LDL particle number.

Each LDL particle contains one molecule of apoB100, and the majority of apoB100 in plasma is on LDL particles (466). Hence, levels of apoB100 correlate directly with LDL particle (LDL-P) number. A large number of studies have shown that levels of apoB100 are superior markers of ASCVD risk compared to LDL-C (467). Because the mass of cholesterol in LDL particles varies, LDL-C levels will result in overestimation apoB levels and the number of LDL particles, when LDL particles are cholesterol-enriched (Figure 8) and underestimate apoB and LDL particle number when the particles are cholesterol depleted (Figure 8) (468).

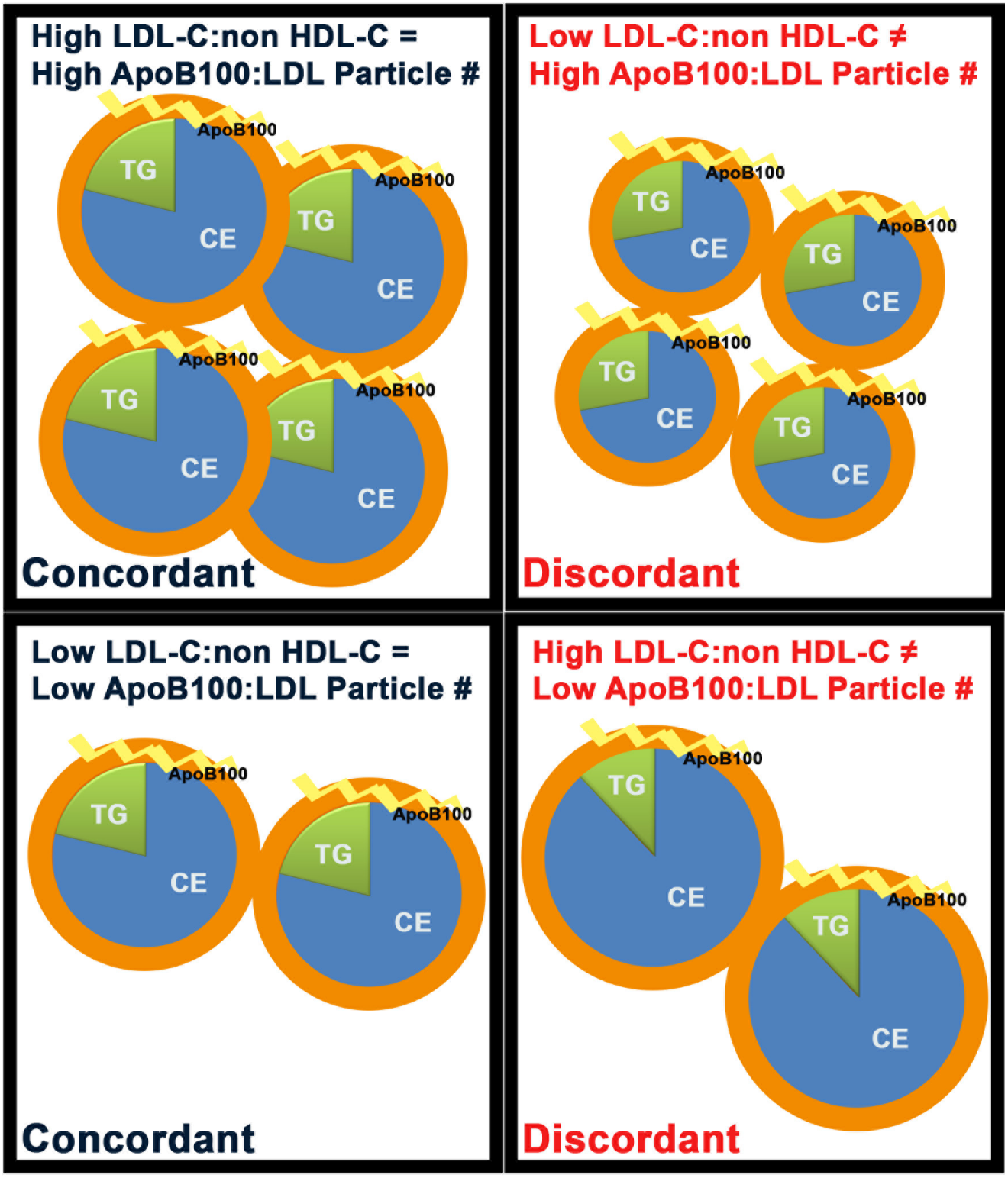

Figure 8. Schematic of the Relationship Between Measurements of LDL-C Versus ApoB100 Particle Number in Concordant and Discordant Human Populations. Subjects with hypertriglyceridemia have enhanced numbers of small dense LDL where each particle is enriched in triglyceride (TG) and relatively poor in cholesteryl ester (CE)

content compared to normal subjects, and measurement of LDL-C underestimates particle numbers and apoB100 levels. Other subjects have enlarged CE-enriched LDL particles and measurement of LDL-C overestimates the number of LDL particles and apoB100 molecules. Thus, LDL particle number or apoB100 levels are a more accurate predictor of cardiovascular risk in the setting of discordance between the percentiles for measures of cholesterol carried by LDL (LDL-C or Non-HDL-C) and particle number (apoB100 or LDL-P). Adapted from Sniderman, A.D. et al. Curr Opin Lipidol 2014, 25:461–467.

Furthermore, all of the major atherogenic lipoproteins contain apoB (LDL, triglyceride rich remnants of VLDL, IDL, chylomicron remnants, and Lp(a)). LDL-C is routinely calculated using the Friedewald formula (LDL-C = TC – HDL-C – TG/5), but this formula is not accurate when serum TG levels are > 400 mg/dl. It has long been recognized that LDL-C underestimates risk of ASCVD in the setting of hypertriglyceridemia (467). Non-HDL cholesterol is the mass of cholesterol in all of the apoB-containing particles: Non-HDL-C = TC – HDL-C. The ATPIII guidelines recommended using Non-HDL-C to estimate risk of ASCVD, when TG > 200 mg/dL (469,470). A meta-analysis by Sniderman *et al.* found that Non-HDL-C was a slightly better marker of ASCVD risk than LDL-C, but apoB was far superior to Non-HDL-C (471). NMR spectroscopy is another way to measure LDL-P concentrations. Table 2 includes selected percentiles for mean levels for the various LDL-related markers from the Framingham Offspring Study (472). In an analysis of the Framingham Offspring Study, LDL-P determined by NMR was more strongly related to incident CVD events than LDL-C levels, and the ability of Non-HDL-C to predict risk was less than LDL-P, but better than LDL-C (473). In addition, they found that low LDL-P numbers were a better index of low CVD risk than low LDL-C (473). In contrast, an earlier meta-analysis from the Emerging Risk Factors Collaboration found LDL-C, Non-HDL and apoB to be equivalent markers of CVE (474). The lack of difference may relate to the population studied. When the LDL particles have normal cholesterol content, then LDL-C, Non-HDL and apoB are equivalent markers (Figure 8) of risk (471,473). Interestingly, data from the Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated that when LDL-C and LDL-P are discordant (Figure 8), then LDL-P proves to be a better predictor of risk for incident CVD events than LDL-C (475).

Table 2. Equivalent Percentiles in the Framingham Offspring Study

Percentile %	LDL-C mg/dL	Non-HDL-C mg/dL	ApoB mg/dL	LDL-P nmol/L
2	**70**	**83**	**54**	**720**
20	**100**	**119**	**78**	**1100**
50	**130**	**153**	**97**	**1440**
80	**160**	**187**	**118**	**1820**
95	**191**	**224**	**140**	**2210**
Adapted from Contois JH, et al. *Clinical Chemistry* 2009; 55:407-419				

For several decades the guidelines for treatment of hypercholesterolemia have focused on LDL-C levels both for risk stratification and as the principal target of therapy to prevent ASCVD. Indeed, therapeutic goals for LDL-C of < 100 mg/dL and < 70 mg/dL for subjects at high-risk

and very high risk of CVE, respectively, were recommended by the 2004 update of the NCEP ATPIII, guidelines (469,470). The 2013 ACC/AHA guidelines for treatment of hypercholesterolemia abandoned these targets in favor of recommending the use of high-intensity statins in high risk individuals (476), there are numerous sets of guidelines that have maintained the recommendation for LDL-C targets, including those of the National Lipid Association (NLA) (477), the American Association for Clinical Endocrinologists (478), and the European Guidelines (479). The Canadian guidelines include targets for levels of apoB(480), and the NLA guidelines include targets for both LDL-C and Non-HDL-C(477). Table 2 includes the percentiles for mean levels for these various LDL markers from the Framingham Offspring Study. The levels of LDL-C shown in Table 2 closely coincide with levels that have been widely used in guidelines for lipid management for decision-making regarding levels at which to initiate therapy and goals of therapy. The recent NLA guidelines recommend using both LDL-C and Non-HDL-C as targets of therapy with only two sets of targets: LDL-C < 70 mg/dL and Non-HDL-C < 100 mg/dL for very high-risk subjects and LDL-C < 100 mg/dL and Non-HDL-C < 130 mg/dL for high, moderate or low risk subjects (who qualify for drug therapy). Most recently, AHA/ACC published a new version of guidelines for cholesterol management (481). These guidelines included evidence from recent 2 large randomized clinical end-point trials of PCSK9 inhibitors (454,455) and a long-awaited ezetimibe trial in patients with recent acute coronary syndromes (482). The new guidelines re-introduced LDL-C treatment goals in some high-risk patient groups, such as those with high risk of ASCVD and those with very high baseline LDL-C. The new AHA/ACC guidelines also stated that elevated apoB particle number, elevated Lp(a) and hypertriglyceridemia are all additional risk factors for ASCVD.

Lp(a)

Lp(a) has been shown to be an independent risk factor for atherothrombotic events, including heart attack, stroke and peripheral vascular disease, in multiple prospective studies (451,483). The new AHA/ACC guidelines list elevated Lp(a) a one of the risk-enhancing factors for developing ASCVD (481). Lp(a) consists of an LDL particle in which apoB100 is covalently linked via a disulfide bridge to apo(a), a glycoprotein with repeating Kringle units that share homology with plasminogen. Although apo(a) is synthesized by the liver, the Lp(a) particles are not formed in the liver but in the plasma. Despite being a modified LDL particle, Lp(a) levels are independent of LDL-C levels. The catabolism of Lp(a) is poorly understood, but Lp(a) is not cleared by the LDLR (484). The number of repeating Kringle units is highly variable but largely genetically determined, and this contributes to tremendous heterogeneity in size of Lp(a). The plasma levels of Lp(a) vary tremendously in humans, and plasma Lp(a) levels are generally inversely related to the size of the apo(a) isoform (485). Thus, smaller Lp(a) particles with fewer Kringle repeats are present at higher levels in the plasma. In American Caucasians, the increased levels of smaller Lp(a) particles is largely explained by the size of the *LPA* gene, based on the size of the repeated KIV_2 domain (486), which is believed to be due to difficulty of hepatic secretion of larger apo(a) isoforms. Nevertheless, this relationship varies in different ethnic populations. Early studies suggested that even though Lp(a) levels are higher in African Americans that Lp(a) levels did not appear to be an independent risk factor for cardiovascular events in this group (487). However, by determining allele specific Lp(a) concentrations, a larger

more recent analysis demonstrated that elevated Lp(a) levels associated with small apo(a) isoform sizes serve as an independent risk factor for CHD in both African Americans and Caucasians (488). Similarly, a 20 year follow up study of the ARIC cohort found that elevated levels of Lp(a) are associated with a similar degree of risk in in both African Americans and Caucasians (489). A recent meta-analysis by the Emerging Risk Factors Collaboration evaluated 36 prospective studies with 126,634 subjects found that Lp(a) is an independent risk factor for CHD (490). In contrast to previous studies that suggested Lp(a) was only relevant as a risk factor when levels were extremely elevated, the meta-analysis demonstrated that risk and that Lp(a) levels are continuously associated with CHD risk (490). The Ile4399Met polymorphism (rs3798220) in the protease-like domain of apo(a) is particularly associated with increased risk for severe CAD (491). Subsequently, Clarke *et al.* found that the rs3798220 and rs10455872 variants were associated with small apo(a) isoform size, increased Lp(a) levels and substantially increased risk of CAD (492). Furthermore, a Mendelian randomization study by Kamstrup *et al.* demonstrated that a genetically determined doubling of Lp(a) plasma levels leads to a 22% increase in the risk of MI, strongly supporting a causal role for elevated levels of Lp(a) and risk for MI (493).

The proatherogenic mechanisms for Lp(a) remain incompletely understood, but recent studies suggest an important role for oxidative modification of Lp(a) by oxidized phospholipids (OxPL) (251). Mounting evidence supports an important role for OxPLs in the development of atherosclerosis (251). Interestingly, OxPLs associate with Lp(a) in preference to native LDL particles in human plasma (250). Hence a physiological role has been proposed for Lp(a) for binding and transporting OxPL in the plasma (251). Although, Lp(a) is found only in humans and Old-World monkeys, mice expressing human Lp(a) have been developed to examine the role of Lp(a) in atherogenesis and lipoprotein metabolism. The first transgenic mice expressing high levels of human apoB100 were created using a 79.5-kb human genomic DNA fragment containing the entire human *APOB* gene that was isolated from a P1 bacteriophage library, and crossing these mice with apo(a) transgenic mice produced high levels of human Lp(a) in plasma (494). In a study of transgenic mice expressing high and low concentrations of Lp(a), high levels of OxPLs were found in transgenic mice with very high levels of Lp(a), but not in LDL of apoB transgenic control mice (495). These studies support the concept of preferential transfer of OxPL to Lp(a). In the Dallas Heart Study, levels of OxPL on apoB were strongly correlated with Lp(a) levels, and inversely related to the size of the apo(a) isoforms (496). In the European Prospective Investigation of Cancer (EPIC)–Norfolk prospective study the impact of OxPL and Lp(a) levels on CHD risk was additive (497). Further studies are needed to define the extent to which the preferential binding of OxPL by Lp(a) is responsible for mediating the increased risk of atherothrombotic events attributable to Lp(a).

Lp(a) is considered an emerging risk factor, but the approach to managing patients with elevated levels of Lp(a) has not been well established. Elevated levels of Lp(a) do not respond well to changes in diet or statin therapy. Analysis of data from the Familial Atherosclerosis Treatment Study (FATS) showed that substantial lowering of LDL-C (with lovastatin plus colestipol or niacin plus colestipol) in subjects with CAD and high apoB100 eliminated the increased risk attributable to having very high Lp(a) (498). The JUPITER trial showed that

treatment of subjects with low levels of LDL-C, but increased hsCRP, with rosuvastatin (20 mg) reduced CVE. In JUPITER, elevated Lp(a) was a significant determinant of residual risk, but the reduction in relative risk with rosuvastatin was similar among participants with high or low Lp(a) (499,500). Treatment with niacin reduces Lp(a) by 20-30%, and the European guidelines recommend treating patients with elevated Lp(a) who are at intermediate to high risk of CVD with extended release niacin to obtain levels of Lp(a) < 50 mg/dL (501). Nonetheless, the recent failure of the AIM-HIGH and HPS-2 THRIVE studies have cast doubt on the use of extended release niacin in subjects fitting the profile of those studies (CAD with LDL well treated on a statin). LDL apheresis is approved and effective for lowering Lp(a) in individuals with recurring CVE in the setting of very high levels of Lp(a). There are a number of new therapies that may prove useful in treating patients with elevated levels of Lp(a). The recently approved monoclonal antibodies to PCSK9 significantly lower Lp(a) by around 30% in addition to lowering LDL-C by 30-50%. Furthermore, a Phase 1 clinical trial of a second-generation antisense to apo(a) has recently reported potent, dose-dependent, selective reductions of plasma Lp(a) (502). This approach has the appeal of specifically targeting apo(a) to reduce Lp(a) levels. Hopefully, these new approaches will ultimately yield an effective approach to lower levels of Lp(a) that translates into reduced cardiovascular events.

INTESTINAL LIPID METABOLISM AND CHYLOMICRON ASSEMBLY

Intestinal Lipid Absorption

Through absorption of dietary lipids, the intestine is a key regulator of stored and circulating lipids. Primarily it is enterocytes in the small intestine that actively regulate the release of dietary lipids into circulation (503-505). The predominant lipids derived from diet are triglycerides, phospholipids and cholesteryl esters. In the intestinal lumen, ingested lipids are emulsified by bile salts to enhance their hydrolysis by lipases (Figure 9) (506-509). Triglycerides make up the largest percentage of the intestinal lipids. Lipolysis of triglycerides releases free fatty acids (non-esterified fatty acids) and monoacylglycerides (Figure 9). These are absorbed on the luminal surface of the enterocytes both by free diffusion and actively by protein-mediated transport into the enterocyte cytosol (Figure 9) (508-510). The principal transporters identified to date are CD36 (now known as SR-B2 (511)) and several fatty acid binding and transport proteins (512-514).

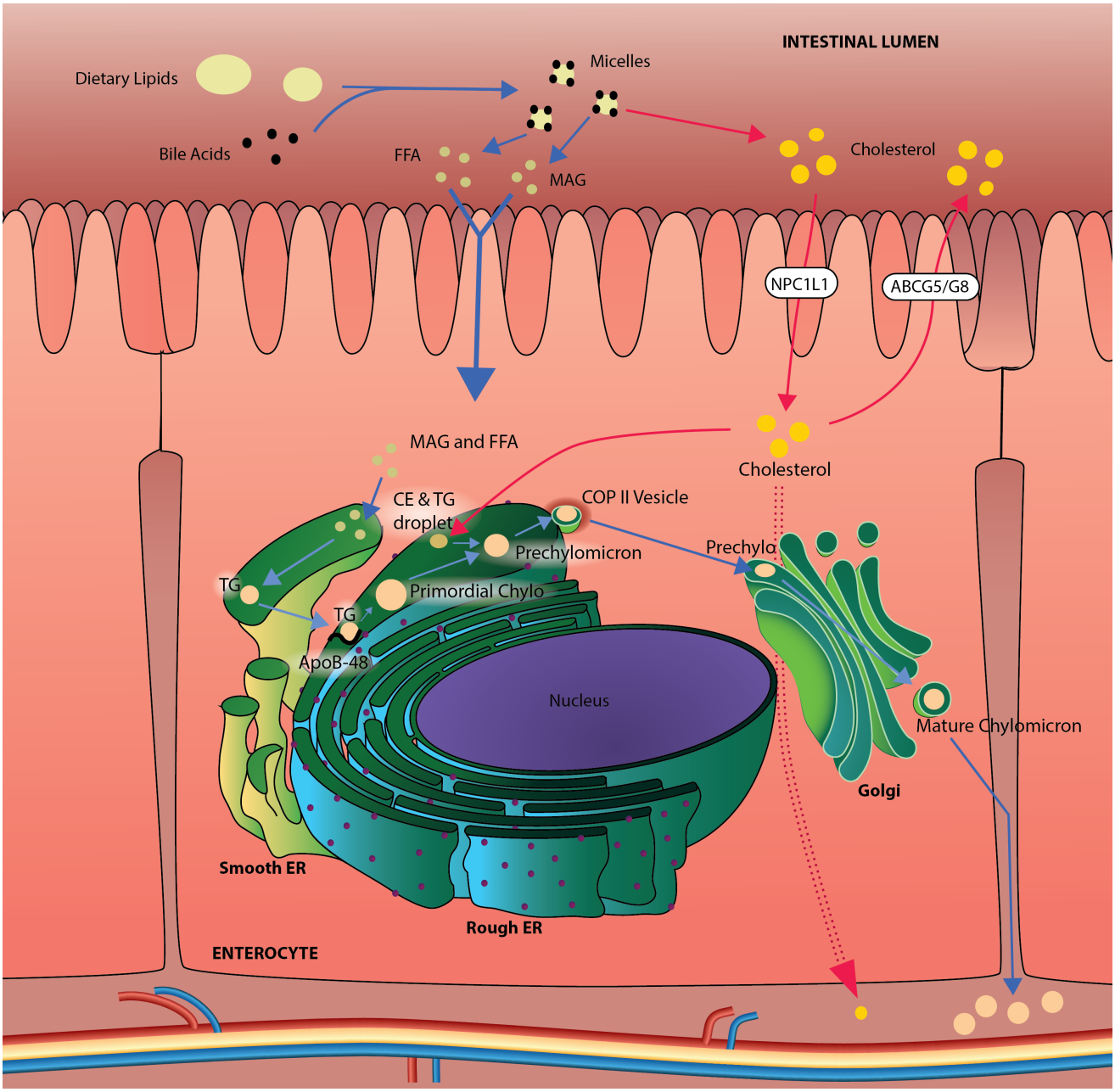

Figure 9. Intestinal Triglyceride and Cholesterol Metabolism. In the intestinal lumen, dietary triglyceride (TG) and cholesterol are emulsified by bile salts which enhance their uptake. Lipases in the intestinal lumen digest triglycerides to free fatty acids (FFA) and monoacylglycerides (MAG). These are absorbed into the enterocyte where they are used in the synthesis of TG, phospholipid and cholesteryl ester (CE). Much of the synthesized TG in enterocytes is packaged, along with phospholipids, cholesterol and proteins into chylomicrons, which are secreted at the basolateral surface of the enterocyte and enter the lymphatic system. The assembly of chylomicrons begins in the endoplasmic reticulum. During the synthesis of apolipoprotein B48 (apoB48), the protein acquires phospholipid from the endoplasmic reticulum membrane and also cholesterol and TG to form a primordial chylomicron. Continued acquisition of TG and CE and smaller,

exchangeable proteins (e.g. apolipoprotein A-IV and apolipoprotein C-III) in the endoplasmic reticulum enlarges the particle to form a prechylomicron. Prechylomcirons are transported to the Golgi apparatus in specialized COPII vesicles. In the Golgi apparatus, the prechylomicron matures into a chylomicron. The maturation process includes the glycosylation of apoB48, the acquisition of additional proteins (e.g. apolipoprotein A-I) and lipid. Secretory vesicles formed from the Golgi carry the mature chylomicrons to the basolateral surface of the enterocyte. Fusion of the secretory vesicle membrane with the plasma membrane releases the chylomicron into the extracellular space where it is taken up into lacteals near the enterocyte and, thus, enters the lymphatic circulation. Dietary cholesterol in the intestinal lumen is taken into the enterocyte by a process involving Niemann-Pick C1-like protein 1 (NPC1L1). Enterocyte cholesterol and CE can be incorporated into chylomicrons and secreted with TG. In addition, enterocyte cholesterol can be directly excreted into the intestinal lumen using the heterodimer ATP-binding cassette transporter G5 and G8 (ABCG5/G8). Enterocyte cholesterol can also be transported to and incorporated into the basolateral membrane for efflux into the circulation.

Chylomicron Assembly and Secretion

In the enterocyte, the free fatty acids and monoacylglycerides are used to synthesize triglycerides, phospholipids, and cholesteryl esters (Figure 9) (508,509,513,515-517). The majority of the triglycerides formed in the enterocytes are repackaged into large, buoyant lipoproteins, called chylomicrons, and secreted from the basolateral surface of the cell (Figure 9). These particles play a central role in the transport of triglycerides and fat-soluble vitamins to the rest of the body (518).

The assembly of the chylomicron particle from precursors is a complex process. Each particle contains a single copy of apolipoprotein B48 and assembly begins with the synthesis of this protein in the rough endoplasmic reticulum. Apolipoprotein B48 is a truncated form of apolipoprotein B100 that is formed by posttranscriptional editing (519,520). As apolipoprotein B48 is synthesized and translocated across the endoplasmic reticulum membrane, it becomes lipidated to form a phospholipid-rich, dense primordial chylomicron in the lumen of the endoplasmic reticulum (Figure 9). The primordial chylomicron contains apolipoprotein B48, phospholipid, cholesterol and minor amounts of cholesteryl ester and triglyceride (513,521,522). The assembly process requires microsomal triglyceride transfer protein (523). In the absence of sufficient lipid, or if microsomal triglyceride transfer protein function is impaired, apolipoprotein B48 is ubiquitinated and targeted for proteasome degradation (524). The importance of this initiating assembly step is seen in patients with a defect in the MTP gene leading to the rare recessive disorder abetalipoproteinemia. Individuals with abetalipoproteinemia have almost undetectable levels of apoB or and very low total cholesterol levels in their plasma because of the inability to assemble apoB-containing lipoproteins in their enterocytes or hepatocytes. Among the sequelae experienced by these patients are accumulation of triglycerides in their intestines and livers and a deficiency of lipid-soluble vitamins in their plasma (525,526). If

untreated, these patients develop severe neurological problems; mostly related to vitamin E and A deficiency.

After formation, the initial primordial particle expands by the acquisition of additional triglyceride and cholesteryl ester (Figure 9). The additional lipid is acquired by fusion with non-apolipoprotein B48 containing particles that are rich in triglyceride and cholesteryl ester. The exact origin of these lipid particles and their precise composition is currently actively debated (504,505,513,527,528), but the fusion of the primordial chylomicron with the apolipoprotein B48-free particles occurs in the endoplasmic reticulum (513). The resulting particle is a prechylomicron (Figure 9). In addition to apolipoprotein B48, the prechylomicron surface can contain multiple copies of other small, exchangeable apoproteins including apolipoprotein A-IV and apolipoprotein C-III. Exchangeable apoproteins are soluble proteins that are not as tightly adherent to the particle surface and so can be exchanged between lipid particles.

Prechylomicrons are transported out of the endoplasmic reticulum and delivered to the Golgi apparatus for further processing (Figure 9). Transport occurs in specialized vesicles that can accommodate their large size. The unique vesicles contain a number of specific proteins necessary for the transport and docking process. Vesicle-associated membrane protein-7, coatomer protein II and Sar1b, a small GTPase component of the coatomer protein II vesicle assembly machinery (Figure 9) are among the specialized proteins on the lipid transport vesicles (505,529-531). The maturation of the particle in the Golgi apparatus includes further glycosylation of apolipoprotein B48 and the addition of apolipoprotein A-I to the surface (505,532,533). After processing, the mature chylomicron is packaged into Golgi-derived secretory vesicles and transported to the basolateral surface and exocytosed into the lymph (Figure 9) (527,534,535).

The assembly of chylomicrons in enterocytes is a complex process requiring a number of coordinated steps and specific factors to work in unison. A failure in any of these can lead to lipid-related disease states. For instance, mutations in the SAR1B gene lead to retention of prechylomicrons within membrane-bound structures in the enterocytes (529). The condition is marked in childhood by decreased blood cholesterol levels, lipid accumulation in the enterocytes, chronic fat malabsorption with steatorrhea, and deficiencies in fat-soluble vitamin and essential fatty acids.

Chylomicron Cholesterol

Although chylomicrons are triglyceride-rich, they also carry substantial amounts of cholesterol (536,537). The cholesterol in chylomicrons comes from the general pool of enterocyte cholesterol. Enterocytes acquire cholesterol by uptake at the luminal surface, acquisition from lipoproteins at the basal lateral surface, and by de novo synthesis within the enterocyte. Niemann-Pick C1-Like 1 protein is a key component of the luminal acquisition machinery (Figure 9) (538), while the low density lipoprotein receptor appears to be a major mediator of cholesterol acquisition at the basolateral surface (539,540). The incorporation of cholesterol into chylomicrons contributes to the circulating levels of cholesterol, and increases in intestinal

synthesis of chylomicrons due to increased dietary lipids contributes to cardiovascular risk and atherosclerosis, albeit by complex mechanisms (516,541,542).

Non-Chylomicron Intestinal Lipid Metabolism

Enterocytes can also regulate circulating lipids by means other than chylomicron secretion. In the presence of excess fatty acids or cholesterol, the enterocyte can store excess lipid in their esterified forms (triglycerides and cholesteryl esters, respectively) within cytoplasmic lipid droplets (543-545). The neutral lipids in the droplets can subsequently be mobilized by hydrolysis as needed by the cell. The free fatty acids liberated from storage droplets can be incorporated into the chylomicron production pathway to become part of secreted chylomicrons.

Finally, the intestine also regulates circulating cholesterol levels by taking up excess circulating cholesterol and excreting it into the intestinal lumen for clearance in the feces. This process is known as trans-intestinal cholesterol excretion. It acts as an adjunct to liver biliary secretion and can account for as much as 30% of neutral sterol excretion (546). Trans-intestinal cholesterol excretion occurs at the luminal surface of the enterocytes by a process that primarily utilizes the ATP-binding cassette transporter pair ABCG5/G8 (Figure 9) but can use other pathways as well (547).

Summary

It is clear that intestinal lipid processing is a key contributor to the circulating levels of both triglyceride and cholesterol. Dietary, genetic and metabolic factors that disrupt the process of enterocyte lipid metabolism potentially can alter lipid homeostasis and produce disease states.

TRIGLYCERIDES, CARDIOVASCULAR DISEASE AND ATHEROSCLEROSIS

Causes of Hypertriglyceridemia

The prevalence of high circulating triglyceride levels is increasing worldwide, particularly in developed countries. In the United States there has been a greater than 7 fold increase in average plasma triglyceride concentration over the last 30 years (548). This increase coincides, in part, with increased instances of obesity and type 2 diabetes (T2DM) although the relationship of these conditions to hypertriglyceridemia is complex (549-553). Most classifications of hypertriglyceridemia are based, at least in part, on the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (469). These guidelines classified circulating triglyceride levels <150 mg/dL as normal. Values between 150 mg/dL and 199 mg/dL are considered borderline high and anything above 200 mg/dL are classified as high, with those above 500 mg/dL deemed to be very high (469,470). Hypertriglyceridemia is generally the result of increases in one or more of the triglyceride-rich lipoproteins; chylomicrons, VLDL, or their remnants. The increase occurs because of increased synthesis, decreased catabolism or both, with the underlying cause generally being the result of alterations in metabolic factors such as apolipoprotein C-II, apolipoprotein C-III, CETP and lipoprotein lipase. However, hypertriglyceridemia can also be secondary to other disease states (e.g. diabetes mellitus, hypothyroidism, renal disease, and nephrotic syndrome) (548,554). Not surprisingly, environmental conditions, particularly a diet with high fat or high glycemic index content and in which energy intake is out of balance with energy utilization, are associated with hypertriglyceridemia as is excess alcohol consumption (548,554). In fact, dietary choices and lack of exercise are widely held to be a major contributor to the recent rise in circulating triglyceride levels in developed countries.

Hypertriglyceridemia as an Independent Risk Factor for Cardiovascular Disease

Individuals with elevated triglyceride levels are at increased risk for cardiovascular complications, particularly atherosclerosis (555,556). The Framingham Study was one of the first large studies to associate hypertriglyceridemia with cardiovascular disease, particularly in women (557). However, many other studies before and since have also shown a univariate association of high triglycerides and increased risk of cardiovascular disease. In many of these studies, however, the affect went away after accounting for other major risk factors (558-561),calling into question whether triglycerides represent an independent risk factor. For instance, a meta-analysis of the Emerging Risk Factors Collaboration data revealed triglycerides as a strong risk factor for cardiovascular disease and stroke, but, after adjusting for standard risk factors (primarily lipoprotein-associated cholesterol), the researchers concluded that triglyceride levels provided no additional predictive value (474). The authors did note, as have other studies (562-565), that patients with triglyceride levels above 500 mg/dL are at increased risk of pancreatitis; providing impetus for measuring triglyceride levels in patients and treating those with high levels irrespective of cardiovascular risk. The lack of strong association of triglyceride concentration with cardiovascular disease (after accounting for other risk factors

such as elevated LDL-C and low HDL-C) has led some to question whether measuring triglyceride levels has any utility for cardiovascular patient management. In contrast, we argue below that there are a number of important reasons for evaluating triglyceride levels in patients, particularly those with cardiovascular disease, metabolic syndrome or diabetes.

First, we would point out that the difficulty in substantiating an independent association of triglycerides with cardiovascular disease may simply reflect the fact that a number of interrelated risk factors make it difficult to determine to what extent triglycerides independently contribute to cardiovascular events. One key issue is that, even in studies suggesting independence, the effect size has been small compared to traditional risk factors like LDL-C (548). Therefore, independence is very hard to detect in small studies. There are also issues regarding the way triglyceride levels are determined, the high variability of triglyceride concentrations in a single individual, and the association of triglyceride levels with other atherogenic conditions such as low HDL-C, obesity and T2DM (548,566-571). These confounding issues are not always considered by authors when drawing conclusions. Moreover, endpoints have differed widely among studies. Despite the confounding issues, an increasing number of case control studies do indicate triglycerides as an independent risk factor for cardiovascular disease even when adjusting for total cholesterol, LDL-C and HDL-C (572-578). The PROCAM study, for instance, found increases in risk for cardiovascular events as triglyceride levels increased and residual risk remained after accounting for other major risk factors (579), and the PROVE IT-TIMI 22 study revealed that triglyceride levels had a substantial impact on cardiovascular outcomes in patients with acute coronary syndrome that was independent of LDL-C (580). Moreover, Mendelian randomization studies strongly suggest a causal relationship between factors involved in regulating triglyceride rich lipoprotein levels and cardiovascular disease (581-583). For instance, analysis of data from the Copenhagen City Heart Study showed that genetic variants of lipoprotein lipase that resulted in reduced circulating triglyceride levels also reduced all-cause mortality (583).

Meta-analyses of randomized, prospective trials probably provide the strongest evidence for triglyceride levels as an independent risk factor. One such analysis assessing the effects of lowering circulating cholesterol levels with statins, indicated that in patients with preexisting coronary heart disease, there was a reduction in residual risk not associated with lowering LDL-C that could be related to other lipoproteins, such as triglyceride-rich lipoproteins (584). Most convincingly, a recent meta-analysis of 29 prospective studies showed that considering triglyceride concentrations yielded an adjusted odds ratio of 1.72 (95% Confidence interval=1.56-1.90) for those in the top tertile of triglyceride levels even after adjusting for other common risk factors (556). A similar odds ratio was reported in a meta-analysis that included data from 26 prospective studies in Asian and Pacific populations (585).

Given the increasing evidence that hypertriglyceridemia is indicative of increased cardiovascular disease risk, a key question is whether reducing triglyceride levels are protective. The results of several studies do suggest that reducing TG levels can reduce risk of cardiovascular events. An analysis of two secondary prevention trials of pravastatin suggests that high HDL-C and low triglycerides were significant predictors of reduced risk for CHD events (586). A recent meta-

analysis of 18 trials evaluating the effects of fibrates on cardiovascular outcomes reported a 10% relative risk reduction for major cardiovascular events in individuals with hypertriglyceridemia alone or in combination with low HDL-C (587). Other meta-analyses have generally shown small but significant associations of low triglycerides and protection from cardiovascular events independent of other major risk factors (588).

Thus, the evidence is mounting for an independent role of circulating triglyceride levels in mediating cardiovascular risk and certainly has established the utility of determining triglyceride levels in at-risk patients. However, the studies also suggest that the association between high triglycerides and cardiovascular disease is complicated, multidimensional, and possibly indirect.

Is There a Direct Role for Triglycerides in Promoting Cardiovascular Disease?

If hypertriglyceridemia does directly affect cardiovascular disease, the mechanism(s) remain to be fully elucidated. Nonetheless, several hypotheses have been put forward. As the most prevalent form of cardiovascular disease, atherosclerosis has been the target for most explorations of a direct role for triglycerides in cardiovascular disease, and there is growing evidence, albeit circumstantial, that triglycerides can directly influence specific aspects of atherosclerotic lesion development. Many of the hypotheses are based on the fact that triglyceride rich lipoproteins (VLDL, chylomicron) also contain significant amounts of cholesterol (536) and could promote foam cell formation by contributing cholesterol to the lesion. Remnants of VLDL and chylomicrons are created by partial hydrolysis of their triglycerides through the action of lipoprotein lipase. These particles have an increased percentage of cholesterol (537,589) and can acquire additional cholesterol by transfer from HDL through the action of cholesterol ester transfer protein(CETP) (590). In hypertriglyceridemia, there is increased VLDL synthesis, delayed clearance and often increases in remnant particles (591,592). In fact, it has been argued that nonfasting triglyceride levels primarily reflect remnant lipoproteins, particularly in hypertriglyceridemia, and these particles may be the atherogenic moiety (593). Although chylomicrons and, to some extent, very low density lipoproteins are generally too large to cross the endothelial layer and invade the arterial intima, conversion to remnants allows these particles to accumulate within atherosclerotic lesions and to deposit their cholesterol (594-596). This would imply that levels of lipoprotein lipase, by increasing remnants, could influence atherosclerotic lesion development and there are animal studies showing just such a correlation (237,238,597). Evidence for the importance of remnants in atherogenesis also comes from individuals with type III hyperlipoproteinemia. Patients with type III hyperlipoproteinemia have decreased clearance of remnant lipoproteins and develop premature atherosclerosis (598). ApoE is crucial for the normal clearance of chylomicrons and VLDL remnants, but the ApoE-2 isoform has reduced ability to bind to lipoprotein receptors and mediate clearance (599). Type III hyperlipoproteinemia occurs most often in subjects who are homozygous for APOE2, but the majority of E2/E2 individuals do not have the Type III phenotype, suggesting that a second hit is required to express the phenotype (600). Interestingly, rare genetic variants of APOE have been described that cause an autosomal dominant form of Type III hyperlipoproteinemia (601,602) and ApoE deficiency in humans is extremely rare but is associated with the Type III phenotype (600,603).

One mitigating factor in evaluating how much delivery of cholesterol in triglyceride-rich particles contributes to atherosclerosis is the fact that, although triglyceride-rich particles and their remnants contain large amounts of cholesterol, they also contain significant amounts of triglyceride. At least with respect to cellular cholesterol accumulation in macrophage foam cells (a hallmark of atherosclerosis), the presence of triglyceride in cells actually promotes the hydrolysis of cholesteryl esters to cholesterol (604,605). Cholesterol stored in foam cells is primarily in the form of cholesteryl esters. In order to be removed from the cell and eventually from the plaque, esterified cholesterol must first be converted to unesterified cholesterol (606). The presence of triglyceride intermixed with cholesteryl esters in foam cells facilitates the hydrolysis and removal of cholesterol (604,605,607). The differing effects of circulating triglyceride levels on cardiovascular disease risk and their cellular effects on cholesterol metabolism have yet to be reconciled.

There are mechanisms other than cholesterol delivery by which triglycerides could influence atherosclerosis. Lipolysis of triglyceride rich particles not only concentrates cholesterol in the particles it also produces free fatty acids and monoglycerides. Cell culture studies have demonstrated that long-chain fatty acids, particularly saturated fatty acids like palmitate and stearate, are cytotoxic (608-610). Thus, the presence of triglyceride lipolysis within atherosclerotic lesions could raise toxic free fatty acid levels in cells of the arterial wall, which would promote cell death and resulting inflammation. Both increased cell death and increased inflammatory signaling are key attributes of atherogenesis (611-614). In support of triglyceride lipolysis as an atherogenic driver, macrophages make and secrete lipoprotein lipase (lipoprotein lipase) and it is estimated that macrophages are the primary source of lipoprotein lipase in atherosclerotic plaques (615). Localized lipolysis of triglyceride-rich lipoproteins and their remnants can also liberate other oxidized fatty acids, which can promote cytotoxicity and inflammation (616-619); key players in atherosclerotic lesion development. Increases in macrophage lipoprotein lipase do stimulate macrophage cytotoxicity (620), while diminution of macrophage lipoprotein lipase in mice reduces atherosclerotic plaque size (237,621,622). Thus, localized hydrolysis of triglyceride-rich particles by macrophages have the potential to produce cytotoxic and inflammatory effects.

It is also becoming clear that the dietary fatty acid composition of lipoproteins, including triglyceride-rich lipoproteins, affects their metabolism in complex and not completely understood ways. The fatty acid composition of lipoproteins (as well as phospholipids and cholesteryl esters) is strongly influenced by dietary intake of fatty acids. Although dietary intake of saturated fatty acids is popularly believed to be bad, whether consuming saturated fat, per se, increases cardiovascular risk is somewhat controversial based on available evidence (623,624). However, in subjects with FH, increased saturated fat in the diet clearly increases LDL-C levels. What also appears clear is that replacing saturated fatty acids in the diet with polyunsaturated fatty acids (PUFA) reduces cardiovascular events (623-627). Omega-6 PUFA are the primary PUFA found in western diets. There is evidence these lower triglyceride levels, in part, by increasing lipolysis of triglyceride-rich lipoproteins (628). Omega-3 PUFA are the other major source of dietary PUFA. Fish are a rich source of long-chain omega-3 PUFA, and there is compelling evidence

that omega-3 PUFA (at least from marine sources) reduce both triglyceride levels and cardiovascular risk (629-631). A recent large scale randomized controlled trial (REDUCE-IT) using an EPA only fish oil product reduced major cardiovascular event by 25% in patients who have hypertriglyceridemia (632). Replacing saturated fat with monounsaturated fatty acids may provide some reduction in cardiovascular events, but PUFA appear to have a stronger correlation with improved cardiovascular risk compared to monounsaturated fatty acids (633-635). In contrast to cis fatty acids, trans unsaturated fatty acids, which are common in processed foods, have been convincingly associated with increased cardiovascular risk (623,636,637). Given this and other evidence, a recent report from the National Lipid Association's Expert Panel recommends, for patients with low or moderate risk for cardiovascular disease, that intake of saturated fatty acids be reduced to <7% of total energy and trans fatty acids should be avoided (638). The reduction in saturated and trans fats should be replaced with PUFA, protein and carbohydrate (638). The guidelines also suggest eating fish twice weekly. For individuals with high triglyceride levels, the Expert Panel also recommends supplementation with omega-3 polyunsaturated fatty acids from marine sources (638). The 2018 AHA/ACC listed persistent hypertriglyceridemia as a risk enhancer for developing ASCVD and recommend using omega-3 fish oil for individuals with high triglyceride levels to prevent pancreatitis. However, the AHA/ACC guidelines did not include the evidence of the REDUCE-IT trial. Therefore, in these individuals with hypertriglyceridemia and other risk factors for ASCVD, one should consider initiating omega-3 fish oil or intensifying statin therapy(481).

Lipoprotein lipase-mediated hydrolysis of triglyceride is not the only mechanism in the artery wall for the metabolism of triglyceride rich particles to produce potentially atherogenic compounds. The foam cell macrophages are also capable of the endocytic uptake of VLDL and remnant particles, which can then be catabolized in the lysosome (Figure 2) (639-642). Interestingly, there is evidence that under atherogenic influences, including macrophage sterol engorgement, the route of triglyceride metabolism in macrophages can shift to favor endocytic delivery of triglyceride-rich lipoproteins rather than surface hydrolysis (641,643). Whereas surface hydrolysis of triglycerides by surface lipases primarily delivers only free fatty acids to cells, endocytic uptake of particles would include the delivery of the particle's full content, including its sterol, which would exacerbate foam cell sterol accumulation.

Another potential way that triglyceride-rich lipoproteins could influence atherosclerosis focuses on the apolipoprotein CIII content of VLDL and remnants. ApoCIII inhibits lipoprotein lipase, inhibits remnant uptake by the liver, and its levels are associated with hypertriglyceridemia (644-648). Thus, high apolipoprotein CIII concentrations could promote arterial retention of VLDL and remnants making them more atherogenic, suggesting apolipoprotein CIII as a therapeutic target. In fact, individuals with certain mutations in APOC3 have low triglycerides and LDL-C (649,650). Two recent studies show that loss-of-function mutations in apoCIII lowered serum triglycerides by >39%, significantly reduced LDL-C and raised HDL-C, and lowered the incidence of cardiovascular events by >36% (651,652). An antisense oligonucleotide selective inhibitor of apoCIII has been developed that lowers serum apoCIII and triglycerides in mice, non-human primates, and humans and is currently in a phase 2 clinical trial (653). These studies indicate that reduction of apoCIII by antisense oligonucleotide inhibition significantly reduces circulating

triglyceride levels (654,655). Besides their effects on circulating lipids, Apo CIII-containing lipoproteins also stimulate a range of processes including activation of monocytes, inflammation, endothelial cell NO production resulting in vascular dysfunction and increased lipid oxidation and binding of lipoproteins to PG which can stimulate macrophage foam cell formation (227,239,656-658).

A final way in which triglyceride levels could influence atherogenesis is related to the finding that patients with hypertriglyceridemia also tend to have increased circulating levels of thrombotic factors such as fibrinogen and plasminogen activator inhibitor and inflammatory mediators (TNF-alpha, IL-6, VCAM-1 and MCP-1) (659-661). Thrombosis and inflammation are key factors in atherosclerosis and its progression to heart attack and stroke.

Reducing Circulating Triglyceride Levels

It is clear, therefore, that there are a variety of ways in which the triglyceride-containing particles in hypertriglyceridemic plasma could contribute either directly or indirectly to multiple aspects of atherosclerotic lesion development. Regardless of whether triglycerides are directly causative of cardiovascular disease, the evidence is mounting that assessment of triglyceride levels has an important role in evaluating and managing cardiovascular risk, and treating elevated triglyceride levels may reduce risk for cardiovascular events (548,662). This is particularly true for patients with coronary heart disease or diabetes (548,662-664). Several agents have shown efficacy in reducing triglyceride levels and also in reducing cardiovascular disease risk. The reduced risk is thought to occur to a large extent by reducing atherosclerosis. Currently, therapeutic agents recommended for treating hypertriglyceridemia are fibrates, statins, niacin and omega-3 PUFA but others are being developed. Unfortunately, clinical trials of the impact of triglyceride lowering medications on cardiovascular events in subjects with severe hypertriglyceridemia have not been undertaken.

Fibrates are the most effective approach for directly lowering triglyceride levels. Fibrates have been shown to lower triglyceride levels by 30%-50% depending on the baseline levels (548). More importantly, fibrate therapy with gemfibrozil has been shown to reduce cardiovascular risk in patients with elevated triglycerides (665-667). Unfortunately, the trials of combination therapy of statins with fenofibrate have failed to meet their primary endpoints in terms of reducing cardiovascular events (668,669). However, posthoc analysis of all of the fibrate trials show significant benefits in terms of reducing CVD events, when looking at the subgroup of patients with elevated triglycerides and low HDL-C and features of the metabolic syndrome or diabetes (670,671).

Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis, and produce dramatic reductions in LDL-C levels; typically from 20%-60% depending upon the particular statin used and dosage (672). However, they also reduce circulating levels of triglycerides (673) and Non-HDL-C (477). Levels of LDL-C are often low in the setting of hypertriglyceridemia, so Non-HDL-C levels are a more useful measure of the burden of atherogenic apoB-containing lipoproteins than LDL-C in patients with hypertriglyceridemia.

Indeed, the National Lipid Association recommends using goals for Non-HDL-C levels of < 130 mg/dl or < 100 mg/dl, in subjects at high- and very-high risk of cardiovascular events, respectively (477). Niacin is a B vitamin that can lower overall circulating lipid levels when given in high doses. The mechanism of action is not entirely clear but niacin reduces VLDL production by the liver. Unfortunately, clinical trial data regarding the use of niacin on cardiovascular outcomes in severe hypertriglyceridemia is lacking. Although in a subgroup analysis of the AIM-HIGH trial, niacin showed a trend toward benefit in the tertile of subjects with the highest triglycerides (>198mg/dl) and lowest HDL-C (<33mg/dl), which is consistent with the post hoc analysis of fibrate trials (674). Finally, evidence indicates that daily intake of omega-3 PUFA from marine sources (which primarily containing eicosapentaenoic and docosahexaenoic acids) can significantly reduce circulating triglyceride levels (675-678). Treatment with 3 – 4 grams a day of omega-3 PUFA (EPA+DHA) is effective in lowering triglycerides. A large meta-analysis of omega-3 FA in 20 studies including 63,000 participants did not see an impact on a combined cardiovascular endpoint or coronary events, but there was a reduction in vascular death (679). However, most omega-3 outcome trials used less than one gram of omega-3 PUFA, which was probably too low of a dose to have meaningful triglyceride lowering effects that could yield clinical efficacy. The JELIS trial, compared the effect of 1.8 g EPA vs. placebo on top of statin in a hypercholesteremic but relatively normal triglycerides patient population (mean LDL-C 182 mg/dl and triglycerides 151 mg/dl) (95). JELIS found a 19% relative risk reduction in CV events but a more pronounced 53% reduction in the subgroup with mixed dyslipidemia, specifically the subgroup with triglycerides >150mg/dl and HDL<40 mg/dl(680). Most recently, a large randomized controlled trial (REDUCE-IT) of an EPA only fish oil product reduced major cardiovascular event by 25% in patients who have hypertriglyceridemia (632). Whether the clinical benefit was confined to EPA only or it can be generalized to all omega-3 PUFA is still yet to be determined. In contrast to marine-derived omega-3 PUFA, plant-derived omega-3 PUFA have generally not shown efficacy for lowering triglycerides(681,682). A number of new approaches for treating hypertriglyceridemia are in development including antisense oligonucleotides to ApoC3(654,655).

Summary

The association of elevated triglyceride levels and cardiovascular disease has been well established (555,556,579,588). What remains a subject of ongoing debate is the extent to which triglycerides directly promote atherogenesis or, alternatively, simply represent a biomarker for other processes that influence cardiovascular risk. (542,548,554,561,570,592,683,684). Nonetheless, the evidence supports measuring triglycerides and including triglyceride and Non-HDL-C reduction in treatment regimens is strengthening especially in patients with metabolic syndrome, diabetes, or cardiovascular disease.

HDL METABOLISM AND ATHEROSCLEROSIS

HDL and Reverse Cholesterol Transport

Apolipoprotein A-I (apoA-I) is the major protein on HDL and provides both structure and function. Lipid-poor apoA-I and mature HDL both contribute to removing cholesterol from macrophages and prevent foam cell formation (Figure 2). Although cholesterol flux from macrophages to HDL (or apoA-I) alleviates cholesterol-accumulation in lesions, the net flux of cholesterol from the lesion has little to no effect on systemic cholesterol levels. Nevertheless, macrophage cholesterol efflux to HDL reduces inflammation and the atherosclerotic burden, and is the first step in reverse cholesterol transport (RCT) (Figure 10) (685-687). This pathway was first described in 1966 (688). The rate at which cholesterol flows through the RCT pathway is of greater importance than steady state levels of HDL-cholesterol (HDL-C). Interestingly, cholesterol movement from macrophages to HDL occurs through at least 4 routes (70). First, lipid-poor apoA-I stimulates the efflux of phospholipid and free cholesterol through interaction with ATP-binding cassette transporter A1 (ABCA1) (Figure 2), which generates pre-beta HDL and nascent discoidal particles (689). The more lipidated the apoA-1 becomes, the discoidal HDL particles transition into a spherical structure and lose their ability to interact with ABCA1 and stimulate cholesterol efflux through ABCA1. Both discoidal HDL particles and mature spherical HDL particles can also promote free cholesterol efflux from another transporter, ATP-binding cassette transport G1 (ABCG1), which is thought to reside on sub-cellular organelles as opposed to the plasma membrane (Figure 2) (690,691). This transporter is a critical regulator of intracellular cholesterol trafficking cellular cholesterol availability, and cholesterol export (690,692). HDL's primary receptor for cholesteryl ester (CE) uptake, scavenger receptor BI (SR-BI), is also a bidirectional free cholesterol transporter in that it facilitates the efflux and influx of free cholesterol between cells and mature HDL (693-695) (Figure 2). The net direction of cholesterol flux is determined by the cholesterol concentration gradient (plasma membrane and HDL ratio of free cholesterol to phospholipid) (696) as well as by the phospholipid subspecies (697,698). Finally, cholesterol can simply move from the plasma membrane to HDL through passive aqueous diffusion, which is a major route of cholesterol efflux from macrophages (Figure 2) (70,687,695). On HDL free cholesterol is solubilized in the phospholipid surface layer and is rapidly esterified by lecithin:cholesterol acyltransferase (LCAT) (Figure 6), and the hydrophobic CE is then mobilized to HDL's core (699,700).

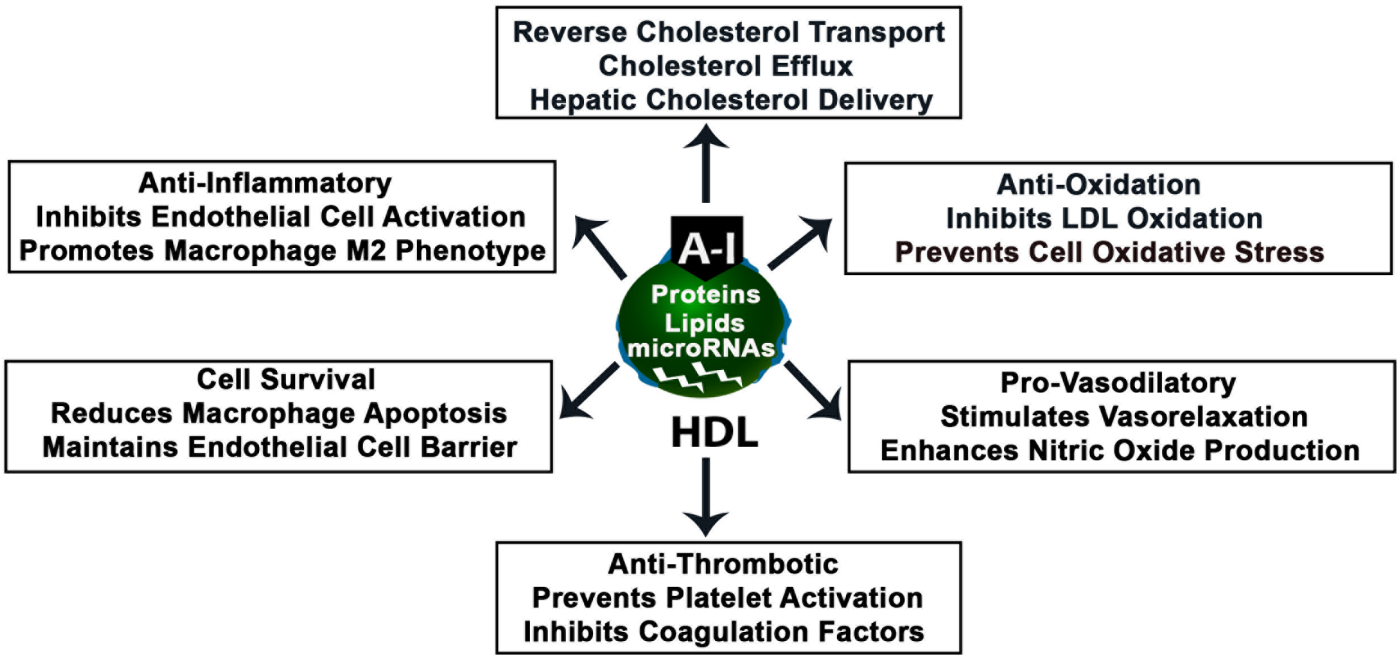

Figure 10. Beneficial Functions of HDL. HDL mediates a number of atheroprotective processes. HDL is critical in reverse cholesterol transport where it mediates the first step of removing cholesterol from the periphery and macrophage foam cells for clearance by the liver. HDL can directly mediate the last step in reverse cholesterol transport by delivering cholesterol to the liver via interaction with SR-BI. HDL reduces LDL oxidation and cell oxidative status by removing lipid hydroperoxides from LDL and cells. HDL also prevents LDL oxidation via its anti-oxidant enzymes (PON1, LCAT, and Lp-PLA2) and by the reduction of lipid hydroperoxides by apoA-I. HDL maintains the endothelial cell barrier by stimulating vasorelaxation resulting from enhanced nitric oxide production from HDL induced signaling via a number of endothelial cell receptors (SR-BI, S1P, ABCG1). HDL prevents thrombus formation by inhibiting coagulation factors and by stimulating efflux of cholesterol from platelets via SR-BI to reduce platelet aggregation. HDL prevents endothelial cell and macrophage apoptosis by signaling pathways which modulate expression of the pro-apoptotic protein, Bid, and the anti-apoptotic factor, Bcl-xl. HDL also reduces apoptosis susceptibility by alleviating endoplasmic reticulum stress by removing excess free cholesterol and lipid hydroperoxides from cells. HDL limits atherosclerotic lesion inflammation by inhibiting endothelial cell activation resulting in less monocyte recruitment. HDL also reduces lesion inflammation by promoting the macrophage anti-inflammatory M2 phenotype via ABCA1/ JAK2 signaling to enhance anti-inflammatory cytokine production (IL-10, TGF-β). HDL inhibits conversion to the macrophage inflammatory M1 phenotype by preventing antigen-specific activation of T helper 1 (Th-1) cell to produce interferon gamma. HDL contains an array of proteins and bioactive lipids that regulate HDL function. In addition, HDL controls a number of atheroprotective processes by modulating gene expression by transferring microRNAs to recipient cells.

Spherical mature HDL then transports CE to peripheral cells and tissues, and back to the liver as part of the RCT pathway (Figure 10). HDL delivers CE to the liver through 2 primary routes. HDL delivers CE to the liver through binding to SR-BI (Figure 6), which drives selective uptake of core lipids (694). Another major route of cholesterol delivery to the liver is mediated through LDL and the LDL receptor (LDLR) (Figure 6) (701). In the circulation, HDL exchanges CE for TG from VLDL and LDL through cholesteryl ester transfer protein (CETP) activity (Figure 6), and this action is responsible for directing CE through the LDL receptor pathway (702). Besides these major routes holoparticle uptake of HDL may also contribute to delivery of HDL-CE to the liver. Hepatocytes, and many other cell types in other tissues, likely participate in HDL retro-endocytosis where apoA-I or HDL particles are taken up by endocytosis and resecreted without degradation in late endosomes and lysosomes (703,704). SR-BI and CD36 may participate in this process as well as other potential HDL receptors (705-707) . For example, the F_0F_1 ATPase and $P2Y_{13}$ receptor have been reported to facilitate the uptake of the entire HDL particle (703,704,708,709). The liver then excretes both cholesterol and bile acids-derived from cholesterol into the bile which are removed from the body in feces, thus completing RCT from peripheral macrophages to bile through HDL and the liver (710). Recent evidence suggests there is also likely an HDL-independent pathway for systemic cholesterol removal through transintestinal cholesterol excretion (TICE) (711). Historically, HDL's anti-atherogenic properties were largely attributed to HDL's role in RCT and removing excess cholesterol from macrophages and peripheral tissues; however, continually emerging alternative HDL functions likely significantly contribute to HDL's protection against CVD.

HDL Levels and Risk of CVD

Historically, HDL-C was synonymous with the term HDL; however, the amount of cholesterol in the HDL pool (HDL-C) and the number and quality of HDL particles (HDL-P) are independent concepts that are important to consider in the context of HDL function. Several decades of high-quality epidemiological studies have clearly shown that HDL-C levels are inversely correlated to CVD risk and events, independent of race, gender, and ethnicity (712). In well-controlled studies assessing CVD risk using multivariate approaches to adjust for covariates, both apoA-I and HDL-C are strong independent predictors of CVD risk (474). Nonetheless, HDL-C levels are also inversely correlated to insulin resistance, obesity, and triglycerides. As such, HDL-C's causality in protection from CVD is difficult to define and is somewhat controversial, mainly due to epidemiological discrepancies between the dose-response of HDL-C levels to CVD outcomes. It is possible that HDL-C levels may simply be a biomarker for CVD and not play a causal role in atherosclerosis; however, an increasing number of functional studies clearly support HDL's functional relevance in biochemical mechanisms of atherosclerosis. In any case, epidemiological studies over the past 50 years have provided many insights into HDL-C and CVD risk. The first evidence came from the Framingham Heart Study in 1966 demonstrating a link between HDL-C and ASCVD (713). In 1975, HDL-C levels were found to be inversely associated with CVD in a Norwegian trial (Tromso Heart Study) (714). In subsequent years, the Honolulu Heart Study (1976) (715) and Framingham Heart Study (1977) (559) both reported that many CVD patients had low HDL-C levels. Over the years, low HDL-C levels have consistently been reported to be associated with increased risk of ASCVD and events (716-

718). By the late 1980s and early 1990s, the relationship between HDL-C and CVD was generally accepted, as studies during this period established that low HDL-C levels were associated with CVD risk independent of other risk factors even in patients with normal total cholesterol levels (719-721).

Clinical Outcomes Trials

Prior to the statin-era, results from randomized controlled clinical trials suggested that increasing HDL-C levels 1 mg/dL or 1% reduces mortality from CVD by 3-4% (722,723). In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), treatment of men and women with average TC and LDL-C levels and below-average HDL-C levels with lovastatin (20-40 mg) reduced LDL-C by 25% and raised HDL-C 6%, resulting in a 37% reduction in the risk for the first major acute coronary event (724). These results showed that statin therapy was effective in reducing risk for CVE in subjects with low-HDL-C. The extent to which the benefit came from HDL-C raising is unclear. Studies completed in subjects on statins have yielded inconsistent results with regard to the importance of raising HDL-C partly due to evidence suggesting that statin (fluvastatin) use in low HDL-C subjects decreased coronary artery disease (CAD) with little to no increase in HDL-C levels (725-727). In the fluvastatin regression study, low HDL-C subjects on placebo showed increased disease (angiographic) progression compared to subjects with high HDL-C levels (727). Collectively, evidence from these and a large number of epidemiological studies overwhelmingly support a clear inverse association between HDL-C levels and CVD risk. This is demonstrated clinically as raising HDL levels through injections of reconstituted HDL (rHDL) resulted in atherosclerotic plaque regression, as determined by intravascular ultrasound (728). A number of animal studies clearly support the HDL-C hypothesis. For example, raising HDL in mice and rabbits consistently blocks atherogenesis(729-731). However, raising HDL-C levels by mono- or combined therapy to reduce risk and events has proven challenging. Two major clinical outcomes trials of raising HDL with niacin failed to show a benefit. In subjects with CAD with LDL-C levels well controlled with a statin, the addition of extended release niacin in AIM-HIGH (732) and extended release niacin plus laropiprant (prostaglandin D2 receptor blocker to inhibit flushing) in HPS-2THRIVE (733) failed to reduce cardiovascular outcomes. However, structural limitations of the two Niacin trials design complicated their interpretation (734). In addition, major cardiovascular outcomes trials of 3 CETP inhibitors torcetrapib (735), dalcetrapib (736), evacetrapib have now failed to show a benefit in reducing cardiovascular events. More recently, the CETP inhibitor (anacetrapib) was tested in the REVEAL trial, which was a positive outcomes trial (737). However, the benefit of anacetrapib in reducing CVE seems to be largely explained by lowering of non-HDL, rather than increases in HDL-C (738). More recently, two recombinant apoA-I products MDCO-216 and CER001 showed no benefit in imaging studies (739,740). Collectively, the failure of these clinical studies has raised doubts about the HDL hypothesis. Indeed, raising HDL-C is presently not a primary target for therapeutic intervention. Nevertheless, HDL infusion in humans has been reported to improve endothelial function, which should contribute to inhibiting atherogenesis (741). At this time, HDL particle infusion therapies have not been proven to be an effective approach to reduce cardiovascular events (742); however, clinical trials with reconstituted HDL are still ongoing. Furthermore, recent studies indicate that HDL

particle number and cholesterol efflux capacity are better indicators of CHD risk than HDL-C levels (743,744). The therapeutic targeting of HDL non-cholesterol cargo, quality, and function are emerging and gaining support, as HDL have many other biological properties that likely contribute to prevention of atherosclerosis and CVD (745). In addition, quantifying HDL function, including cholesterol efflux capacity, will provide a better risk index than steady-state HDL-C levels (746).

Particle Number and Cholesterol Efflux

A major blow to HDL causality in atherosclerosis comes from genetic studies. Mendelian disorders resulting in very low HDL-C levels have yielded conflicting data, as mutations to critical lipoprotein genes (e.g. apoA-I) were found to be associated with protection from atherosclerosis in one study (747) and increased risk in another study (748). The ApoA-I Milano mutation is associated with low levels of HDL-C and reduced risk of CVD (747). Infusion of recombinant apoA-I Milano was reported to induce regression of atherosclerosis (749), but there has not been clear progress in developing it as an approach to therapy since the initial regression study was published. The evidence that some genetic causes of low HDL-C are associated with increased risk for premature atherosclerosis, whereas others are not, supports the notion that HDL function may be more important than HDL-C levels. Nonetheless, Mendelian disorders of low HDL-C levels are rare, and thus the sample sizes in these studies are limited and it is difficult to draw accurate conclusions. To address this issue, genome-wide association studies were completed to attempt to resolve if HDL-C is a risk index or causal factor. These studies are limited in that many variants that raise or lower HDL-C levels also affect other lipoproteins, namely LDL-C levels. For example, variants in *CETP* raise HDL-C levels and reduce LDL-C levels, which complicates risk prediction based on HDL-C levels (750). Nevertheless, studies have found that variance solely associated with HDL-C levels is not linked to cardiovascular events. For example, single nucleotide polymorphisms (SNPs) in endothelial lipase (*LIPG*), which raises HDL-C levels, are not associated with decreased CVD(751).

As failed clinical trials aimed at raising HDL-C levels and genetic studies do not uniformly support causality for HDL-C in CVD, HDL functional tests in future prospective studies will likely provide more resolution to HDL's causal role in CVD. Cholesterol efflux capacity, a marker of HDL function, has been reported to be inversely associated with CVD risk independent of HDL-C levels (744,746). This was first demonstrated in a cross-sectional study using radio-tracing of cholesterol efflux (746). A subsequent study also found an inverse association between HDL efflux capacity and atherosclerosis, but reported a positive link to cardiovascular events (752). In a third study assessing HDL cholesterol efflux in a US cohort using a fluorescence method, efflux was again linked to decreased risk of CVD (743). Recently, HDL cholesterol efflux capacity was found to be inversely associated with CVD risk and events in a large nested case-control prospective study (n=3,494 subjects) from the EPIC-Norfolk Study (744,753). These associations were independent of many other co-founding factors, including HDL-C, T2DM, obesity, LDL-C, and age amongst others (744).

In addition to HDL cholesterol efflux and functional indices as risk predictors, HDL particle number (HDL-P) has also been reported to provide biomarker potential. HDL-P numbers can be quantified using nuclear magnetic resonance (754) or calibrated ion mobility assays (755). HDL-P was found to be inversely associated with carotid intima medial thickness (cIMT) and coronary heart disease (CHD) independent of LDL particle numbers and HDL-C levels in the large multi-ethnic study of atherosclerosis (MESA) (756). Importantly, HDL-P remains inversely associated to CHD after adjusting for triglycerides and apolipoprotein B (apoB), thus suggesting that HDL-P is far superior to HDL-C levels as a biomarker of ASCVD and events (757,758). Furthermore, neither HDL-C levels nor HDL-P levels correlate to cholesterol efflux from macrophages; therefore, the rate of cholesterol efflux is still critical to understanding RCT and HDL function. Likewise, HDL quality is more important than apoA-I levels, which also do not correlate with HDL function, e.g. RCT (759). Serum samples with identical apoA-I and HDL-C levels were found to have differing cholesterol acceptance capacities, mostly due to pre-beta HDL levels, which contributed to altered ABCA1-mediated cholesterol efflux (759). These studies strongly suggest that HDL function (cholesterol efflux capacity), as opposed to HDL-C, HDL-P, and apoA-I levels, provide a more important risk assessment and better predictor of future events as well as a more reasoned therapeutic target for reducing CVD risk and events. However, clinical assays for apoA-I and HDL-P are widely available and well-established, whereas assays for cholesterol efflux capacity have not been standardized and remain a research tool at present.

HDL Composition and Analysis

Historically, HDL have been isolated by density-gradient ultracentrifugation (DGUC) based on isopycnic equilibrium, and HDL have been defined by their density 1.063-1.21 g/mL since the 1950s (760,761). Based on mass, HDL can also be separated from other lipoproteins by size-exclusion chromatography (fast protein liquid chromatography, FPLC), and HDL's molecular weight ranges from 175,000 - 360,000 Da (762). In addition to DGUC and FPLC, affinity chromatography can also be used to purify HDL from plasma using antibodies against apoA-I (763) or apoA-II, as HDL heterogeneity includes particles containing apoA-I:apoA-II (75%) or apoA-I only (25%) (763,764). Furthermore, asymmetric flow field-flow fractionation is now being used to isolate and characterize HDL (765). HDL can also be separated by non-denaturing gradient gel electrophoresis, e.g. polyacrylamide gel electrophoresis. Large HDL (HDL_2, 8.8-12.9 nm in diameter) and small HDL (HDL_3, 7.2-8.8 nm) are both α migrating particles (high negative charge), whereas pre-β HDL (5.4-7 nm) are β migrating particles for which they are defined. To quantify pre-β HDL particles, 2-D gel electrophoresis is often used to separate pre-β from mature HDL (766). HDL-P numbers can be quantified by either nuclear magnetic resonance spectroscopy or calibrated ion mobility assays. HDL can also be quantified and qualified by other methods, including vertical rotor ultracentrifugation, and transmission electron microscopy.

HDL are very dynamic and should be acknowledged as a heterogeneous pool of sub-classes with differing sizes, shapes, densities, protein compositions, and lipid diversity. Lipid-free apoA-I is secreted from the liver and small intestine as an amphipathic helix, and it quickly becomes lipidated by ABCA1 to form pre-β HDL, which then becomes discoidal after accepting

phospholipid and free cholesterol from hepatocytes and peripheral cells. Upon further lipidation and cholesterol accumulation and esterification, nascent spherical HDL forms that range 7-12 nm in diameter. Mature HDL contains 3-4 apoA-I molecules of which 1 remains on the particle and the other apoA-I are free to (dis)associate (exchange) on and off the particle with other HDL. This is predominantly associated with rearrangement of HDL's aqueous phase and surface area (767). As such, HDL are in a constant state of remodeling and interconversion. Each spherical HDL particle has approximately 50-130 phospholipids, 10-50 free cholesterol molecules, 30-90 CE molecules, and 10-20 triglyceride (TG) molecules (536). Phosphatidylcholine makes up the largest amount of lipid on HDL (approximately 90%); however, over 200 species of lipids have been reported, including sphingolipids, acylglycerols, isoprenoids, glycerophospholipids, and vitamins (768,769). The HDL proteome has been extensively studied and there is a general consensus of approximately 80 proteins (770,771). In addition to apoA-I and apoA-II, HDL transports over a dozen other apolipoproteins, as well as many enzymes and other factors. HDL have also been found to transport small RNAs, namely microRNAs (miRNA), which were found to be altered in hypercholesterolemia and atherosclerosis (772,773). Most interestingly, HDL have been demonstrated to transport a wide-variety of exogenous non-host small RNAs, including rRNA and tRNA fragments derived from bacterial and fungal species present in the microbiome and environment (774).The size of HDL is determined by the amount of CE and triglyceride (TG) in the hydrophobic core, and HDL is generally separated into 5 sub-classes based on size. Distinct HDL sub-species have been associated with CVD risk, and the sub-species have differential biological functions, e.g. large HDL are less anti-inflammatory (775-777). Many of the cargo or components of HDL are enriched in the small HDL sub-class which provides many of the alternative functions to the total HDL pool (778,779). The concentration of all HDL particles in plasma is approximately 20 umol/L; however, small HDL particles are the most abundant sub-class at approximately 10 umol/L. HDL are heterogeneous particles that transport a wide-variety of proteins, lipids, and nucleic acids, which confer many of HDL's biological properties and beneficial functions in health and dysfunction in specific diseases.

HDL Cell Signaling

Many of HDL's cellular functions – cell survival, proliferation, vasodilation -- are mediated by HDL-induced cell signaling cascades (780). As such, HDL can be characterized as hormone-like agonists. Although substantial work still remains in identifying HDL binding proteins and receptors on the cell surface, HDL have been found to activate many signaling cascades through various receptors. The most studied example of this is HDL's ability to bind to the plasma membrane and through cell signaling mobilize cholesterol from intracellular stores in organelles to the plasma membrane for efflux. This has been attributed to HDL-induced activation of protein kinase C (PKC) (781). Specifically, apoA-I binds to ABCA1 and activates phosphatidylcholine lipases, which activate PKC leading to the movement of cellular cholesterol from intracellular stores to the plasma membrane for efflux, as well as PKC-mediated phosphorylation of ABCA1, which increases the transporter's stability and efflux activity (782-784). This is a prime example of HDL-induced cell signaling that contributes to HDL cholesterol efflux capacity, which reduces the cholesterol burden for macrophages in the lesion, prevents

foam cell formation, and antagonizes atherogenesis. Other HDL-induced signaling pathways that result in increased cholesterol and lipid efflux include protein kinase A (PKA) (785,786), cell division control protein 42 (Cdc42) (787), and Janus kinases-2 (JAK2) (788,789) cascades. HDL (i.e. apoA-I)-induced cell signaling through ABCA1 also suppresses macrophage M1 phenotype activation and pro-inflammatory cytokine production (Figure 10), and promotes M2 phenotype anti-inflammatory cytokine secretion (e.g. interleukin 10 (IL-10)) through JAK2 signaling and activation of signal transducer and activator of transcription 3 (STAT3) (75). In addition, the apoA-I:ABCA1:JAK2 axis was reported to suppress inflammation in endothelial cells through cyclooxygenase-2 (COX-2) activation leading to increased prostaglandins (PGI_2), which also suppresses atherogenesis (790). HDL have also been reported to induce cell signaling through SR-BI. HDL binding to SR-BI's extracellular loop was reported to trigger activation of SR-BI's cytoplasmic C terminal domain leading to the phosphorylation of protein kinase Src and activation of both liver kinase B1 (LKB1) and calmodulin-dependent protein kinase (CAMK) (791,792). This results in cell signaling through downstream kinases – AMP-activated protein kinases (AMPK) (792), protein kinase Akt (791), and mitogen-activated protein kinase (MAPK)(791) – which ultimately regulates angiogenesis (ubiquitin ligase Siah (Siah1/2) and hypoxia-inducible factor 1α (HIF1α) (793)), insulin sensitivity (glucose transporter 4 (Glut4)(794)), re-vascularization (Rac1(795)), and vasodilation (COX(796), endothelial nitric oxide synthase (eNOS)(797,798)). Interestingly, macrophage SR-BI has recently been shown to mediate efferocytosis (phagocytosis of dead cells) in the setting of atherosclerosis via a Src/Akt/Rac1 signaling pathway, reducing necrosis in lesions (185). All of these downstream effects contribute to HDL function, and to a lesser degree atherogenesis.

The most robust HDL signaling activation is mediated by bioactive lipids on HDL, namely the lysosphingolipid sphingosine-1-phosphate (S1P). A majority of S1P in circulation is associated with HDL, and HDL-S1P activates the G-coupled S1P receptors ($S1P_{1-5}$) on the surface of many vascular cell types, including macrophages, endothelial cells, and smooth muscle cells. Activation of $S1P_1$ and $S1P_2$ receptors turns on a host of signaling cascades and factors that directly contribute to the many anti-atherogenic properties of HDL, including increasing endothelial barrier function (799) and angiogenesis (800,801) while decreasing inflammation (802) and apoptosis (803). HDL were also found to inhibit smooth muscle migration through S1P signaling, a key factor in restenosis and plaque development (804). All of these are critical processes to atherogenesis. In support of these studies, subjects with CAD were found to have decreased HDL-S1P levels (805). The key terminal effector factors in these G-protein receptor signaling cascades are focal adhesion kinase (FAK), nuclear factor κ beta (NF-κB), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, eNOS, STAT3, and B-cell lymphoma-extra-large (Bcl-xl) (780). This HDL-S1P signaling pathway has also been linked to vasorelaxation (806) and cytoprotection (e.g. cardiomyocytes) (807). In addition to these direct pathways, HDL also likely activates cell signaling indirectly through ATP (β-ATPase/$P2Y_{12/13}$)(808) or toll-like receptors (809). Collectively, HDL induced cell signaling in vascular and inflammatory cells underlies HDL's anti-atherogenic properties in health, and deficits in HDL signaling likely link HDL dysfunction in metabolic diseases to increased risk of atherosclerosis.

Anti-Inflammatory HDL

Outside reverse cholesterol transport, HDL's anti-inflammatory properties have been the most extensively studied HDL function and likely play a large role in HDL's anti-atherogenicity (Figure 10). HDL's anti-inflammatory properties are conferred by numerous mechanisms in many types of cells. In addition to providing the vascular barrier, endothelial cells control vascular inflammation through expressing adhesion molecules that aid in monocyte adhesion and ultimate migration into the atherosclerotic lesion. Moreover, activated endothelial cells secrete cytokines and recruit monocytes through chemokine release. The induction of adhesion molecules, cytokines, and chemokines in activated endothelial cells is largely due to NF-□B transcriptional activation. In humans, injection of apoA-I resulted in decreased adhesion molecule expression in atherosclerotic plaques (810). One mechanism by which HDL suppresses endothelial cell and monocyte activation is through inhibiting NF-kB activity by attenuating IkB kinase activity (811). Nonetheless, HDL decreases adhesion molecule expression through multiple mechanisms. Cells pre-treated with HDL or apoA-I are protected from TNFα or oxidized LDL (oxLDL)-induced adhesion molecule expression. In addition, HDL binding to SR-BI may also contribute to inhibition of adhesion molecule expression, as SR-BI-mediated Akt activation promoted heme oxygenase-1 expression. In addition, up-regulation of 3-beta-hydroxysteroid-delta 24 (DHCR24) by HDL binding to SR-BI was reported to underlie HDL's ability to suppress adhesion molecules (812). Furthermore, HDL suppression of intracellular adhesion molecule-1 (ICAM-1) in endothelial cells was found to be mediated, in part, through the transfer of miR-223 to recipient cells (773). Recent studies also suggest that TGFβ and AMPK also contribute to HDL's suppression of adhesion molecule expression (813).

In addition to HDL's profound effects on vascular endothelium, HDL suppresses myelopoiesis, monocyte recruitment, macrophage activation, proliferation, and emigration from atherosclerotic lesions. Similar to its impact on endothelial cells, HDL also suppresses adhesion molecule expression in monocytes, which inhibits monocyte adhesion and migration to atherosclerotic lesions (814). HDL and apoA-I were demonstrated to suppress CD11b expression on human monocytes through both ABCA1-dependent and independent mechanisms (814). HDL inhibition of monocyte activation, which includes suppression of cytokines and adhesion molecules, is mediated through both peroxisome proliferator-activated receptor gamma (PPARγ) and NF-kB transcription factors (815). Suppression of chemokine and cytokines in myeloid cells inhibits infiltration and migration of circulating monocytes, and thus antagonizes atherosclerosis. HDL have also been reported to mediate macrophage reprogramming through the transcription factor ATF3 that reduces Toll-like receptor signaling (816). Importantly, much of HDL's (and apoA-I's) inhibition of macrophage activation is mediated through altering cholesterol levels in plasma membrane lipid rafts through cholesterol efflux mediated by ABCG1/SR-BI and ABCA1; however, apoA-I induced signaling through ABCA1 and the JAK/STAT pathway independent of cholesterol efflux may also contribute to HDL's effect, as described above (75,817) (814,818). HDL have also been demonstrated to promote macrophage emigration through removing excess cholesterol and induction of signaling pathways (208). In addition to HDL's impact on monocytes and macrophages, HDL also strongly suppresses neutrophil activation and vascular smooth muscle cell secretion of monocyte chemoattractant protein-1 (MCP1) (819).

In addition to HDL's roles in innate immunity, recent evidence suggests that HDL play multiple roles in adaptive immunity (820). Mice lacking apoA-I develop autoimmunity when challenged with a high cholesterol (diet and background, *Ldlr*$^{-/-}$), which includes T cell activation and production of autoantibodies (821,822). This phenotype was rescued by apoA-I injections. HDL have also been reported to repress both antigen-presenting cell (APC) activation of T cells and T cell activation of monocytes, thus preventing the secretion of proinflammatory cytokines and chemokines (Figure 10) (823,824). ApoA-I also prevents the phenotypic switching of T-regs into pro-inflammatory follicular helper T cells during atheroprogression (92). Moreover, cholesterol efflux to HDL and apoA-I have been reported to suppress myelopoiesis and proliferation of myelopoietic stem and progenitor cells, as loss of function for both *Abca1* and *Abcg1* in mice resulted in increased myelopoiesis (820). Injection of apoA-I was also found to rescue this phenotype (825). In addition, HDL and cholesterol efflux were reported to suppress megakaryocyte progenitor proliferation, platelet levels, and thrombocytosis (826). Collectively, HDL and apoA-I inhibit circulating levels of hematopoietic progenitor cells, monocytes, neutrophils, and platelets all of which contribute to HDL's capacity to limit inflammation and atherosclerosis.

Antithrombotic HDL

Another anti-atherogenic function of HDL is the capacity to directly and indirectly inhibit platelet activation, aggregation, and thrombus formation (Figure 10). HDL-C levels were found to be inversely associated with thrombus formation in humans (827). HDL is required to remove excess cholesterol from the plasma membrane of platelets for proper function, and platelets isolated from mice lacking SR-BI to mediate cholesterol efflux to HDL were found to be more susceptible to activation (828,829). Both HDL and cyclodextrin-mediated cholesterol efflux were found to inhibit platelet aggregation (828). However, HDL-induced cell signaling through binding to glycoprotein IIb/IIIa on the surface of platelets was reported to activate phospholipase C (PLC) and PKC, thus leading to flux through the Na+/H+ antiport system (717). This pathway can result in alkalization of the cytoplasm and calcium release, which can reduce platelet activation (830). Furthermore, HDL dose-dependently inhibits stimulated platelet activation, which leads to reduced platelet aggregation, granule secretion and fibrinogen binding. In rats, apoA-I injections inhibited thrombus formation and reduced thrombus mass (831). HDL's anti-thrombotic effects are also mediated, in part, through HDL's ability to inhibit tissue factor and factors X, Va, and VIIIa (Figure 10) (832). HDL also prevents thrombus formation through cell signaling and nitric oxide (NO) production in endothelial cells (828), and suppression of tissue factor and platelet-activating factor expression in endothelial cells (833,834). HDL also reduces erythrocyte influence on thrombus formation (835). Collectively, HDL has multiple biological mechanisms that inhibit thrombus formation, and thus, contribute to HDL's anti-atherogenic properties.

Pro-Vasodilatory HDL

The endothelium significantly contributes to vascular tone, and HDL confer protection against endothelial cell activation, apoptosis, and loss of barrier function, which is critical to

atherogenesis. HDL have been reported to induce endothelium-dependent vasodilation in aortic rings (806), and individuals with low HDL have reduced endothelium-dependent vasorelaxation (Figure 10) (741). HDL's benefit to endothelial cells is largely mediated by cell signaling through phosphatidylinositol 3-kinase (PI3K) and Akt and is induced by bioactive lipids and associated proteins on HDL, including lysosulfatide, S1P, and sphingosylphosphorylcholine (SPC) (791,798,806). A key outcome of HDL-induced cell signaling is the production of NO (Figure 10) through both signaling induced phosphorylation of eNOS and increased eNOS expression (791,836). HDL can trigger eNOS-phosphorylation through SR-BI, S1P receptor ($S1P_{1-5}$), and ABCG1-mediated cholesterol efflux (806,837). HDL-induced NO underlies many of HDL's beneficial properties to endothelial cells, including HDL-induced vasodilation, tightening of cell-to-cell junctions and increased barrier function, differentiation of endothelial progenitor cells, cell survival and proliferation, cell migration, inhibition of apoptosis, and suppression of adhesion molecule expression. In addition, HDL also has NO-independent properties on endothelial cells, including induced proliferation, increased barrier function, suppressed inflammation and decreased apoptosis (838). These studies clearly define a beneficial role for HDL in vascular integrity, which underlies HDL protection against atherosclerosis.

Anti-Apoptotic HDL

HDL have multiple anti-apoptotic properties that enhance cell survival (Figure 10). By various metrics, HDL support mitochondrial function and prevent the release of apoptotic signals, including cytochrome C (205,839). Moreover, HDL drives the expression of Bcl-xl, which is a strong anti-apoptotic factor and suppresses Bid, which is a pro-apoptic protein (839,840). HDL mediates these gene expression changes through cell signaling and NO production through activation of surface receptors by HDL-associated proteins and bioactive lipids, including apolipoprotein J (apoJ) and S1P (803,840). In addition, there are likely alternative anti-apoptotic mechanisms resulting from HDL-induced signaling. Nonetheless, HDL has been demonstrated to suppress apoptosis in endothelial cells (Figure 10) activated with tumor necrosis factor (TNFα) and oxLDL (839,841,842). HDL proteins (apolipoprotein M, apoM) and apoM-binding lipids (S1P) contribute to HDL's ability to increase tight junctions and endothelial cell survival (843). Mice deficient in apoM have reduced S1P levels and loss of endothelium barrier function (843). HDL's ability to support the endothelium barrier function is a key feature of its anti-atherosclerosis properties and represents a classic example of HDL's control of cellular gene expression and phenotype that are beneficial to vascular health. However, HDL also have many capacities in the extracellular space (e.g. plasma) that protect against atherosclerosis.

Anti-Oxidative HDL

A key factor in monocyte activation and chemotaxis in the vascular wall is the accumulation of oxLDL, which is more pro-inflammatory and pro-atherogenic than unmodified LDL. LDL can become oxidized by a variety of endogenous mechanisms (844). In the vascular wall, LDL can be modified (oxidized) by many cell types, including vascular smooth muscle cells, endothelial cells, and macrophages (776). Remarkably, HDL prevents the oxidation of LDL (Figure 10) and recent evidence suggests that this may occur through 4 distinct proteins circulating on HDL –

apoA-I (845,846), LCAT (847), lipoprotein-associated phospholipase A2 (Lp-PLA2)(848,849), and paraoxonase 1 (PON1) (430,846). First, HDL can simply soak up oxidized lipids or oxidizing factors from cells preventing their association with LDL and their modification of LDL lipids and proteins. In addition, HDL removes lipid hydroperoxides from LDL particles (846). Specifically, small apoAI containing HDL particles are the most efficient at accepting lipid hydroperoxides, which are reduced to their inactive lipid hydroxides via oxidation of the methionine residues in apoA-I (850). Compared to apoA-II the methionine residues in apoA-I are more conformationally conducive to reducing lipid hydroperoxides (851,852). In addition, HDL with low surface free cholesterol and sphingomyelin are more efficient at accepting lipid hydroperoxides (745,853). The capacity of HDL to prevent oxidation via this mechanism is also maintained by the selective removal of HDL lipid hydroperoxides and hydroxides by hepatocyte SR-BI (854). In addition, ApoA-I methionine sulfoxide is reduced to methionine by methionine sulfoxide reductases.(850). LCAT circulates on HDL and has also been reported to block LDL oxidation, as LCAT over-expression in mice reduced LDL oxidation as determined by reduced LDL autoantibodies (855). Lp-PLA_2 appears to be pro-atherogenic on LDL and anti-atherogenic on HDL (856). Its activity on HDL likely contributes to HDL's anti-oxidative capacity, as inhibition of HDL-associated Lp-PLA_2 attenuated HDL's ability to block LDL oxidation (848). The strongest anti-oxidative HDL protein is likely PON1. Over-expression of PON1 in mice confers enhanced HDL anti-oxidative capacity, and PON1 itself prevents LDL oxidation in vitro (432). Most importantly, HDL isolated from mice lacking PON1 have reduced ability to prevent LDL oxidation. HDL's anti-oxidative capacity likely plays a large role in preventing inflammation and atherogenesis, and like many of the other alternative functions, confer HDL's beneficial role in health.

HDL Intercellular Communication

HDL also likely participate in intercellular communication through the transfer of nucleic acids between tissues. Recently, HDL have been reported to transport miRNA (Figure 10), which are small non-coding RNAs that suppress gene expression through binding to complimentary target sites in the 3' untranslated region of mRNAs, and thus inhibit translation and induce mRNA degradation (772). Most interestingly, the HDL-miRNA profile is significantly altered in hypercholesterolemia and atherosclerosis (772). miRNAs have been reported to be exported from macrophages to HDL, and HDL has been demonstrated to transfer specific miRNAs to recipient hepatoma cells (Huh7) and endothelial cells, likely through HDL's receptor SR-BI (773). In endothelial cells, HDL was found to deliver miR-223 to recipient cells, where it directly targeted intracellular adhesion molecule-1 (ICAM-1) expression (Figure 10), and thus inhibited neutrophil adhesion to the cells (773). miR-223 is not transcribed or processed in endothelial cells and HDL delivery of mature miR-223 to endothelium likely confers, in part, HDL's anti-inflammatory capacity associated with adhesion molecule suppression. Future studies are needed to determine the physiological relevance and functional impact of HDL-miRNAs in humans and animal models in the context of atherosclerosis and other inflammatory diseases.

Anti-Infectious HDL

HDL also contributes to innate immunity by modulating immune cell function. However, this hypothesis has not been extensively studied in the context of atherosclerosis. HDL are anti-infectious, anti-parasitic, and anti-viral. HDL have the unique capacity to prevent endotoxic shock and readily binds to lipopolysaccharides (LPS) and contributes to removing LPS through biliary excretion thus aiding innate immunity (857-859). Amongst the many proteins that circulate on HDL, apolipoprotein L1 (apo-L1) (also known as trypanosome lytic factor) is present in specific sub-classes of HDL (860,861). This factor kills *Trypanosome brucei* and *Trypanosome brucei rhdesiense*, parasites that cause sleeping sickness, through creating ionic pores in endosomes (860-862). Although promising, future studies are required to define how HDL regulation of innate immunity contributes to the inhibition of atherogenesis.

HDL Dysfunction

HDL confer many anti-atherogenic properties that are lost in atherosclerosis and other inflammatory and metabolic diseases. These include 9 key processes –

- Loss of cholesterol efflux capacity from macrophages
- Reduced ability to inhibit LDL oxidation
- Decreased vasodilation through reduced NO production in endothelial cells
- Reduced ability to inhibit monocyte chemotactic activity
- Loss of the ability to metabolize hydroperoxides on erythrocyte membranes
- Reduced ability to suppress TNFα-induced NF-κB activation and adhesion molecule expression
- Loss of anti-apoptotic capacity in endothelial cells
- Decreased capacity to block TNFα-induced NADPH oxidase activity and superoxide production
- Suppression of cytokine inhibition in activated inflammatory cells.

Many of these defects are due to changes in HDL cargo, e.g. decreased PON1 levels or increased serum amyloid A (SAA) levels. Moreover, changes in the content of bioactive lipids or increased oxidative modifications to HDL's lipids and protein cargo likely confer dysfunction. HDL-miRNAs have been shown to be significantly altered in hypercholesterolemia and atherosclerosis (772). It is unknown how these changes contribute to HDL's loss of anti-atherogenic properties, but they hold great potential for future studies. In CHD, acute coronary syndrome (ACS), and ischemic cardiomyopathy, HDL have reduced ability to inhibit oxidation of LDL, likely through reduced PON1 levels as reported in CHD (845,863,864). Loss of PON1 also reduces HDL's ability to prevent oxidation of its own lipids and proteins, which has been reported in metabolic syndrome as oxidation of apoA-I impairs HDL's RCT and anti-inflammatory functions (865). Reduced HDL-PON1 levels are also found in other cardiometabolic diseases, including type 2 diabetic mellitus (T2DM) (866,867), type 1 diabetes mellitus (T1DM) (868), rheumatoid arthritis (RA) (869,870), dyslipidemia (e.g. hyperalphalipoproteinemia (HALP) (871)), and patients after cardiac surgery (872). In subjects with ACS and CAD, HDL have been reported to have decreased ability to prevent endothelial cell apoptosis likely through decreased activation (phosphorylation) of Bcl-xl and increased activation of Bcl-2, which are anti-apoptotic and pro-apoptotic proteins, respectively (840). Loss

of HDL's anti-apoptotic capacity has been proposed to be due to increased apoCIII and possibly decreased clusterin levels on HDL (840). HDL from subjects with CHD also have decreased ability to prevent monocyte adhesion to endothelial cells and recruitment in arterial wall co-cultures, which could be associated with reduced PON1 levels amongst other cargo (845,873,874). HDL from ischemic cardiomyopathy and CAD subjects also have reduced cholesterol efflux acceptance capacity, which likely leads to increased foam cell formation in the atherosclerotic lesion and increased atherogenesis (746,863). Although the molecular basis for all of HDL's loss of anti-atherogenicity in CHD is not known, other functions of HDL are compromised in these subjects, including the ability to reduce hydroperoxides on erythrocyte membranes (875). This loss of HDL's anti-oxidant capacity is also found in T2DM (875) and T1DM (868,876). HDL in metabolic syndrome have been reported to have decreased capacity to prevent oxidation of LDL and inhibit endothelial cell apoptosis (877,878). This loss of anti-atherogenic properties is also found in hypertension (879), T2DM (867,880,881), end-stage renal disease (ESRD) (882,883), RA (869,870,884,885), systemic erythematosus lupus (SLE) (884), obstructive sleep apnea (886), and dyslipidemia (HALP) (871). Reduced ability of HDL to stimulate NO production from endothelial cells and decreased vasorelaxation properties are reported for T2DM (887,888), T1DM (889), mild chronic kidney disease (CKD) (890), and rare forms of autoimmunity (ALPS) (891). Loss of HDL-mediated cholesterol efflux capacity has been found in patients with hyperhomocysteinemia (892), sepsis (893), psoriasis (894), SLE (895), RA (885,896), ESRD (897,898), and T2DM (899,900). Not only does HDL dysfunction result from loss of key proteins and cargo, HDL can gain pro-atherogenic cargo and properties in cardiometabolic diseases. Due to loss of PON1, HDL accumulate malonaldehydes, which inhibits NO production through increased phosphorylation of eNOS through LOX-1 receptor signaling (901).

HDL Summary

Years of sound epidemiological studies have clearly established an inverse relationship between HDL-C levels and risk of CVD. Nevertheless, recent GWAS studies suggest that individuals with high HDL-C levels are not protected from CVD. Furthermore, clinical studies aimed at raising HDL-C levels through niacin and CETP inhibitors have failed to reduce risk of cardiovascular events and have been stopped prematurely due to lack of efficacy or increased number of events. Although they're often lumped together, HDL-C levels do not represent HDL particle numbers or HDL function (e.g. cholesterol efflux capacity); both of which have been reported to be better indicators of CVD risk than HDL-C. In addition to HDL's transport of cholesterol and lipids in the RCT pathway, HDL transports a wide-variety of cargo, including a diverse group of proteins, small RNAs, bioactive lipids, and many other small molecules. These alternative cargos may confer many of HDL's alternative functions outside of RCT. In fact, HDL have many beneficial properties, including anti-inflammatory, anti-oxidative, anti-thrombotic, anti-infectious, anti-apoptotic, intercellular communication, and pro-vasodilatory capacities. Recently, HDL dysfunction has been reported in many cardiometabolic diseases, including CAD, T2D, and CKD. Current and future challenges include the need to better define HDL anti-atherogenic properties in health and pro-atherogenic influences in disease to better control HDL function to potentially prevent and treat CVD.

ACKNOWLEGEMENTS

:

This work was supported in part by National Institutes of Health grants HL116263 and HL127173.

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 2015; 131:e29-322
2. Mayerl C, Lukasser M, Sedivy R, Niederegger H, Seiler R, Wick G. Atherosclerosis research from past to present--on the track of two pathologists with opposing views, Carl von Rokitansky and Rudolf Virchow. Virchows Archiv : an international journal of pathology 2006; 449:96-103
3. Ross R. Atherosclerosis--an inflammatory disease. New England Journal of Medicine 1999; 340:115-126
4. Luscher TF, Dohi Y, Tanner FC, Boulanger C. Endothelium-dependent control of vascular tone: effects of age, hypertension and lipids. Basic research in cardiology 1991; 86 Suppl 2:143-158
5. Dahlback B. Blood coagulation. Lancet 2000; 355:1627-1632
6. Luscinskas FW, Gimbrone MA, Jr. Endothelial-dependent mechanisms in chronic inflammatory leukocyte recruitment. Annual review of medicine 1996; 47:413-421
7. Davies PF. Flow-mediated endothelial mechanotransduction. Physiological reviews 1995; 75:519-560
8. Gimbrone MA, Jr., Topper JN, Nagel T, Anderson KR, Garcia-Cardena G. Endothelial dysfunction, hemodynamic forces, and atherogenesis. Annals of the New York Academy of Sciences 2000; 902:230-239; discussion 239-240
9. Gimbrone MA, Jr., Garcia-Cardena G. Vascular endothelium, hemodynamics, and the pathobiology of atherosclerosis. Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology 2013; 22:9-15
10. Nerem RM, Levesque MJ, Cornhill JF. Vascular endothelial morphology as an indicator of the pattern of blood flow. Journal of biomechanical engineering 1981; 103:172-176
11. Gouverneur M, Berg B, Nieuwdorp M, Stroes E, Vink H. Vasculoprotective properties of the endothelial glycocalyx: effects of fluid shear stress. Journal of internal medicine 2006; 259:393-400
12. Civelek M, Manduchi E, Riley RJ, Stoeckert CJ, Jr., Davies PF. Chronic endoplasmic reticulum stress activates unfolded protein response in arterial endothelium in regions of susceptibility to atherosclerosis. Circulation research 2009; 105:453-461

13. Gerrity RG, Richardson M, Somer JB, Bell FP, Schwartz CJ. Endothelial cell morphology in areas of in vivo Evans blue uptake in the aorta of young pigs. II. Ultrastructure of the intima in areas of differing permeability to proteins. The American journal of pathology 1977; 89:313-334
14. Hansson GK, Chao S, Schwartz SM, Reidy MA. Aortic endothelial cell death and replication in normal and lipopolysaccharide-treated rats. The American journal of pathology 1985; 121:123-127
15. Koo A, Dewey CF, Jr., Garcia-Cardena G. Hemodynamic shear stress characteristic of atherosclerosis-resistant regions promotes glycocalyx formation in cultured endothelial cells. American journal of physiology Cell physiology 2013; 304:C137-146
16. Zeng L, Zampetaki A, Margariti A, Pepe AE, Alam S, Martin D, Xiao Q, Wang W, Jin ZG, Cockerill G, Mori K, Li YS, Hu Y, Chien S, Xu Q. Sustained activation of XBP1 splicing leads to endothelial apoptosis and atherosclerosis development in response to disturbed flow. Proceedings of the National Academy of Sciences of the United States of America 2009; 106:8326-8331
17. Chiplunkar AR, Curtis BC, Eades GL, Kane MS, Fox SJ, Haar JL, Lloyd JA. The Kruppel-like factor 2 and Kruppel-like factor 4 genes interact to maintain endothelial integrity in mouse embryonic vasculogenesis. BMC developmental biology 2013; 13:40
18. Topper JN, Cai J, Falb D, Gimbrone MA, Jr. Identification of vascular endothelial genes differentially responsive to fluid mechanical stimuli: cyclooxygenase-2, manganese superoxide dismutase, and endothelial cell nitric oxide synthase are selectively up-regulated by steady laminar shear stress. Proceedings of the National Academy of Sciences of the United States of America 1996; 93:10417-10422
19. SenBanerjee S, Lin Z, Atkins GB, Greif DM, Rao RM, Kumar A, Feinberg MW, Chen Z, Simon DI, Luscinskas FW, Michel TM, Gimbrone MA, Jr., Garcia-Cardena G, Jain MK. KLF2 Is a novel transcriptional regulator of endothelial proinflammatory activation. The Journal of experimental medicine 2004; 199:1305-1315
20. Lei J, Vodovotz Y, Tzeng E, Billiar TR. Nitric oxide, a protective molecule in the cardiovascular system. Nitric oxide : biology and chemistry / official journal of the Nitric Oxide Society 2013; 35:175-185
21. Gerrity RG, Naito HK, Richardson M, Schwartz CJ. Dietary induced atherogenesis in swine. Morphology of the intima in prelesion stages. The American journal of pathology 1979; 95:775-792
22. Schwenke DC, Carew TE. Initiation of atherosclerotic lesions in cholesterol-fed rabbits. II. Selective retention of LDL vs. selective increases in LDL permeability in susceptible sites of arteries. Arteriosclerosis 1989; 9:908-918
23. Yurdagul A, Jr., Chen J, Funk SD, Albert P, Kevil CG, Orr AW. Altered nitric oxide production mediates matrix-specific PAK2 and NF-kappaB activation by flow. Molecular biology of the cell 2013; 24:398-408
24. Hamik A, Lin Z, Kumar A, Balcells M, Sinha S, Katz J, Feinberg MW, Gerzsten RE, Edelman ER, Jain MK. Kruppel-like factor 4 regulates endothelial inflammation. The Journal of biological chemistry 2007; 282:13769-13779

25. Ungvari Z, Wolin MS, Csiszar A. Mechanosensitive production of reactive oxygen species in endothelial and smooth muscle cells: role in microvascular remodeling? Antioxidants & redox signaling 2006; 8:1121-1129
26. Steinbrecher UP. Role of superoxide in endothelial-cell modification of low-density lipoproteins. Biochim Biophys Acta 1988; 959:20-30
27. Cominacini L, Pasini AF, Garbin U, Davoli A, Tosetti ML, Campagnola M, Rigoni A, Pastorino AM, Lo Cascio V, Sawamura T. Oxidized low density lipoprotein (ox-LDL) binding to ox-LDL receptor-1 in endothelial cells induces the activation of NF-kappaB through an increased production of intracellular reactive oxygen species. The Journal of biological chemistry 2000; 275:12633-12638
28. Collins T, Read MA, Neish AS, Whitley MZ, Thanos D, Maniatis T. Transcriptional regulation of endothelial cell adhesion molecules: NF-kappa B and cytokine-inducible enhancers. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 1995; 9:899-909
29. Park S, Yoon SJ, Tae HJ, Shim CY. RAGE and cardiovascular disease. Frontiers in bioscience 2011; 16:486-497
30. Dauphinee SM, Karsan A. Lipopolysaccharide signaling in endothelial cells. Laboratory investigation; a journal of technical methods and pathology 2006; 86:9-22
31. Kratzer A, Giral H, Landmesser U. High-density lipoproteins as modulators of endothelial cell functions: alterations in patients with coronary artery disease. Cardiovascular research 2014; 103:350-361
32. Galkina E, Ley K. Vascular adhesion molecules in atherosclerosis. Arteriosclerosis, thrombosis, and vascular biology 2007; 27:2292-2301
33. Gu L, Okada Y, Clinton SK, Gerard C, Sukhova GK, Libby P, Rollins BJ. Absence of monocyte chemoattractant protein-1 reduces atherosclerosis in low density lipoprotein receptor-deficient mice. Molecular Cell 1998; 2:275-281
34. Gerszten RE, Garcia-Zepeda EA, Lim YC, Yoshida M, Ding HA, Gimbrone MA, Jr., Luster AD, Luscinskas FW, Rosenzweig A. MCP-1 and IL-8 trigger firm adhesion of monocytes to vascular endothelium under flow conditions. Nature 1999; 398:718-723
35. Boisvert WA, Santiago R, Curtiss LK, Terkeltaub RA. A leukocyte homologue of the IL-8 receptor CXCR-2 mediates the accumulation of macrophages in atherosclerotic lesions of LDL receptor-deficient mice. Journal of Clinical Investigation 1998; 101:353-363
36. Swirski FK, Libby P, Aikawa E, Alcaide P, Luscinskas FW, Weissleder R, Pittet MJ. Ly-6Chi monocytes dominate hypercholesterolemia-associated monocytosis and give rise to macrophages in atheromata. J Clin Invest 2007; 117:195-205
37. Libby P, Nahrendorf M, Swirski FK. Monocyte heterogeneity in cardiovascular disease. Seminars in immunopathology 2013; 35:553-562
38. Swirski FK, Nahrendorf M, Etzrodt M, Wildgruber M, Cortez-Retamozo V, Panizzi P, Figueiredo JL, Kohler RH, Chudnovskiy A, Waterman P, Aikawa E, Mempel TR, Libby P, Weissleder R, Pittet MJ. Identification of splenic reservoir monocytes and their deployment to inflammatory sites. Science 2009; 325:612-616
39. Ley K, Miller YI, Hedrick CC. Monocyte and macrophage dynamics during atherogenesis. Arteriosclerosis, thrombosis, and vascular biology 2011; 31:1506-1516

40. Christensen JJ, Osnes LT, Halvorsen B, Retterstol K, Bogsrud MP, Wium C, Svilaas A, Narverud I, Ulven SM, Aukrust P, Holven KB. Altered leukocyte distribution under hypercholesterolemia: A cross-sectional study in children with familial hypercholesterolemia. Atherosclerosis 2017; 256:67-74
41. van der Valk FM, Kuijk C, Verweij SL, Stiekema LCA, Kaiser Y, Zeerleder S, Nahrendorf M, Voermans C, Stroes ESG. Increased haematopoietic activity in patients with atherosclerosis. European heart journal 2017; 38:425-432
42. Rogacev KS, Cremers B, Zawada AM, Seiler S, Binder N, Ege P, Grosse-Dunker G, Heisel I, Hornof F, Jeken J, Rebling NM, Ulrich C, Scheller B, Bohm M, Fliser D, Heine GH. CD14++CD16+ monocytes independently predict cardiovascular events: a cohort study of 951 patients referred for elective coronary angiography. Journal of the American College of Cardiology 2012; 60:1512-1520
43. Robbins CS, Hilgendorf I, Weber GF, Theurl I, Iwamoto Y, Figueiredo JL, Gorbatov R, Sukhova GK, Gerhardt LM, Smyth D, Zavitz CC, Shikatani EA, Parsons M, van Rooijen N, Lin HY, Husain M, Libby P, Nahrendorf M, Weissleder R, Swirski FK. Local proliferation dominates lesional macrophage accumulation in atherosclerosis. Nature medicine 2013; 19:1166-1172
44. Brown M, Goldstein J, Krieger M, Ho Y, Anderson R. Reversible accumulation of cholesteryl esters in macrophages incubated with acetylated lipoproteins. J Cell Biol 1979; 82:597-613
45. Brown MS, Goldstein JL. Lipoprotein metabolism in the macrophage: implications for cholesterol deposition in atherosclerosis. Annu Rev Biochem 1983; 52:223-261
46. Moore KJ, Freeman MW. Scavenger receptors in atherosclerosis: beyond lipid uptake. Arteriosclerosis, thrombosis, and vascular biology 2006; 26:1702-1711
47. Younis N, Sharma R, Soran H, Charlton-Menys V, Elseweidy M, Durrington PN. Glycation as an atherogenic modification of LDL. Current opinion in lipidology 2008; 19:378-384
48. Torzewski M, Lackner KJ. Initiation and progression of atherosclerosis--enzymatic or oxidative modification of low-density lipoprotein? Clinical chemistry and laboratory medicine : CCLM / FESCC 2006; 44:1389-1394
49. Torzewski M, Suriyaphol P, Paprotka K, Spath L, Ochsenhirt V, Schmitt A, Han SR, Husmann M, Gerl VB, Bhakdi S, Lackner KJ. Enzymatic modification of low-density lipoprotein in the arterial wall: a new role for plasmin and matrix metalloproteinases in atherogenesis. Arteriosclerosis, thrombosis, and vascular biology 2004; 24:2130-2136
50. Schwartz EA, Reaven PD. Lipolysis of triglyceride-rich lipoproteins, vascular inflammation, and atherosclerosis. Biochimica et biophysica acta 2012; 1821:858-866
51. Fujioka Y, Cooper A, Fong L. Multiple processes are involved in the uptake of chylomicron remnants by mouse peritoneal macrophages. J Lipid Res 1998; 39:2339-2349
52. Anzinger JJ, Chang J, Xu Q, Barthwal MK, Bohnacker T, Wymann MP, Kruth HS. Murine bone marrow-derived macrophages differentiated with GM-CSF become foam cells by PI3Kgamma-dependent fluid-phase pinocytosis of native LDL. J Lipid Res 2012; 53:34-42

53. Kruth HS. Fluid-phase pinocytosis of LDL by macrophages: a novel target to reduce macrophage cholesterol accumulation in atherosclerotic lesions. Current pharmaceutical design 2013; 19:5865-5872
54. Colin S, Chinetti-Gbaguidi G, Staels B. Macrophage phenotypes in atherosclerosis. Immunological reviews 2014; 262:153-166
55. Adamson S, Leitinger N. Phenotypic modulation of macrophages in response to plaque lipids. Current opinion in lipidology 2011; 22:335-342
56. Bolick DT, Skaflen MD, Johnson LE, Kwon SC, Howatt D, Daugherty A, Ravichandran KS, Hedrick CC. G2A deficiency in mice promotes macrophage activation and atherosclerosis. Circulation research 2009; 104:318-327
57. Wang XQ, Panousis CG, Alfaro ML, Evans GF, Zuckerman SH. Interferon-gamma-mediated downregulation of cholesterol efflux and ABC1 expression is by the Stat1 pathway. Arteriosclerosis, thrombosis, and vascular biology 2002; 22:e5-9
58. Brand K, Mackman N, Curtiss LK. Interferon-gamma inhibits macrophage apolipoprotein E production by posttranslational mechanisms. J Clin Invest 1993; 91:2031-2039
59. Peled M, Fisher EA. Dynamic Aspects of Macrophage Polarization during Atherosclerosis Progression and Regression. Frontiers in immunology 2014; 5:579
60. Chinetti-Gbaguidi G, Staels B. Macrophage polarization in metabolic disorders: functions and regulation. Current opinion in lipidology 2011; 22:365-372
61. Ye D, Lammers B, Zhao Y, Meurs I, Van Berkel TJ, Van Eck M. ATP-binding cassette transporters A1 and G1, HDL metabolism, cholesterol efflux, and inflammation: important targets for the treatment of atherosclerosis. Current drug targets 2011; 12:647-660
62. Tall AR, Yvan-Charvet L. Cholesterol, inflammation and innate immunity. Nature reviews Immunology 2015; 15:104-116
63. Lu X, Kakkar V. Inflammasome and atherogenesis. Current pharmaceutical design 2014; 20:108-124
64. Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, Abela GS, Franchi L, Nunez G, Schnurr M, Espevik T, Lien E, Fitzgerald KA, Rock KL, Moore KJ, Wright SD, Hornung V, Latz E. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature 2010; 464:1357-1361
65. Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ, Group CT. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet 2018; 391:319-328
66. Yancey PG, Jerome WG, Yu H, Griffin EE, Cox BE, Babaev VR, Fazio S, Linton MF. Severely altered cholesterol homeostasis in macrophages lacking apoE and SR-BI. J Lipid Res 2007; 48:1140-1149
67. Fioravanti J, Medina-Echeverz J, Berraondo P. Scavenger receptor class B, type I: a promising immunotherapy target. Immunotherapy 2011; 3:395-406
68. Kellner-Weibel G, de la Llera-Moya M. Update on HDL receptors and cellular cholesterol transport. Current atherosclerosis reports 2011; 13:233-241
69. Phillips MC. Molecular mechanisms of cellular cholesterol efflux. The Journal of biological chemistry 2014; 289:24020-24029

70. Yancey PG, Bortnick AE, Kellner-Weibel G, de la Llera-Moya M, Phillips MC, Rothblat GH. Importance of different pathways of cellular cholesterol efflux. Arteriosclerosis, thrombosis, and vascular biology 2003; 23:712-719
71. Oram JF, Wolfbauer G, Vaughan AM, Tang C, Albers JJ. Phospholipid transfer protein interacts with and stabilizes ATP-binding cassette transporter A1 and enhances cholesterol efflux from cells. The Journal of biological chemistry 2003; 278:52379-52385
72. Ghosh S, Zhao B, Bie J, Song J. Macrophage cholesteryl ester mobilization and atherosclerosis. Vascul Pharmacol 2010; 52:1-10
73. Ouimet M, Marcel YL. Regulation of lipid droplet cholesterol efflux from macrophage foam cells. Arteriosclerosis, thrombosis, and vascular biology 2012; 32:575-581
74. Ouimet M, Franklin V, Mak E, Liao X, Tabas I, Marcel YL. Autophagy regulates cholesterol efflux from macrophage foam cells via lysosomal acid lipase. Cell Metab 2011; 13:655-667
75. Tang C, Liu Y, Kessler PS, Vaughan AM, Oram JF. The macrophage cholesterol exporter ABCA1 functions as an anti-inflammatory receptor. The Journal of biological chemistry 2009; 284:32336-32343
76. Donaldson CJ, Lao KH, Zeng L. The salient role of microRNAs in atherogenesis. Journal of molecular and cellular cardiology 2018; 122:98-113
77. Michell DL, Vickers KC. Lipoprotein carriers of microRNAs. Biochimica et biophysica acta 2016; 1861:2069-2074
78. Horie T, Baba O, Kuwabara Y, Chujo Y, Watanabe S, Kinoshita M, Horiguchi M, Nakamura T, Chonabayashi K, Hishizawa M, Hasegawa K, Kume N, Yokode M, Kita T, Kimura T, Ono K. MicroRNA-33 deficiency reduces the progression of atherosclerotic plaque in ApoE-/- mice. Journal of the American Heart Association 2012; 1:e003376
79. Nishino T, Horie T, Baba O, Sowa N, Hanada R, Kuwabara Y, Nakao T, Nishiga M, Nishi H, Nakashima Y, Nakazeki F, Ide Y, Koyama S, Kimura M, Nagata M, Yoshida K, Takagi Y, Nakamura T, Hasegawa K, Miyamoto S, Kimura T, Ono K. SREBF1/MicroRNA-33b Axis Exhibits Potent Effect on Unstable Atherosclerotic Plaque Formation In Vivo. Arteriosclerosis, thrombosis, and vascular biology 2018; 38:2460-2473
80. Rayner KJ, Sheedy FJ, Esau CC, Hussain FN, Temel RE, Parathath S, van Gils JM, Rayner AJ, Chang AN, Suarez Y, Fernandez-Hernando C, Fisher EA, Moore KJ. Antagonism of miR-33 in mice promotes reverse cholesterol transport and regression of atherosclerosis. The Journal of clinical investigation 2011; 121:2921-2931
81. Ganta VC, Choi MH, Kutateladze A, Fox TE, Farber CR, Annex BH. A MicroRNA93-Interferon Regulatory Factor-9-Immunoresponsive Gene-1-Itaconic Acid Pathway Modulates M2-Like Macrophage Polarization to Revascularize Ischemic Muscle. Circulation 2017; 135:2403-2425
82. Vickers KC, Landstreet SR, Levin MG, Shoucri BM, Toth CL, Taylor RC, Palmisano BT, Tabet F, Cui HL, Rye KA, Sethupathy P, Remaley AT. MicroRNA-223 coordinates cholesterol homeostasis. Proceedings of the National Academy of Sciences of the United States of America 2014; 111:14518-14523
83. Zhuang G, Meng C, Guo X, Cheruku PS, Shi L, Xu H, Li H, Wang G, Evans AR, Safe S, Wu C, Zhou B. A novel regulator of macrophage activation: miR-223 in obesity-associated adipose tissue inflammation. Circulation 2012; 125:2892-2903

84. Choi JH, Do Y, Cheong C, Koh H, Boscardin SB, Oh YS, Bozzacco L, Trumpfheller C, Park CG, Steinman RM. Identification of antigen-presenting dendritic cells in mouse aorta and cardiac valves. The Journal of experimental medicine 2009; 206:497-505
85. Paulson KE, Zhu SN, Chen M, Nurmohamed S, Jongstra-Bilen J, Cybulsky MI. Resident intimal dendritic cells accumulate lipid and contribute to the initiation of atherosclerosis. Circulation research 2010; 106:383-390
86. Veillard NR, Kwak B, Pelli G, Mulhaupt F, James RW, Proudfoot AE, Mach F. Antagonism of RANTES receptors reduces atherosclerotic plaque formation in mice. Circulation research 2004; 94:253-261
87. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. Nature reviews Cardiology 2009; 6:399-409
88. Gil-Pulido J, Zernecke A. Antigen-presenting dendritic cells in atherosclerosis. Eur J Pharmacol 2017; 816:25-31
89. Pirillo A, Bonacina F, Norata GD, Catapano AL. The Interplay of Lipids, Lipoproteins, and Immunity in Atherosclerosis. Curr Atheroscler Rep 2018; 20:12
90. Abdolmaleki F, Gheibi Hayat SM, Bianconi V, Johnston TP, Sahebkar A. Atherosclerosis and immunity: A perspective. Trends Cardiovasc Med 2018;
91. Tabas I, Lichtman AH. Monocyte-Macrophages and T Cells in Atherosclerosis. Immunity 2017; 47:621-634
92. Gaddis DE, Padgett LE, Wu R, McSkimming C, Romines V, Taylor AM, McNamara CA, Kronenberg M, Crotty S, Thomas MJ, Sorci-Thomas MG, Hedrick CC. Apolipoprotein AI prevents regulatory to follicular helper T cell switching during atherosclerosis. Nat Commun 2018; 9:1095
93. Srikakulapu P, McNamara CA. B cells and atherosclerosis. Am J Physiol Heart Circ Physiol 2017; 312:H1060-H1067
94. Que X, Hung MY, Yeang C, Gonen A, Prohaska TA, Sun X, Diehl C, Maatta A, Gaddis DE, Bowden K, Pattison J, MacDonald JG, Yla-Herttuala S, Mellon PL, Hedrick CC, Ley K, Miller YI, Glass CK, Peterson KL, Binder CJ, Tsimikas S, Witztum JL. Oxidized phospholipids are proinflammatory and proatherogenic in hypercholesterolaemic mice. Nature 2018; 558:301-306
95. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K, Japan EPAlisI. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007; 369:1090-1098
96. Linton MF, Hasty AH, Babaev VR, Fazio S. Hepatic ApoE expression is required for remnant lipoprotein clearance in the absence of the low density lipoprotein receptor. J Clin Invest 1998; 101:1726-1736
97. Zhang S, Reddick R, Piedrahita J, Maeda N. Spontaneous hypercholesterolemia and arterial lesions in mice lacking apolipoprotein E. Science 1992; 258:468-471
98. Plump A, Smith J, Hayek T, Aalto-Setala K, Walsh A, Verstuyft J, Rubin E, Breslow J. Severe hypercholesterolemia and atherosclerosis in apolipoprotein E-deficient mice created by homologous recombination in ES cells. Cell 1992; 71:343-353

99. Linton MF, Atkinson JB, Fazio S. Prevention of atherosclerosis in apolipoprotein E-deficient mice by bone marrow transplantation. Science 1995; 267:1034-1037
100. Fazio S, Babaev VR, Murray AB, Hasty AH, Carter KJ, Gleaves LA, Atkinson JB, Linton MF. Increased atherosclerosis in C57BL/6 mice reconstituted with apolipoprotein E null macrophages. Proc Natl Acad Sci USA 1997; 94:4647-4652
101. Fazio S, Babaev VR, Burleigh ME, Major AS, Hasty AH, Linton MF. Physiological expression of macrophage apoE in the artery wall reduces atherosclerosis in severely hyperlipidemic mice. J Lipid Res 2002; 43:1602-1609
102. Murphy AJ, Akhtari M, Tolani S, Pagler T, Bijl N, Kuo CL, Wang M, Sanson M, Abramowicz S, Welch C, Bochem AE, Kuivenhoven JA, Yvan-Charvet L, Tall AR. ApoE regulates hematopoietic stem cell proliferation, monocytosis, and monocyte accumulation in atherosclerotic lesions in mice. J Clin Invest 2011;
103. Wu D, Sharan C, Yang H, Goodwin JS, Zhou L, Grabowski GA, Du H, Guo Z. Apolipoprotein E-deficient lipoproteins induce foam cell formation by downregulation of lysosomal hydrolases in macrophages. J Lipid Res 2007; 48:2571-2578
104. Yancey PG, Yu H, Linton MF, Fazio S. A Pathway-Dependent on ApoE, ApoAI, and ABCA1 Determines Formation of Buoyant High-Density Lipoprotein by Macrophage Foam Cells. Arteriosclerosis, thrombosis, and vascular biology 2007; 27:1123-1131
105. Mazzone T, Reardon C. Expression of heterolgous human apolipoprotein E by J774 macrophages enhances cholesterol effux to HDL_3. J Lipid Res 1994; 35:1345-1353
106. Langer C, Yadong H, Cullen P, Wiesenhutter B, Mahley RW, Assmann G, von Eckardstein A. Endogenous apolipoprotein E modulates cholesterol efflux and cholesteryl ester hydrolysis mediated by high-density lipoprotein-3 and lipid-free apoproteins in mouse peritoneal macrophages. J Mol Med 2000; 78:217-222
107. Huang Z, Mazzone T. ApoE-dependent sterol efflux from macrophages is modulated by scavenger receptor class B type I expression. J Lipid Res 2002; 43:375-382
108. Zanotti I, Pedrelli M, Poti F, Stomeo G, Gomaraschi M, Calabresi L, Bernini F. Macrophage, but not systemic, apolipoprotein E is necessary for macrophage reverse cholesterol transport in vivo. Arteriosclerosis, thrombosis, and vascular biology 2011; 31:74-80
109. Kim WS, Rahmanto AS, Kamili A, Rye KA, Guillemin GJ, Gelissen IC, Jessup W, Hill AF, Garner B. Role of ABCG1 and ABCA1 in regulation of neuronal cholesterol efflux to apolipoprotein E discs and suppression of amyloid-beta peptide generation. The Journal of biological chemistry 2007; 282:2851-2861
110. Lammers B, Out R, Hildebrand RB, Quinn CM, Williamson D, Hoekstra M, Meurs I, Van Berkel TJ, Jessup W, Van Eck M. Independent protective roles for macrophage Abcg1 and Apoe in the atherosclerotic lesion development. Atherosclerosis 2009; 205:420-426
111. Chroni A, Nieland T, Kypreos K, Krieger M, Zannis V. SR-BI mediates cholesterol efflux via its interactions with lipid-bound apoE. Structural mutations in SR-BI diminish cholesterol efflux. Biochemistry 2005; 44:13132-13143
112. Ito J, Zhang L-Y, Asai M, Yokoyama S. Differential generation of high-density lipoprotein by endogenous and exogenous apolipoproteins in cultured fetal rat astrocytes. J of Neurochemistry 1999; 72:2362-2369

113. Lin C, Duan H, Mazzone T. Apolipoprotein E-dependent cholesterol efflux from macrophages: kinetic study and divergent mechanisms for endogenous versus exogenous apolipoprotein. J Lipid Res 1999; 40:1618-1626
114. Bielicki J, McCall M, Forte T. Apolipoprotein A-I promotes cholesterol release and apolipoprotein E recruitment from THP-1 macrophage-like foam cells. J Lipid Res 1999; 40:85-92
115. Kruth H, Skarlatos S, Gaynor P, Gamble W. Production of cholesterol-enriched nascent high density lipoproteins by human monocyte-derived macrophages is a mechanism that contributes to macrophage cholesterol efflux. The Journal of biological chemistry 1994; 269:24511-24518
116. Zhang W, Gaynor P, Kruth H. Apolipoprotein E produced by human monocyte-derived macrophages mediates cholesterol efflux that occurs in the absence of added cholesterol acceptors. The Journal of biological chemistry 1996; 271:28641-28646
117. Jofre-Monseny L, Loboda A, Wagner AE, Huebbe P, Boesch-Saadatmandi C, Jozkowicz A, Minihane AM, Dulak J, Rimbach G. Effects of apoE genotype on macrophage inflammation and heme oxygenase-1 expression. Biochem Biophys Res Commun 2007; 357:319-324
118. Ali K, Middleton M, Pure E, Rader DJ. Apolipoprotein E suppresses the type I inflammatory response in vivo. Circulation research 2005; 97:922-927
119. Yu S, Duan RS, Chen Z, Quezada HC, Bao L, Nennesmo I, Zhu SW, Winblad B, Ljunggren HG, Zhu J. Increased susceptibility to experimental autoimmune neuritis after upregulation of the autoreactive T cell response to peripheral myelin antigen in apolipoprotein E-deficient mice. J Neuropathol Exp Neurol 2004; 63:120-128
120. Li K, Ching D, Luk FS, Raffai RL. Apolipoprotein E enhances microRNA-146a in monocytes and macrophages to suppress nuclear factor-kappaB-driven inflammation and atherosclerosis. Circulation research 2015; 117:e1-e11
121. Maor I, Kaplan M, Hayek T, Vaya J, Hoffman A, Aviram M. Oxidized monocyte-derived macrophages in aortic atherosclerotic lesion from apolipoprotein E-deficient mice and from human carotid artery contain lipid peroxides and oxysterols. Biochem Biophys Res Commun 2000; 269:775-780
122. Rosenblat M, Coelman R, Aviram M. Increased macrophage glutathione content reduces cell-mediated oxidation of LDL and atherosclerosis in apolipoprotein E deficient mice. Atheroscler 2002; 163:17-28
123. Rosenblat M, Aviram M. Oxysterols-induced activation of macrophage NADPH oxidase enhances cell-mediated oxidation of LDL in the atherosclerotic apolipoprotein E deficient mouse: inhibitory role for vitamin E. Atherosclerosis 2002; 100:69-80
124. Miyata M, Smith JD. Apolipoprotein E allele-specific antioxidant activity and effects on cytotoxicity by oxidative insults and b-amyloid peptides. Nature Genetics 1996; 14:55-61
125. Ishiguro H, Yoshida H, Major AS, Zhu T, Babaev VR, Linton MF, Fazio S. Retrovirus-mediated expression of apolipoprotein A-I in the macrophage protects against atherosclerosis in vivo. The Journal of biological chemistry 2001; 276:36742-36748
126. Davignon J, Gregg RE, Sing CF. Apolipoprotein E polymorphism and atherosclerosis. Arteriosclerosis 1988; 8:1–21

127. Okoro EU, Zhao Y, Guo Z, Zhou L, Lin X, Yang H. Apolipoprotein E4 is deficient in inducing macrophage ABCA1 expression and stimulating the Sp1 signaling pathway. PloS one 2012; 7:e44430
128. Cullen P, Cignarella A, Brennhausen B, Mohr S, Assmann G, von Eckardstein A. Phenotype-dependent differences in apolipoprotein E metabolism and in cholesterol homeostasis in human monocyte-derived macrophages. J Clin Invest 1998; 101:1670-1677
129. Gong JS, Kobayashi M, Hayashi H, Zou K, Sawamura N, Fujita SC, Yanagisawa K, Michikawa M. Apolipoprotein E (ApoE) isoform-dependent lipid release from astrocytes prepared from human ApoE3 and ApoE4 knock-in mice. The Journal of biological chemistry 2002; 277:29919-29926
130. Michikawa M, Fan QW, Isobe I, Yanagisawa K. Apolipoprotein E exhibits isoform-specific promotion of lipid efflux from astrocytes and neurons in culture. J Neurochem 2000; 74:1008-1016
131. Huebbe P, Lodge JK, Rimbach G. Implications of apolipoprotein E genotype on inflammation and vitamin E status. Molecular nutrition & food research 2010; 54:623-630
132. Utermann G, Hardewig A, Zimmer F. Apolipoprotein E phenotypes in patients with myocardial infarction. Hum Genet 1984; 65:237–241
133. Song Y, Stampfer MJ, Liu S. Meta-analysis: apolipoprotein E genotypes and risk for coronary heart disease. Annals of internal medicine 2004; 141:137-147
134. Fisher EA, Feig JE, Hewing B, Hazen SL, Smith JD. High-density lipoprotein function, dysfunction, and reverse cholesterol transport. Arteriosclerosis, thrombosis, and vascular biology 2012; 32:2813-2820
135. Puri R, Nissen SE, Ballantyne CM, Barter PJ, Chapman MJ, Erbel R, Libby P, Raichlen JS, St John J, Wolski K, Uno K, Kataoka Y, Nicholls SJ. Factors underlying regression of coronary atheroma with potent statin therapy. European heart journal 2013; 34:1818-1825
136. Schwartz SM. The intima : A new soil. Circulation research 1999; 85:877-879
137. Raines EW. PDGF and cardiovascular disease. Cytokine & growth factor reviews 2004; 15:237-254
138. Johnson JL. Matrix metalloproteinases: influence on smooth muscle cells and atherosclerotic plaque stability. Expert review of cardiovascular therapy 2007; 5:265-282
139. Yang X, Liaw L, Prudovsky I, Brooks PC, Vary C, Oxburgh L, Friesel R. Fibroblast growth factor signaling in the vasculature. Current atherosclerosis reports 2015; 17:509
140. Molloy CJ, Taylor DS, Pawlowski JE. Novel cardiovascular actions of the activins. The Journal of endocrinology 1999; 161:179-185
141. Libby P. Changing concepts of atherogenesis. Journal of internal medicine 2000; 247:349-358
142. Bobik A. Transforming growth factor-betas and vascular disorders. Arteriosclerosis, thrombosis, and vascular biology 2006; 26:1712-1720
143. Ortiz-Munoz G, Houard X, Martin-Ventura JL, Ishida BY, Loyau S, Rossignol P, Moreno JA, Kane JP, Chalkley RJ, Burlingame AL, Michel JB, Meilhac O. HDL antielastase activity prevents smooth muscle cell anoikis, a potential new antiatherogenic property.

FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2009; 23:3129-3139
144. Feil S, Fehrenbacher B, Lukowski R, Essmann F, Schulze-Osthoff K, Schaller M, Feil R. Transdifferentiation of vascular smooth muscle cells to macrophage-like cells during atherogenesis. Circulation research 2014; 115:662-667
145. Rong JX, Shapiro M, Trogan E, Fisher EA. Transdifferentiation of mouse aortic smooth muscle cells to a macrophage-like state after cholesterol loading. Proceedings of the National Academy of Sciences of the United States of America 2003; 100:13531-13536
146. Shankman LS, Gomez D, Cherepanova OA, Salmon M, Alencar GF, Haskins RM, Swiatlowska P, Newman AA, Greene ES, Straub AC, Isakson B, Randolph GJ, Owens GK. KLF4-dependent phenotypic modulation of smooth muscle cells has a key role in atherosclerotic plaque pathogenesis. Nature medicine 2015; 21:628-637
147. Argmann CA, Sawyez CG, Li S, Nong Z, Hegele RA, Pickering JG, Huff MW. Human smooth muscle cell subpopulations differentially accumulate cholesteryl ester when exposed to native and oxidized lipoproteins. Arteriosclerosis, thrombosis, and vascular biology 2004; 24:1290-1296
148. Zingg JM, Ricciarelli R, Andorno E, Azzi A. Novel 5' exon of scavenger receptor CD36 is expressed in cultured human vascular smooth muscle cells and atherosclerotic plaques. Arteriosclerosis, thrombosis, and vascular biology 2002; 22:412-417
149. Chao F, Blanchette-Mackie E, Chen Y, Dickens B, Berlin E, Amende L, Skarlatos S, Gamble W, Resau J, Mergner W, Kruth H. Characterization of two unique cholesterol-rich lipid particles isolated from human atherosclerotic lesions. The American journal of pathology 1990; 136:169-179
150. Kruth H. Localization of unesterified cholesterol in human atherosclerotic lesions. Demonstration of filipin-positive, oil-red-O-negative particles. The American journal of pathology 1984; 114:201-208
151. Minor LK, Rothblat GH, Glick JM. Triglyceride and cholesteryl ester hydrolysis in a cell culture model of smooth muscle foam cells. J Lipid Res 1989; 30:189-197
152. Minor LK, Mahlberg FH, Jerome WG, Lewis JC, Rothblat GH, Glick JM. Lysosomal hydrolysis of lipids in a cell culture model of smooth muscle foam cells. Exp Molec Pathol 1991; 54:159-171
153. Jerome WG, Minor LK, Glick JM, Rothblat GH, Lewis JC. Lysosomal lipid accumulation in vascular smooth muscle cells. Exp Molec Pathol 1991; 54:144-158
154. Allahverdian S, Chehroudi AC, McManus BM, Abraham T, Francis GA. Contribution of intimal smooth muscle cells to cholesterol accumulation and macrophage-like cells in human atherosclerosis. Circulation 2014; 129:1551-1559
155. Li Q, Komaba A, Yokoyama S. Cholesterol is poorly available for free apolipoprotein-mediated cellular lipid efflux from smooth muscle cells. Biochemistry 1993; 32:4597-4603
156. Goldfischer S, Schiller B, Wolinsky H. Lipid accumulation in smooth muscle cell lysosomes in primate atherosclerosis. The American journal of pathology 1975; 78:497-504
157. Haley N, Fowler SD, deDuve C. Lysosomal acid cholesteryl esterase activity in normal and lipid-laden aortic cells. J Lipid Res 1980; 21:961-969

158. Jerome WG. Advanced atherosclerotic foam cell formation has features of an acquired lysosomal storage disorder. Rejuvenation research 2006; 9:245-255
159. Hoppe G, O'Neil J, Hoff HF. Inactivation of lysosomal proteases by oxidized low density lipoprotein is partially responsible for its poor degradation by mouse peritoneal macrophages. J Clin Invest 1994; 94:1506-1512
160. Cox BE, Griffin EE, Ullery JC, Jerome WG. Effects of cellular cholesterol loading on macrophage foam cell lysosome acidification. J Lipid Res 2007; 48:1012-1021
161. Yancey PG, Jerome WG. Lysosomal cholesterol derived from mildly oxidized low density lipoprotein is resistant to efflux. J Lipid Res 2001; 42:317-327
162. Griffin EE, Ullery JC, Cox BE, Jerome WG. Aggregated LDL and lipid dispersions induce lysosomal cholesteryl ester accumulation in macrophage foam cells. J Lipid Res 2005; 46:2052-2060
163. Yancey PG, Jerome WG. Lysosomal sequestration of free and esterified cholesterol from oxidized low density lipoprotein in macrophages of different species. J Lipid Res 1998; 39:1349-1361
164. Suzuki M, Becker L, Pritchard DK, Gharib SA, Wijsman EM, Bammler TK, Beyer RP, Vaisar T, Oram JF, Heinecke JW. Cholesterol accumulation regulates expression of macrophage proteins implicated in proteolysis and complement activation. Arteriosclerosis, thrombosis, and vascular biology 2012; 32:2910-2918
165. Heusch G, Libby P, Gersh B, Yellon D, Bohm M, Lopaschuk G, Opie L. Cardiovascular remodelling in coronary artery disease and heart failure. Lancet 2014; 383:1933-1943
166. Alexander MR, Moehle CW, Johnson JL, Yang Z, Lee JK, Jackson CL, Owens GK. Genetic inactivation of IL-1 signaling enhances atherosclerotic plaque instability and reduces outward vessel remodeling in advanced atherosclerosis in mice. J Clin Invest 2012; 122:70-79
167. Alexander MR, Owens GK. Epigenetic control of smooth muscle cell differentiation and phenotypic switching in vascular development and disease. Annual review of physiology 2012; 74:13-40
168. Virmani R, Burke AP, Kolodgie FD, Farb A. Vulnerable plaque: the pathology of unstable coronary lesions. Journal of interventional cardiology 2002; 15:439-446
169. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. The New England journal of medicine 2013; 368:2004-2013
170. Stegemann C, Drozdov I, Shalhoub J, Humphries J, Ladroue C, Didangelos A, Baumert M, Allen M, Davies AH, Monaco C, Smith A, Xu Q, Mayr M. Comparative lipidomics profiling of human atherosclerotic plaques. Circulation Cardiovascular genetics 2011; 4:232-242
171. Tabas I. Macrophage death and defective inflammation resolution in atherosclerosis. Nature reviews Immunology 2010; 10:36-46
172. Linton MF, Babaev VR, Huang J, Linton EF, Tao H, Yancey PG. Macrophage Apoptosis and Efferocytosis in the Pathogenesis of Atherosclerosis. Circ J 2016; 80:2259-2268
173. Thorp E, Tabas I. Mechanisms and consequences of efferocytosis in advanced atherosclerosis. Journal of leukocyte biology 2009; 86:1089-1095
174. Tabas I. The role of endoplasmic reticulum stress in the progression of atherosclerosis. Circulation research 2010; 107:839-850

175. Myoishi M, Hao H, Minamino T, Watanabe K, Nishihira K, Hatakeyama K, Asada Y, Okada K, Ishibashi-Ueda H, Gabbiani G, Bochaton-Piallat ML, Mochizuki N, Kitakaze M. Increased endoplasmic reticulum stress in atherosclerotic plaques associated with acute coronary syndrome. Circulation 2007; 116:1226-1233
176. Han S, Liang CP, DeVries-Seimon T, Ranalletta M, Welch CL, Collins-Fletcher K, Accili D, Tabas I, Tall AR. Macrophage insulin receptor deficiency increases ER stress-induced apoptosis and necrotic core formation in advanced atherosclerotic lesions. Cell Metab 2006; 3:257-266
177. Erbay E, Babaev VR, Mayers JR, Makowski L, Charles KN, Snitow ME, Fazio S, Wiest MM, Watkins SM, Linton MF, Hotamisligil GS. Reducing endoplasmic reticulum stress through a macrophage lipid chaperone alleviates atherosclerosis. Nature medicine 2009; 15:1383-1391
178. Seimon TA, Nadolski MJ, Liao X, Magallon J, Nguyen M, Feric NT, Koschinsky ML, Harkewicz R, Witztum JL, Tsimikas S, Golenbock D, Moore KJ, Tabas I. Atherogenic lipids and lipoproteins trigger CD36-TLR2-dependent apoptosis in macrophages undergoing endoplasmic reticulum stress. Cell Metab 2010; 12:467-482
179. Yvan-Charvet L, Pagler TA, Seimon TA, Thorp E, Welch CL, Witztum JL, Tabas I, Tall AR. ABCA1 and ABCG1 protect against oxidative stress-induced macrophage apoptosis during efferocytosis. Circulation research 2010; 106:1861-1869
180. Ben J, Zhang Y, Zhou R, Zhang H, Zhu X, Li X, Zhang H, Li N, Zhou X, Bai H, Yang Q, Li D, Xu Y, Chen Q. Major vault protein regulates class A scavenger receptor-mediated tumor necrosis factor-alpha synthesis and apoptosis in macrophages. The Journal of biological chemistry 2013; 288:20076-20084
181. Devries-Seimon T, Li Y, Yao PM, Stone E, Wang Y, Davis RJ, Flavell R, Tabas I. Cholesterol-induced macrophage apoptosis requires ER stress pathways and engagement of the type A scavenger receptor. J Cell Biol 2005; 171:61-73
182. Schrijvers DM, De Meyer GR, Kockx MM, Herman AG, Martinet W. Phagocytosis of apoptotic cells by macrophages is impaired in atherosclerosis. Arteriosclerosis, thrombosis, and vascular biology 2005; 25:1256-1261
183. Thorp E, Cui D, Schrijvers DM, Kuriakose G, Tabas I. Mertk receptor mutation reduces efferocytosis efficiency and promotes apoptotic cell accumulation and plaque necrosis in atherosclerotic lesions of apoe-/- mice. Arteriosclerosis, thrombosis, and vascular biology 2008; 28:1421-1428
184. Yancey PG, Ding Y, Fan D, Blakemore JL, Zhang Y, Ding L, Zhang J, Linton MF, Fazio S. Low-density lipoprotein receptor-related protein 1 prevents early atherosclerosis by limiting lesional apoptosis and inflammatory Ly-6Chigh monocytosis: evidence that the effects are not apolipoprotein E dependent. Circulation 2011; 124:454-464
185. Tao H, Yancey PG, Babaev VR, Blakemore JL, Zhang Y, Ding L, Fazio S, Linton MF. Macrophage SR-BI mediates efferocytosis via Src/PI3K/Rac1 signaling and reduces atherosclerotic lesion necrosis. J Lipid Res 2015; 56:1449-1460
186. Wu Y, Tibrewal N, Birge RB. Phosphatidylserine recognition by phagocytes: a view to a kill. Trends in cell biology 2006; 16:189-197

187. Yancey PG, Blakemore J, Ding L, Fan D, Overton CD, Zhang Y, Linton MF, Fazio S. Macrophage LRP-1 controls plaque cellularity by regulating efferocytosis and Akt activation. Arteriosclerosis, thrombosis, and vascular biology 2010; 30:787-795
188. Grainger DJ, Reckless J, McKilligin E. Apolipoprotein E modulates clearance of apoptotic bodies in vitro and in vivo, resulting in a systemic proinflammatory state in apolipoprotein E-deficient mice. J Immunol 2004; 173:6366-6375
189. Thorp E, Subramanian M, Tabas I. The role of macrophages and dendritic cells in the clearance of apoptotic cells in advanced atherosclerosis. European journal of immunology 2011; 41:2515-2518
190. Yurdagul A, Jr., Doran AC, Cai B, Fredman G, Tabas IA. Mechanisms and Consequences of Defective Efferocytosis in Atherosclerosis. Front Cardiovasc Med 2017; 4:86
191. Cash JG, Kuhel DG, Basford JE, Jaeschke A, Chatterjee TK, Weintraub NL, Hui DY. Apolipoprotein E4 impairs macrophage efferocytosis and potentiates apoptosis by accelerating endoplasmic reticulum stress. The Journal of biological chemistry 2012; 287:27876-27884
192. Li Y, Gerbod-Giannone MC, Seitz H, Cui D, Thorp E, Tall AR, Matsushima GK, Tabas I. Cholesterol-induced apoptotic macrophages elicit an inflammatory response in phagocytes, which is partially attenuated by the Mer receptor. The Journal of biological chemistry 2006; 281:6707-6717
193. Kojima Y, Volkmer JP, McKenna K, Civelek M, Lusis AJ, Miller CL, Direnzo D, Nanda V, Ye J, Connolly AJ, Schadt EE, Quertermous T, Betancur P, Maegdefessel L, Matic LP, Hedin U, Weissman IL, Leeper NJ. CD47-blocking antibodies restore phagocytosis and prevent atherosclerosis. Nature 2016; 536:86-90
194. Kojima Y, Downing K, Kundu R, Miller C, Dewey F, Lancero H, Raaz U, Perisic L, Hedin U, Schadt E, Maegdefessel L, Quertermous T, Leeper NJ. Cyclin-dependent kinase inhibitor 2B regulates efferocytosis and atherosclerosis. J Clin Invest 2014; 124:1083-1097
195. Geng YJ, Henderson LE, Levesque EB, Muszynski M, Libby P. Fas is expressed in human atherosclerotic intima and promotes apoptosis of cytokine-primed human vascular smooth muscle cells. Arteriosclerosis, thrombosis, and vascular biology 1997; 17:2200-2208
196. Boyle JJ, Weissberg PL, Bennett MR. Tumor necrosis factor-alpha promotes macrophage-induced vascular smooth muscle cell apoptosis by direct and autocrine mechanisms. Arteriosclerosis, thrombosis, and vascular biology 2003; 23:1553-1558
197. Lee JY, Jung GY, Heo HJ, Yun MR, Park JY, Bae SS, Hong KW, Lee WS, Kim CD. 4-Hydroxynonenal induces vascular smooth muscle cell apoptosis through mitochondrial generation of reactive oxygen species. Toxicology letters 2006; 166:212-221
198. Fruhwirth GO, Moumtzi A, Loidl A, Ingolic E, Hermetter A. The oxidized phospholipids POVPC and PGPC inhibit growth and induce apoptosis in vascular smooth muscle cells. Biochimica et biophysica acta 2006; 1761:1060-1069
199. Vengrenyuk Y, Nishi H, Long X, Ouimet M, Savji N, Martinez FO, Cassella CP, Moore KJ, Ramsey SA, Miano JM, Fisher EA. Cholesterol loading reprograms the microRNA-143/145-myocardin axis to convert aortic smooth muscle cells to a dysfunctional

macrophage-like phenotype. Arteriosclerosis, thrombosis, and vascular biology 2015; 35:535-546
200. Fadok VA, Bratton DL, Konowal A, Freed PW, Westcott JY, Henson PM. Macrophages that have ingested apoptotic cells in vitro inhibit proinflammatory cytokine production through autocrine/paracrine mechanisms involving TGF-beta, PGE2, and PAF. J Clin Invest 1998; 101:890-898
201. Quillard T, Araujo HA, Franck G, Tesmenitsky Y, Libby P. Matrix metalloproteinase-13 predominates over matrix metalloproteinase-8 as the functional interstitial collagenase in mouse atheromata. Arteriosclerosis, thrombosis, and vascular biology 2014; 34:1179-1186
202. Galis ZS, Sukhova GK, Kranzhofer R, Clark S, Libby P. Macrophage foam cells from experimental atheroma constitutively produce matrix-degrading proteinases. Proceedings of the National Academy of Sciences of the United States of America 1995; 92:402-406
203. Schneider F, Sukhova GK, Aikawa M, Canner J, Gerdes N, Tang SM, Shi GP, Apte SS, Libby P. Matrix-metalloproteinase-14 deficiency in bone-marrow-derived cells promotes collagen accumulation in mouse atherosclerotic plaques. Circulation 2008; 117:931-939
204. Liu J, Sukhova GK, Sun JS, Xu WH, Libby P, Shi GP. Lysosomal cysteine proteases in atherosclerosis. Arteriosclerosis, thrombosis, and vascular biology 2004; 24:1359-1366
205. Nofer JR, Junker R, Pulawski E, Fobker M, Levkau B, von Eckardstein A, Seedorf U, Assmann G, Walter M. High density lipoproteins induce cell cycle entry in vascular smooth muscle cells via mitogen activated protein kinase-dependent pathway. Thrombosis and haemostasis 2001; 85:730-735
206. Muller C, Salvayre R, Negre-Salvayre A, Vindis C. Oxidized LDLs trigger endoplasmic reticulum stress and autophagy: prevention by HDLs. Autophagy 2011; 7:541-543
207. Niculescu LS, Sanda GM, Sima AV. HDL inhibits endoplasmic reticulum stress by stimulating apoE and CETP secretion from lipid-loaded macrophages. Biochem Biophys Res Commun 2013; 434:173-178
208. Feig JE, Rong JX, Shamir R, Sanson M, Vengrenyuk Y, Liu J, Rayner K, Moore K, Garabedian M, Fisher EA. HDL promotes rapid atherosclerosis regression in mice and alters inflammatory properties of plaque monocyte-derived cells. Proceedings of the National Academy of Sciences of the United States of America 2011; 108:7166-7171
209. Fredman G, Tabas I. Boosting Inflammation Resolution in Atherosclerosis: The Next Frontier for Therapy. The American journal of pathology 2017; 187:1211-1221
210. Fredman G, Hellmann J, Proto JD, Kuriakose G, Colas RA, Dorweiler B, Connolly ES, Solomon R, Jones DM, Heyer EJ, Spite M, Tabas I. An imbalance between specialized pro-resolving lipid mediators and pro-inflammatory leukotrienes promotes instability of atherosclerotic plaques. Nature communications 2016; 7:12859
211. Rinne P, Guillamat-Prats R, Rami M, Bindila L, Ring L, Lyytikainen LP, Raitoharju E, Oksala N, Lehtimaki T, Weber C, van der Vorst EPC, Steffens S. Palmitoylethanolamide Promotes a Proresolving Macrophage Phenotype and Attenuates Atherosclerotic Plaque Formation. Arteriosclerosis, thrombosis, and vascular biology 2018; 38:2562-2575
212. Viola JR, Lemnitzer P, Jansen Y, Csaba G, Winter C, Neideck C, Silvestre-Roig C, Dittmar G, Doring Y, Drechsler M, Weber C, Zimmer R, Cenac N, Soehnlein O.

Resolving Lipid Mediators Maresin 1 and Resolvin D2 Prevent Atheroprogression in Mice. Circ Res 2016; 119:1030-1038
213. Fredman G, Kamaly N, Spolitu S, Milton J, Ghorpade D, Chiasson R, Kuriakose G, Perretti M, Farokzhad O, Tabas I. Targeted nanoparticles containing the proresolving peptide Ac2-26 protect against advanced atherosclerosis in hypercholesterolemic mice. Science translational medicine 2015; 7:275ra220
214. Kamaly N, Fredman G, Fojas JJ, Subramanian M, Choi WI, Zepeda K, Vilos C, Yu M, Gadde S, Wu J, Milton J, Carvalho Leitao R, Rosa Fernandes L, Hasan M, Gao H, Nguyen V, Harris J, Tabas I, Farokhzad OC. Targeted Interleukin-10 Nanotherapeutics Developed with a Microfluidic Chip Enhance Resolution of Inflammation in Advanced Atherosclerosis. ACS nano 2016; 10:5280-5292
215. Proto JD, Doran AC, Gusarova G, Yurdagul A, Jr., Sozen E, Subramanian M, Islam MN, Rymond CC, Du J, Hook J, Kuriakose G, Bhattacharya J, Tabas I. Regulatory T Cells Promote Macrophage Efferocytosis during Inflammation Resolution. Immunity 2018; 49:666-677 e666
216. Fazio S, Linton MF. Regulation and Clearance of Apoliprotein B-Containing Lipoproteins. In: Ballantyne CM, ed. Clinical Lipidology, a companion to Braunwald's Heart Disease. Vol Second Edition: Elsevier Saunders; 2015:11-24.
217. Anant S, Davidson NO. Identification and regulation of protein components of the apolipoprotein B mRNA editing enzyme. A complex event. Trends in cardiovascular medicine 2002; 12:311-317
218. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Bases of Inherited Disease. Vol II. 7th ed. New York: McGraw-Hill; 1995:1981-2030.
219. Raffai RL, Hasty AH, Wang Y, Mettler SE, Sanan DA, Linton MF, Fazio S, Weisgraber KH. Hepatocyte-derived ApoE is more effective than non-hepatocyte-derived ApoE in remnant lipoprotein clearance. Journal of Biological Chemistry 2003; 278:11670-11675
220. Anitschkow NNC, S. Ueber experimentelle Cholesterinsteatose und ihre Bedeutung fur die Entstehung einiger pathologischer Prozesse. Zentralbl Allg Pathol 1913; 24:1-9
221. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J, 3rd. Factors of risk in the development of coronary heart disease--six year follow-up experience. The Framingham Study. Annals of internal medicine 1961; 55:33-50
222. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356 222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). J Am Med Assoc 1986; 256:2823-2828
223. Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. Jama 1986; 256:2835-2838
224. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber RT. High density lipoprotein as a protective factor against coronary heart disease. The Framingham study. Am J Med 1977; 62:707-714
225. Keys A, Menotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R, Djordjevic BS, Dontas AS, Fidanza F, Keys MH, Kromhout D, Nedeljkovic S, Punsar S, Seccareccia F,

Toshima H. The diet and 15-year death rate in the Seven Countries Study. Am J Epidemiol 1986; 124:903-915
226. Steinberg D. In celebration of the 100th anniversary of the lipid hypothesis of atherosclerosis. J Lipid Res 2013; 54:2946-2949
227. Williams KJ, Tabas I. The response-to-retention hypothesis of early atherogenesis. Arteriosclerosis, thrombosis, and vascular biology 1995; 15:551-561
228. Camejo G, Lalaguna F, Lopez F, Starosta R. Characterization and properties of a lipoprotein-complexing proteoglycan from human aorta. Atherosclerosis 1980; 35:307-320
229. Iverius PH. The interaction between human plasma lipoproteins and connective tissue glycosaminoglycans. The Journal of biological chemistry 1972; 247:2607-2613
230. Fogelstrand P, Boren J. Retention of atherogenic lipoproteins in the artery wall and its role in atherogenesis. Nutrition, metabolism, and cardiovascular diseases : NMCD 2012; 22:1-7
231. Boren J, Olin K, Lee I, Chait A, Wight TN, Innerarity TL. Identification of the principal proteoglycan-binding site in LDL. A single-point mutation in apo-B100 severely affects proteoglycan interaction without affecting LDL receptor binding. J Clin Invest 1998; 101:2658-2664
232. Skalen K, Gustafsson M, Rydberg EK, Hulten LM, Wiklund O, Innerarity TL, Boren J. Subendothelial retention of atherogenic lipoproteins in early atherosclerosis. Nature 2002; 417:750-754
233. Flood C, Gustafsson M, Richardson PE, Harvey SC, Segrest JP, Boren J. Identification of the proteoglycan binding site in apolipoprotein B48. The Journal of biological chemistry 2002; 277:32228-32233
234. Flood C, Gustafsson M, Pitas RE, Arnaboldi L, Walzem RL, Boren J. Molecular mechanism for changes in proteoglycan binding on compositional changes of the core and the surface of low-density lipoprotein-containing human apolipoprotein B100. Arteriosclerosis, thrombosis, and vascular biology 2004; 24:564-570
235. Olivecrona G, Olivecrona T. Triglyceride lipases and atherosclerosis. Curr Opin Lipidol 1995; 6:291-305
236. Merkel M, Kako Y, Radner H, Cho IS, Ramasamy R, Brunzell JD, Goldberg IJ, Breslow JL. Catalytically inactive lipoprotein lipase expression in muscle of transgenic mice increases very low density lipoprotein uptake: direct evidence that lipoprotein lipase bridging occurs in vivo. Proceedings of the National Academy of Sciences of the United States of America 1998; 95:13841-13846
237. Babaev V, Fazio S, Gleaves L, Carter K, Semenkovich C, Linton M. Macrophage lipoprotein lipase promotes foam cell formation and atherosclerosis in vivo. J Clin Invest 1999; 103:1697-1705
238. Babaev V, Patel M, Semenkovich C, Fazio S, Linton M. Macrophage lipoprotein lipase promotes foam cell formation and atherosclerosis in low density lipoprotein receptor-deficient mice. The Journal of biological chemistry 2000; 275:26293-26299
239. Tabas I, Li Y, Brocia RW, Xu SW, Swenson TL, Williams KJ. Lipoprotein lipase and sphingomyelinase synergistically enhance the association of atherogenic lipoproteins with smooth muscle cells and extracellular matrix. A possible mechanism for low density

lipoprotein and lipoprotein(a) retention and macrophage foam cell formation. The Journal of biological chemistry 1993; 268:20419-20432
240. Devlin CM, Leventhal AR, Kuriakose G, Schuchman EH, Williams KJ, Tabas I. Acid sphingomyelinase promotes lipoprotein retention within early atheromata and accelerates lesion progression. Arteriosclerosis, thrombosis, and vascular biology 2008; 28:1723-1730
241. Oorni K, Hakala JK, Annila A, Ala-Korpela M, Kovanen PT. Sphingomyelinase induces aggregation and fusion, but phospholipase A2 only aggregation, of low density lipoprotein (LDL) particles. Two distinct mechanisms leading to increased binding strength of LDL to human aortic proteoglycans. The Journal of biological chemistry 1998; 273:29127-29134
242. Watson AD, Leitinger N, Navab M, Faull KF, Horkko S, Witztum JL, Palinski W, Schwenke D, Salomon RG, Sha W, Subbanagounder G, Fogelman AM, Berliner JA. Structural identification by mass spectrometry of oxidized phospholipids in minimally oxidized low density lipoprotein that induce monocyte/endothelial interactions and evidence for their presence in vivo. The Journal of biological chemistry 1997; 272:13597-13607
243. Davies SS, Pontsler AV, Marathe GK, Harrison KA, Murphy RC, Hinshaw JC, Prestwich GD, Hilaire AS, Prescott SM, Zimmerman GA, McIntyre TM. Oxidized Alkyl Phospholipids Are Specific, High Affinity Peroxisome Proliferator-activated Receptor Î³ Ligands and Agonists. The Journal of biological chemistry 2001; 276:16015-16023
244. Subbanagounder G, Wong JW, Lee H, Faull KF, Miller E, Witztum JL, Berliner JA. Epoxyisoprostane and epoxycyclopentenone phospholipids regulate monocyte chemotactic protein-1 and interleukin-8 synthesis. Formation of these oxidized phospholipids in response to interleukin-1beta. The Journal of biological chemistry 2002; 277:7271-7281
245. Morrow JD, Awad JA, Boss HJ, Blair IA, Roberts LJ, 2nd. Non-cyclooxygenase-derived prostanoids (F2-isoprostanes) are formed in situ on phospholipids. Proceedings of the National Academy of Sciences of the United States of America 1992; 89:10721-10725
246. Palinski W, Rosenfeld ME, Yla-Herttuala S, Gurtner GC, Socher SS, Butler SW, Parthasarathy S, Carew TE, Steinberg D, Witztum JL. Low density lipoprotein undergoes oxidative modification in vivo. Proceedings of the National Academy of Sciences of the United States of America 1989; 86:1372-1376
247. Brame CJ, Salomon RG, Morrow JD, Roberts LJ, 2nd. Identification of extremely reactive gamma-ketoaldehydes (isolevuglandins) as products of the isoprostane pathway and characterization of their lysyl protein adducts. The Journal of biological chemistry 1999; 274:13139-13146
248. Fogelman AM, Shechter I, Seager J, Hokom M, Child JS, Edwards PA. Malondialdehyde alteration of low density lipoproteins leads to cholesteryl ester accumulation in human monocyte-macrophages. Proc Natl Acad Sci USA 1980; 77:2214-2218
249. Bergmark C, Dewan A, Orsoni A, Merki E, Miller ER, Shin MJ, Binder CJ, Horkko S, Krauss RM, Chapman MJ, Witztum JL, Tsimikas S. A novel function of lipoprotein [a] as a preferential carrier of oxidized phospholipids in human plasma. J Lipid Res 2008; 49:2230-2239

250. Tsimikas S, Bergmark C, Beyer RW, Patel R, Pattison J, Miller E, Juliano J, Witztum JL. Temporal increases in plasma markers of oxidized low-density lipoprotein strongly reflect the presence of acute coronary syndromes. J Am Coll Cardiol 2003; 41:360-370
251. Taleb A, Witztum JL, Tsimikas S. Oxidized phospholipids on apoB-100-containing lipoproteins: a biomarker predicting cardiovascular disease and cardiovascular events. Biomarkers in medicine 2011; 5:673-694
252. Proudfoot JM, Barden AE, Loke WM, Croft KD, Puddey IB, Mori TA. HDL is the major lipoprotein carrier of plasma F2-isoprostanes. J Lipid Res 2009; 50:716-722
253. Tsimikas S, Witztum JL, Miller ER, Sasiela WJ, Szarek M, Olsson AG, Schwartz GG, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study I. High-dose atorvastatin reduces total plasma levels of oxidized phospholipids and immune complexes present on apolipoprotein B-100 in patients with acute coronary syndromes in the MIRACL trial. Circulation 2004; 110:1406-1412
254. Rodenburg J, Vissers MN, Wiegman A, Miller ER, Ridker PM, Witztum JL, Kastelein JJ, Tsimikas S. Oxidized low-density lipoprotein in children with familial hypercholesterolemia and unaffected siblings: effect of pravastatin. J Am Coll Cardiol 2006; 47:1803-1810
255. Tsimikas S, Kiechl S, Willeit J, Mayr M, Miller ER, Kronenberg F, Xu Q, Bergmark C, Weger S, Oberhollenzer F, Witztum JL. Oxidized phospholipids predict the presence and progression of carotid and femoral atherosclerosis and symptomatic cardiovascular disease: five-year prospective results from the Bruneck study. J Am Coll Cardiol 2006; 47:2219-2228
256. Tanaga K, Bujo H, Inoue M, Mikami K, Kotani K, Takahashi K, Kanno T, Saito Y. Increased circulating malondialdehyde-modified LDL levels in patients with coronary artery diseases and their association with peak sizes of LDL particles. Arteriosclerosis, thrombosis, and vascular biology 2002; 22:662-666
257. Wang J, Hu B, Meng Y, Zhang C, Li K, Hui C. The level of malondialdehyde-modified LDL and LDL immune complexes in patients with rheumatoid arthritis. Clin Biochem 2009; 42:1352-1357
258. Kondo A, Morita H, Nakamura H, Kotani K, Kobori K, Ito S, Manabe M, Saito K, Kanno T, Maekawa M. Influence of fibrate treatment on malondialdehyde-modified LDL concentration. Clin Chim Acta 2004; 339:97-103
259. Esterbauer H, Rotheneder M, Striegel G, Waeg G, Ashy A, Sattler W, Jurgens G. Vitamin E and other lipophilic antioxidants protect LDL against oxidation. Fat Sci Technol 1989; 8:316-324
260. Hussein O, Rosenblat M, Refael G, Aviram M. Dietary selenium increases cellular glutathione peroxidase activity and reduces the enhanced susceptibility to lipid peroxidation of plasma and low-density lipoprotein in kidney transplant recipients. Transplantation 1997; 63:679-685
261. Guo Z, Van Remmen H, Yang H, Chen X, Mele J, Vijg J, Epstein CJ, Ho YS, Richardson A. Changes in expression of antioxidant enzymes affect cell-mediated LDL oxidation and oxidized LDL-induced apoptosis in mouse aortic cells. Arteriosclerosis, thrombosis, and vascular biology 2001; 21:1131-1138

262. Steinbrecher UP, Pritchard PH. Hydrolysis of phosphatidylcholine during LDL oxidation is mediated by platelet-activating factor acetylhydrolase. J Lipid Res 1989; 30:305-315
263. Tjoelker LW, Wilder C, Eberhardt C, Stafforini DM, Dietsch G, Schimpf B, Hooper S, Le Trong H, Cousens LS, Zimmerman GA, Yamada Y, McIntyre TM, Prescott SM, Gray PW. Anti-inflammatory properties of a platelet-activating factor acetylhydrolase. Nature 1995; 374:549-553
264. Watson AD, Berliner JA, Hama SY, La Du BN, Faull KF, Fogelman AM, Navab M. Protective effect of high density lipoprotein associated paraoxonase. Inhibition of the biological activity of minimally oxidized low density lipoprotein. J Clin Invest 1995; 96:2882-2891
265. Durrington PN, Mackness B, Mackness MI. Paraoxonase and atherosclerosis. Arteriosclerosis, thrombosis, and vascular biology 2001; 21:473-480
266. Hazen SL, Heinecke JW. 3-Chlorotyrosine, a specific marker of myeloperoxidase-catalyzed oxidation, is markedly elevated in low density lipoprotein isolated from human atherosclerotic intima. J Clin Invest 1997; 99:2075-2081
267. George J, Struthers AD. Role of urate, xanthine oxidase and the effects of allopurinol in vascular oxidative stress. Vascular health and risk management 2009; 5:265-272
268. Aviram M, Rosenblat M, Etzioni A, Levy R. Activation of NADPH oxidase required for macrophage-mediated oxidation of low-density lipoprotein. Metabolism: clinical and experimental 1996; 45:1069-1079
269. Miyoshi T, Li Y, Shih DM, Wang X, Laubach VE, Matsumoto AH, Helm GA, Lusis AJ, Shi W. Deficiency of inducible NO synthase reduces advanced but not early atherosclerosis in apolipoprotein E-deficient mice. Life sciences 2006; 79:525-531
270. Upston JM, Neuzil J, Stocker R. Oxidation of LDL by recombinant human 15-lipoxygenase: evidence for alpha-tocopherol-dependent oxidation of esterified core and surface lipids. J Lipid Res 1996; 37:2650-2661
271. Ezaki M, Witztum JL, Steinberg D. Lipoperoxides in LDL incubated with fibroblasts that overexpress 15-lipoxygenase. J Lipid Res 1995; 36:1996-2004
272. Baldus S, Eiserich JP, Mani A, Castro L, Figueroa M, Chumley P, Ma W, Tousson A, White CR, Bullard DC, Brennan ML, Lusis AJ, Moore KP, Freeman BA. Endothelial transcytosis of myeloperoxidase confers specificity to vascular ECM proteins as targets of tyrosine nitration. J Clin Invest 2001; 108:1759-1770
273. Pignatelli P, Loffredo L, Martino F, Catasca E, Carnevale R, Zanoni C, Del Ben M, Antonini R, Basili S, Violi F. Myeloperoxidase overexpression in children with hypercholesterolemia. Atherosclerosis 2009; 205:239-243
274. Puntoni M, Sbrana F, Bigazzi F, Minichilli F, Ferdeghini E, Sampietro T. Myeloperoxidase modulation by LDL apheresis in familial hypercholesterolemia. Lipids in health and disease 2011; 10:185
275. Karakas M, Koenig W, Zierer A, Herder C, Rottbauer W, Baumert J, Meisinger C, Thorand B. Myeloperoxidase is associated with incident coronary heart disease independently of traditional risk factors: results from the MONICA/KORA Augsburg study. Journal of internal medicine 2012; 271:43-50
276. Ferrante G, Nakano M, Prati F, Niccoli G, Mallus MT, Ramazzotti V, Montone RA, Kolodgie FD, Virmani R, Crea F. High levels of systemic myeloperoxidase are

associated with coronary plaque erosion in patients with acute coronary syndromes: a clinicopathological study. Circulation 2010; 122:2505-2513
277. Michowitz Y, Kisil S, Guzner-Gur H, Rubinstein A, Wexler D, Sheps D, Keren G, George J. Usefulness of serum myeloperoxidase in prediction of mortality in patients with severe heart failure. The Israel Medical Association journal : IMAJ 2008; 10:884-888
278. Dolley G, Lamarche B, Despres JP, Bouchard C, Perusse L, Vohl MC. Myeloperoxidase gene sequence variations are associated with low-density-lipoprotein characteristics. Journal of human genetics 2008; 53:439-446
279. Nikpoor B, Turecki G, Fournier C, Theroux P, Rouleau GA. A functional myeloperoxidase polymorphic variant is associated with coronary artery disease in French-Canadians. American heart journal 2001; 142:336-339
280. Podrez EA, Poliakov E, Shen Z, Zhang R, Deng Y, Sun M, Finton PJ, Shan L, Gugiu B, Fox PL, Hoff HF, Salomon RG, Hazen SL. Identification of a novel family of oxidized phospholipids that serve as ligands for the macrophage scavenger receptor CD36. The Journal of biological chemistry 2002; 277:38503-38516
281. Sokolov AV, Chekanov AV, Kostevich VA, Aksenov DV, Vasilyev VB, Panasenko OM. Revealing binding sites for myeloperoxidase on the surface of human low density lipoproteins. Chem Phys Lipids 2011; 164:49-53
282. Huang Y, Wu Z, Riwanto M, Gao S, Levison BS, Gu X, Fu X, Wagner MA, Besler C, Gerstenecker G, Zhang R, Li XM, DiDonato AJ, Gogonea V, Tang WH, Smith JD, Plow EF, Fox PL, Shih DM, Lusis AJ, Fisher EA, DiDonato JA, Landmesser U, Hazen SL. Myeloperoxidase, paraoxonase-1, and HDL form a functional ternary complex. J Clin Invest 2013; 123:3815-3828
283. May-Zhang LS, Yermalitsky V, Huang J, Pleasent T, Borja MS, Oda MN, Jerome WG, Yancey PG, Linton MF, Davies SS. Modification by isolevuglandins, highly reactive gamma-ketoaldehydes, deleteriously alters high-density lipoprotein structure and function. J Biol Chem 2018; 293:9176-9187
284. Guo L, Chen Z, Amarnath V, Davies SS. Identification of novel bioactive aldehyde-modified phosphatidylethanolamines formed by lipid peroxidation. Free Radic Biol Med 2012; 53:1226-1238
285. Shao B, Pennathur S, Pagani I, Oda MN, Witztum JL, Oram JF, Heinecke JW. Modifying apolipoprotein A-I by malondialdehyde, but not by an array of other reactive carbonyls, blocks cholesterol efflux by the ABCA1 pathway. J Biol Chem 2010; 285:18473-18484
286. Noguchi N, Nakano K, Aratani Y, Koyama H, Kodama T, Niki E. Role of myeloperoxidase in the neutrophil-induced oxidation of low density lipoprotein as studied by myeloperoxidase-knockout mouse. Journal of biochemistry 2000; 127:971-976
287. Rausch PG, Moore TG. Granule enzymes of polymorphonuclear neutrophils: A phylogenetic comparison. Blood 1975; 46:913-919
288. McMillen TS, Heinecke JW, LeBoeuf RC. Expression of human myeloperoxidase by macrophages promotes atherosclerosis in mice. Circulation 2005; 111:2798-2804
289. Brennan ML, Anderson MM, Shih DM, Qu XD, Wang X, Mehta AC, Lim LL, Shi W, Hazen SL, Jacob JS, Crowley JR, Heinecke JW, Lusis AJ. Increased atherosclerosis in myeloperoxidase-deficient mice. J Clin Invest 2001; 107:419-430

290. Liu C, Desikan R, Ying Z, Gushchina L, Kampfrath T, Deiuliis J, Wang A, Xu X, Zhong J, Rao X, Sun Q, Maiseyeu A, Parthasarathy S, Rajagopalan S. Effects of a novel pharmacologic inhibitor of myeloperoxidase in a mouse atherosclerosis model. PloS one 2012; 7:e50767
291. Cyrus T, Witztum JL, Rader DJ, Tangirala R, Fazio S, Linton MF, Funk CD. Disruption of the 12/15-lipoxygenase gene diminishes atherosclerosis in apo E-deficient mice [see comments]. Journal of Clinical Investigation 1999; 103:1597-1604
292. Assimes TL, Knowles JW, Priest JR, Basu A, Borchert A, Volcik KA, Grove ML, Tabor HK, Southwick A, Tabibiazar R, Sidney S, Boerwinkle E, Go AS, Iribarren C, Hlatky MA, Fortmann SP, Myers RM, Kuhn H, Risch N, Quertermous T. A near null variant of 12/15-LOX encoded by a novel SNP in ALOX15 and the risk of coronary artery disease. Atherosclerosis 2008; 198:136-144
293. McGeachie M, Ramoni RL, Mychaleckyj JC, Furie KL, Dreyfuss JM, Liu Y, Herrington D, Guo X, Lima JA, Post W, Rotter JI, Rich S, Sale M, Ramoni MF. Integrative predictive model of coronary artery calcification in atherosclerosis. Circulation 2009; 120:2448-2454
294. Burdon KP, Rudock ME, Lehtinen AB, Langefeld CD, Bowden DW, Register TC, Liu Y, Freedman BI, Carr JJ, Hedrick CC, Rich SS. Human lipoxygenase pathway gene variation and association with markers of subclinical atherosclerosis in the diabetes heart study. Mediators of inflammation 2010; 2010:170153
295. Jurgens G, Hoff HF, Chisolm GM, 3rd, Esterbauer H. Modification of human serum low density lipoprotein by oxidation--characterization and pathophysiological implications. Chemistry and physics of lipids 1987; 45:315-336
296. Greaves DR, Gough PJ, Gordon S. Recent progress in defining the role of scavenger receptors in lipid transport, atherosclerosis and host defence. Current opinion in lipidology 1998; 9:425-432
297. van Berkel TJ, Fluiter K, van Velzen AG, Vogelezang CJ, Ziere GJ. LDL receptor-independent and -dependent uptake of lipoproteins. Atherosclerosis 1995; 118 Suppl:S43-50
298. Goldstein JL, Ho YK, Basu SK, Brown MS. Binding site on macrophages that mediates uptake and degradation of acetylated low density lipoprotein, producing massive cholesterol deposition. Proc Natl Acad Sci USA 1979; 76:333-337
299. Brown MS, Goldstein JL. Receptor-mediated endocytosis: insights from the lipoprotein receptor system. Proc Natl Acad Sci USA 1979; 76:3330–3337
300. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. Science 1986; 232:34-47
301. Linton MF, Fazio S. Macrophages, inflammation, and atherosclerosis. International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity 2003; 27:S35-40
302. Greig FH, Kennedy S, Spickett CM. Physiological effects of oxidized phospholipids and their cellular signaling mechanisms in inflammation. Free Radic Biol Med 2012; 52:266-280

303. Maiolino G, Rossitto G, Caielli P, Bisogni V, Rossi GP, Calo LA. The role of oxidized low-density lipoproteins in atherosclerosis: the myths and the facts. Mediators of inflammation 2013; 2013:714653
304. Miller YI, Chang MK, Binder CJ, Shaw PX, Witztum JL. Oxidized low density lipoprotein and innate immune receptors. Current opinion in lipidology 2003; 14:437-445
305. Takei A, Huang Y, Lopes-Virella MF. Expression of adhesion molecules by human endothelial cells exposed to oxidized low density lipoprotein. Influences of degree of oxidation and location of oxidized LDL. Atherosclerosis 2001; 154:79-86
306. Vielma SA, Mironova M, Ku JR, Lopes-Virella MF. Oxidized LDL further enhances expression of adhesion molecules in Chlamydophila pneumoniae-infected endothelial cells. J Lipid Res 2004; 45:873-880
307. Khan BV, Parthasarathy SS, Alexander RW, Medford RM. Modified low density lipoprotein and its constituents augment cytokine-activated vascular cell adhesion molecule-1 gene expression in human vascular endothelial cells. J Clin Invest 1995; 95:1262-1270
308. Leitinger N, Tyner TR, Oslund L, Rizza C, Subbanagounder G, Lee H, Shih PT, Mackman N, Tigyi G, Territo MC, Berliner JA, Vora DK. Structurally similar oxidized phospholipids differentially regulate endothelial binding of monocytes and neutrophils. Proceedings of the National Academy of Sciences of the United States of America 1999; 96:12010-12015
309. Vora DK, Fang ZT, Liva SM, Tyner TR, Parhami F, Watson AD, Drake TA, Territo MC, Berliner JA. Induction of P-selectin by oxidized lipoproteins. Separate effects on synthesis and surface expression. Circulation research 1997; 80:810-818
310. Berliner JA, Schwartz DS, Territo MC, Andalibi A, Almada L, Lusis AJ, Quismorio D, Fang ZP, Fogelman AM. Induction of chemotactic cytokines by minimally oxidized LDL. Adv Exp Med Biol 1993; 351:13-18
311. Parhami F, Fang ZT, Fogelman AM, Andalibi A, Territo MC, Berliner JA. Minimally modified low density lipoprotein-induced inflammatory responses in endothelial cells are mediated by cyclic adenosine monophosphate. J Clin Invest 1993; 92:471-478
312. Liu A, Ming JY, Fiskesund R, Ninio E, Karabina SA, Bergmark C, Frostegard AG, Frostegard J. Induction of dendritic cell-mediated T-cell activation by modified but not native low-density lipoprotein in humans and inhibition by annexin a5: involvement of heat shock proteins. Arteriosclerosis, thrombosis, and vascular biology 2015; 35:197-205
313. Horkko S, Binder CJ, Shaw PX, Chang MK, Silverman G, Palinski W, Witztum JL. Immunological responses to oxidized LDL. Free Radic Biol Med 2000; 28:1771-1779
314. Huang YH, Ronnelid J, Frostegard J. Oxidized LDL induces enhanced antibody formation and MHC class II-dependent IFN-gamma production in lymphocytes from healthy individuals. Arteriosclerosis, thrombosis, and vascular biology 1995; 15:1577-1583
315. Oinuma T, Yamada T, Sakurai I. Effects of copper-zinc type superoxide dismutase on the proliferation and migration of cultured vascular smooth muscle cells induced by oxidized low density lipoprotein. Journal of atherosclerosis and thrombosis 1997; 4:79-84

316. Liu J, Ren Y, Kang L, Zhang L. Oxidized low-density lipoprotein increases the proliferation and migration of human coronary artery smooth muscle cells through the upregulation of osteopontin. International journal of molecular medicine 2014; 33:1341-1347
317. Cherepanova OA, Pidkovka NA, Sarmento OF, Yoshida T, Gan Q, Adiguzel E, Bendeck MP, Berliner J, Leitinger N, Owens GK. Oxidized phospholipids induce type VIII collagen expression and vascular smooth muscle cell migration. Circulation research 2009; 104:609-618
318. Kiyan Y, Tkachuk S, Hilfiker-Kleiner D, Haller H, Fuhrman B, Dumler I. oxLDL induces inflammatory responses in vascular smooth muscle cells via urokinase receptor association with CD36 and TLR4. J Mol Cell Cardiol 2014; 66:72-82
319. Jovinge S, Ares MP, Kallin B, Nilsson J. Human monocytes/macrophages release TNF-alpha in response to Ox-LDL. Arteriosclerosis, thrombosis, and vascular biology 1996; 16:1573-1579
320. Frostegard J, Huang YH, Ronnelid J, Schafer-Elinder L. Platelet-activating factor and oxidized LDL induce immune activation by a common mechanism. Arteriosclerosis, thrombosis, and vascular biology 1997; 17:963-968
321. Terkeltaub R, Banka CL, Solan J, Santoro D, Brand K, Curtiss LK. Oxidized LDL induces monocytic cell expression of interleukin-8, a chemokine with T-lymphocyte chemotactic activity. Arterioscler Thromb 1994; 14:47-53
322. Wang GP, Deng ZD, Ni J, Qu ZL. Oxidized low density lipoprotein and very low density lipoprotein enhance expression of monocyte chemoattractant protein-1 in rabbit peritoneal exudate macrophages. Atherosclerosis 1997; 133:31-36
323. Seo JW, Yang EJ, Yoo KH, Choi IH. Macrophage Differentiation from Monocytes Is Influenced by the Lipid Oxidation Degree of Low Density Lipoprotein. Mediators of inflammation 2015; 2015:235797
324. Sedgwick JB, Hwang YS, Gerbyshak HA, Kita H, Busse WW. Oxidized low-density lipoprotein activates migration and degranulation of human granulocytes. Am J Respir Cell Mol Biol 2003; 29:702-709
325. Hashimoto K, Kataoka N, Nakamura E, Tsujioka K, Kajiya F. Oxidized LDL specifically promotes the initiation of monocyte invasion during transendothelial migration with upregulated PECAM-1 and downregulated VE-cadherin on endothelial junctions. Atherosclerosis 2007; 194:e9-17
326. Ishikawa K, Navab M, Leitinger N, Fogelman AM, Lusis AJ. Induction of heme oxygenase-1 inhibits the monocyte transmigration induced by mildly oxidized LDL. J Clin Invest 1997; 100:1209-1216
327. Han KH, Hong KH, Ko J, Rhee KS, Hong MK, Kim JJ, Kim YH, Park SJ. Lysophosphatidylcholine up-regulates CXCR4 chemokine receptor expression in human CD4 T cells. Journal of leukocyte biology 2004; 76:195-202
328. Ramkhelawon B, Yang Y, van Gils JM, Hewing B, Rayner KJ, Parathath S, Guo L, Oldebeken S, Feig JL, Fisher EA, Moore KJ. Hypoxia induces netrin-1 and Unc5b in atherosclerotic plaques: mechanism for macrophage retention and survival. Arteriosclerosis, thrombosis, and vascular biology 2013; 33:1180-1188

329. Baird SK, Hampton MB, Gieseg SP. Oxidized LDL triggers phosphatidylserine exposure in human monocyte cell lines by both caspase-dependent and -independent mechanisms. FEBS letters 2004; 578:169-174
330. Reid VC, Hardwick SJ, Mitchinson MJ. Fragmentation of DNA in P388D1 macrophages exposed to oxidised low-density lipoprotein. FEBS letters 1993; 332:218-220
331. Hardwick SJ, Hegyi L, Clare K, Law NS, Carpenter KL, Mitchinson MJ, Skepper JN. Apoptosis in human monocyte-macrophages exposed to oxidized low density lipoprotein. The Journal of pathology 1996; 179:294-302
332. Selley ML, Bartlett MR, Czeti AL, Ardlie NG. The role of (E)-4-hydroxy-2-nonenal in platelet activation by low density lipoprotein and iron. Atherosclerosis 1998; 140:105-112
333. Chen R, Chen X, Salomon RG, McIntyre TM. Platelet activation by low concentrations of intact oxidized LDL particles involves the PAF receptor. Arteriosclerosis, thrombosis, and vascular biology 2009; 29:363-371
334. Magwenzi S, Woodward C, Wraith KS, Aburima A, Raslan Z, Jones H, McNeil C, Wheatcroft S, Yuldasheva N, Febbriao M, Kearney M, Naseem KM. Oxidized LDL activates blood platelets through CD36/NOX2-mediated inhibition of the cGMP/protein kinase G signaling cascade. Blood 2015; 125:2693-2703
335. Wraith KS, Magwenzi S, Aburima A, Wen Y, Leake D, Naseem KM. Oxidized low-density lipoproteins induce rapid platelet activation and shape change through tyrosine kinase and Rho kinase-signaling pathways. Blood 2013; 122:580-589
336. Zhang YC, Tang Y, Chen Y, Huang XH, Zhang M, Chen J, Sun YG, Li YG. Oxidized low-density lipoprotein and C-reactive protein have combined utility for better predicting prognosis after acute coronary syndrome. Cell biochemistry and biophysics 2014; 68:379-385
337. Ho YK, Faust JR, Bilheimer DW, Brown MS, Goldstein JL. Regulation of cholesterol synthesis by low density lipoprotein in isolated human lymphocytes. Comparison of cells from normal subjects and patients with homozygous familial hypercholesterolemia and abetalipoproteinemia. The Journal of experimental medicine 1977; 145:1531-1549
338. Parthasarathy S, Fong L, Otero D, Steinberg D. Recognition of solubilized apoproteins from delipidated, oxidized low density lipoprotein (LDL) by the acetyl-LDL receptor. Proc Natl Acad Sci USA 1987; 84:537-540
339. Kodama T, Freeman M, Rohrer L, Zabrecky J, Matsudaira P, Krieger M. Type I macrophage scavenger receptor contains a-helical and collagen-like coiled coils. Nature 1990; 343:531-535
340. Babaev VR, Gleaves LA, Carter KJ, Suzuki H, Kodama T, Fazio S, Linton MF. Reduced atherosclerotic lesions in mice deficient for total or macrophage-specific expression of scavenger receptor-A. Arteriosclerosis, Thrombosis & Vascular Biology (Online) 2000; 20:2593-2599
341. Yamada Y, Doi T, Hamakubo T, Kodama T. Scavenger receptor family proteins: roles for atherosclerosis, host defence and disorders of the central nervous system. Cellular and molecular life sciences : CMLS 1998; 54:628-640
342. Kunjathoor VV, Febbraio M, Podrez EA, Moore KJ, Andersson L, Koehn S, Rhee JS, Silverstein R, Hoff HF, Freeman MW. Scavenger receptors class A-I/II and CD36 are the principal receptors responsible for the uptake of modified low density lipoprotein leading

to lipid loading in macrophages. The Journal of biological chemistry 2002; 277:49982-49988
343. Boullier A, Friedman P, Harkewicz R, Hartvigsen K, Green SR, Almazan F, Dennis EA, Steinberg D, Witztum JL, Quehenberger O. Phosphocholine as a pattern recognition ligand for CD36. J Lipid Res 2005; 46:969-976
344. Stuart LM, Deng J, Silver JM, Takahashi K, Tseng AA, Hennessy EJ, Ezekowitz RA, Moore KJ. Response to Staphylococcus aureus requires CD36-mediated phagocytosis triggered by the COOH-terminal cytoplasmic domain. J Cell Biol 2005; 170:477-485
345. Kuchibhotla S, Vanegas D, Kennedy DJ, Guy E, Nimako G, Morton RE, Febbraio M. Absence of CD36 protects against atherosclerosis in ApoE knock-out mice with no additional protection provided by absence of scavenger receptor A I/II. Cardiovascular research 2008; 78:185-196
346. Moore KJ, Kunjathoor VV, Koehn SL, Manning JJ, Tseng AA, Silver JM, McKee M, Freeman MW. Loss of receptor-mediated lipid uptake via scavenger receptor A or CD36 pathways does not ameliorate atherosclerosis in hyperlipidemic mice. J Clin Invest 2005; 115:2192-2201
347. Manning-Tobin JJ, Moore KJ, Seimon TA, Bell SA, Sharuk M, Alvarez-Leite JI, de Winther MP, Tabas I, Freeman MW. Loss of SR-A and CD36 activity reduces atherosclerotic lesion complexity without abrogating foam cell formation in hyperlipidemic mice. Arteriosclerosis, thrombosis, and vascular biology 2009; 29:19-26
348. Chavez-Sanchez L, Madrid-Miller A, Chavez-Rueda K, Legorreta-Haquet MV, Tesoro-Cruz E, Blanco-Favela F. Activation of TLR2 and TLR4 by minimally modified low-density lipoprotein in human macrophages and monocytes triggers the inflammatory response. Human immunology 2010; 71:737-744
349. Kadl A, Sharma PR, Chen W, Agrawal R, Meher AK, Rudraiah S, Grubbs N, Sharma R, Leitinger N. Oxidized phospholipid-induced inflammation is mediated by Toll-like receptor 2. Free Radic Biol Med 2011; 51:1903-1909
350. Choi SH, Harkewicz R, Lee JH, Boullier A, Almazan F, Li AC, Witztum JL, Bae YS, Miller YI. Lipoprotein accumulation in macrophages via toll-like receptor-4-dependent fluid phase uptake. Circulation research 2009; 104:1355-1363
351. Stewart CR, Stuart LM, Wilkinson K, van Gils JM, Deng J, Halle A, Rayner KJ, Boyer L, Zhong R, Frazier WA, Lacy-Hulbert A, Khoury JE, Golenbock DT, Moore KJ. CD36 ligands promote sterile inflammation through assembly of a Toll-like receptor 4 and 6 heterodimer. Nat Immunol 2010; 11:155-161
352. Karper JC, Ewing MM, Habets KL, de Vries MR, Peters EA, van Oeveren-Rietdijk AM, de Boer HC, Hamming JF, Kuiper J, Kandimalla ER, La Monica N, Jukema JW, Quax PH. Blocking toll-like receptors 7 and 9 reduces postinterventional remodeling via reduced macrophage activation, foam cell formation, and migration. Arteriosclerosis, thrombosis, and vascular biology 2012; 32:e72-80
353. von Schlieffen E, Oskolkova OV, Schabbauer G, Gruber F, Bluml S, Genest M, Kadl A, Marsik C, Knapp S, Chow J, Leitinger N, Binder BR, Bochkov VN. Multi-hit inhibition of circulating and cell-associated components of the toll-like receptor 4 pathway by oxidized phospholipids. Arteriosclerosis, thrombosis, and vascular biology 2009; 29:356-362

354. Bluml S, Kirchberger S, Bochkov VN, Kronke G, Stuhlmeier K, Majdic O, Zlabinger GJ, Knapp W, Binder BR, Stockl J, Leitinger N. Oxidized phospholipids negatively regulate dendritic cell maturation induced by TLRs and CD40. J Immunol 2005; 175:501-508
355. Sun L, Ishida T, Yasuda T, Kojima Y, Honjo T, Yamamoto Y, Yamamoto H, Ishibashi S, Hirata K, Hayashi Y. RAGE mediates oxidized LDL-induced pro-inflammatory effects and atherosclerosis in non-diabetic LDL receptor-deficient mice. Cardiovascular research 2009; 82:371-381
356. Chang MK, Binder CJ, Torzewski M, Witztum JL. C-reactive protein binds to both oxidized LDL and apoptotic cells through recognition of a common ligand: Phosphorylcholine of oxidized phospholipids. Proceedings of the National Academy of Sciences of the United States of America 2002; 99:13043-13048
357. van Tits L, de Graaf J, Toenhake H, van Heerde W, Stalenhoef A. C-reactive protein and annexin A5 bind to distinct sites of negatively charged phospholipids present in oxidized low-density lipoprotein. Arteriosclerosis, thrombosis, and vascular biology 2005; 25:717-722
358. Palinski W, Horkko S, Miller E, Steinbrecher UP, Powell HC, Curtiss LK, Witztum JL. Cloning of monoclonal autoantibodies to epitopes of oxidized lipoproteins from apolipoprotein E-deficient mice. Demonstration of epitopes of oxidized low density lipoprotein in human plasma. J Clin Invest 1996; 98:800-814
359. Horkko S, Miller E, Dudl E, Reaven P, Curtiss LK, Zvaifler NJ, Terkeltaub R, Pierangeli SS, Branch DW, Palinski W, Witztum JL. Antiphospholipid antibodies are directed against epitopes of oxidized phospholipids. Recognition of cardiolipin by monoclonal antibodies to epitopes of oxidized low density lipoprotein. J Clin Invest 1996; 98:815-825
360. Heery JM, Kozak M, Stafforini DM, Jones DA, Zimmerman GA, McIntyre TM, Prescott SM. Oxidatively modified LDL contains phospholipids with platelet-activating factor-like activity and stimulates the growth of smooth muscle cells. J Clin Invest 1995; 96:2322-2330
361. Smiley PL, Stremler KE, Prescott SM, Zimmerman GA, McIntyre TM. Oxidatively fragmented phosphatidylcholines activate human neutrophils through the receptor for platelet-activating factor. The Journal of biological chemistry 1991; 266:11104-11110
362. Marathe GK, Davies SS, Harrison KA, Silva AR, Murphy RC, Castro-Faria-Neto H, Prescott SM, Zimmerman GA, McIntyre TM. Inflammatory platelet-activating factor-like phospholipids in oxidized low density lipoproteins are fragmented alkyl phosphatidylcholines. The Journal of biological chemistry 1999; 274:28395-28404
363. Li R, Mouillesseaux KP, Montoya D, Cruz D, Gharavi N, Dun M, Koroniak L, Berliner JA. Identification of prostaglandin E2 receptor subtype 2 as a receptor activated by OxPAPC. Circulation research 2006; 98:642-650
364. Montine TJ, Milatovic D, Gupta RC, Valyi-Nagy T, Morrow JD, Breyer RM. Neuronal oxidative damage from activated innate immunity is EP2 receptor-dependent. J Neurochem 2002; 83:463-470
365. Singleton PA, Chatchavalvanich S, Fu P, Xing J, Birukova AA, Fortune JA, Klibanov AM, Garcia JG, Birukov KG. Akt-mediated transactivation of the S1P1 receptor in caveolin-enriched microdomains regulates endothelial barrier enhancement by oxidized phospholipids. Circulation research 2009; 104:978-986

366. Lee H, Shi W, Tontonoz P, Wang S, Subbanagounder G, Hedrick CC, Hama S, Borromeo C, Evans RM, Berliner JA, Nagy L. Role for peroxisome proliferator-activated receptor alpha in oxidized phospholipid-induced synthesis of monocyte chemotactic protein-1 and interleukin-8 by endothelial cells. Circulation research 2000; 87:516-521
367. Yeh M, Gharavi NM, Choi J, Hsieh X, Reed E, Mouillesseaux KP, Cole AL, Reddy ST, Berliner JA. Oxidized phospholipids increase interleukin 8 (IL-8) synthesis by activation of the c-src/signal transducers and activators of transcription (STAT)3 pathway. The Journal of biological chemistry 2004; 279:30175-30181
368. Afonyushkin T, Oskolkova OV, Philippova M, Resink TJ, Erne P, Binder BR, Bochkov VN. Oxidized phospholipids regulate expression of ATF4 and VEGF in endothelial cells via NRF2-dependent mechanism: novel point of convergence between electrophilic and unfolded protein stress pathways. Arteriosclerosis, thrombosis, and vascular biology 2010; 30:1007-1013
369. Jyrkkanen HK, Kansanen E, Inkala M, Kivela AM, Hurttila H, Heinonen SE, Goldsteins G, Jauhiainen S, Tiainen S, Makkonen H, Oskolkova O, Afonyushkin T, Koistinaho J, Yamamoto M, Bochkov VN, Yla-Herttuala S, Levonen AL. Nrf2 regulates antioxidant gene expression evoked by oxidized phospholipids in endothelial cells and murine arteries in vivo. Circulation research 2008; 103:e1-9
370. Frei B. Ascorbic acid protects lipids in human plasma and low-density lipoprotein against oxidative damage. Am J Clin Nutr 1991; 54:1113S-1118S
371. Babaev VR, Li L, Shah S, Fazio S, Linton MF, May JM. Combined vitamin C and vitamin E deficiency worsens early atherosclerosis in apolipoprotein E-deficient mice. Arteriosclerosis, thrombosis, and vascular biology 2010; 30:1751-1757
372. Frikke-Schmidt H, Lykkesfeldt J. Role of marginal vitamin C deficiency in atherogenesis: in vivo models and clinical studies. Basic Clin Pharmacol Toxicol 2009; 104:419-433
373. May JM, Harrison FE. Role of vitamin C in the function of the vascular endothelium. Antioxidants & redox signaling 2013; 19:2068-2083
374. Crawford RS, Kirk EA, Rosenfeld ME, LeBoeuf RC, Chait A. Dietary antioxidants inhibit development of fatty streak lesions in the LDL receptor-deficient mouse. Arteriosclerosis, thrombosis, and vascular biology 1998; 18:1506-1513
375. Black TM, Wang P, Maeda N, Coleman RA. Palm tocotrienols protect ApoE +/- mice from diet-induced atheroma formation. J Nutr 2000; 130:2420-2426
376. Witting PK, Pettersson K, Letters J, Stocker R. Anti-atherogenic effect of coenzyme Q10 in apolipoprotein E gene knockout mice. Free Radic Biol Med 2000; 29:295-305
377. Peluzio MC, Homem AP, Cesar GC, Azevedo GS, Amorim R, Cara DC, Saliba H, Vieira EC, Arantes RE, Alvarez-Leite J. Influences of alpha-tocopherol on cholesterol metabolism and fatty streak development in apolipoprotein E-deficient mice fed an atherogenic diet. Braz J Med Biol Res 2001; 34:1539-1545
378. Suarna C, Wu BJ, Choy K, Mori T, Croft K, Cynshi O, Stocker R. Protective effect of vitamin E supplements on experimental atherosclerosis is modest and depends on preexisting vitamin E deficiency. Free Radic Biol Med 2006; 41:722-730
379. Salonen JT, Nyyssonen K, Salonen R, Lakka HM, Kaikkonen J, Porkkala-Sarataho E, Voutilainen S, Lakka TA, Rissanen T, Leskinen L, Tuomainen TP, Valkonen VP, Ristonmaa U, Poulsen HE. Antioxidant Supplementation in Atherosclerosis Prevention

(ASAP) study: a randomized trial of the effect of vitamins E and C on 3-year progression of carotid atherosclerosis. Journal of internal medicine 2000; 248:377-386
380. Azen SP, Qian D, Mack WJ, Sevanian A, Selzer RH, Liu CR, Liu CH, Hodis HN. Effect of supplementary antioxidant vitamin intake on carotid arterial wall intima-media thickness in a controlled clinical trial of cholesterol lowering. Circulation 1996; 94:2369-2372
381. Levy AP, Friedenberg P, Lotan R, Ouyang P, Tripputi M, Higginson L, Cobb FR, Tardif JC, Bittner V, Howard BV. The effect of vitamin therapy on the progression of coronary artery atherosclerosis varies by haptoglobin type in postmenopausal women. Diabetes Care 2004; 27:925-930
382. Plantinga Y, Ghiadoni L, Magagna A, Giannarelli C, Franzoni F, Taddei S, Salvetti A. Supplementation with vitamins C and E improves arterial stiffness and endothelial function in essential hypertensive patients. Am J Hypertens 2007; 20:392-397
383. Pruthi S, Allison TG, Hensrud DD. Vitamin E supplementation in the prevention of coronary heart disease. Mayo Clin Proc 2001; 76:1131-1136
384. Tornwall ME, Virtamo J, Haukka JK, Albanes D, Huttunen JK. Alpha-tocopherol (vitamin E) and beta-carotene supplementation does not affect the risk for large abdominal aortic aneurysm in a controlled trial. Atherosclerosis 2001; 157:167-173
385. Kinlay S, Behrendt D, Fang JC, Delagrange D, Morrow J, Witztum JL, Rifai N, Selwyn AP, Creager MA, Ganz P. Long-term effect of combined vitamins E and C on coronary and peripheral endothelial function. J Am Coll Cardiol 2004; 43:629-634
386. Devaraj S, Tang R, Adams-Huet B, Harris A, Seenivasan T, de Lemos JA, Jialal I. Effect of high-dose alpha-tocopherol supplementation on biomarkers of oxidative stress and inflammation and carotid atherosclerosis in patients with coronary artery disease. Am J Clin Nutr 2007; 86:1392-1398
387. Zureik M, Galan P, Bertrais S, Mennen L, Czernichow S, Blacher J, Ducimetiere P, Hercberg S. Effects of long-term daily low-dose supplementation with antioxidant vitamins and minerals on structure and function of large arteries. Arteriosclerosis, thrombosis, and vascular biology 2004; 24:1485-1491
388. Traber MG, Frei B, Beckman JS. Vitamin E revisited: do new data validate benefits for chronic disease prevention? Current opinion in lipidology 2008; 19:30-38
389. Roberts LJ, 2nd, Traber MG, Frei B. Vitamins E and C in the prevention of cardiovascular disease and cancer in men. Free Radic Biol Med 2009; 46:1558
390. Roberts LJ, 2nd, Oates JA, Linton MF, Fazio S, Meador BP, Gross MD, Shyr Y, Morrow JD. The relationship between dose of vitamin E and suppression of oxidative stress in humans. Free Radic Biol Med 2007; 43:1388-1393
391. Michels AJ, Frei B. Myths, artifacts, and fatal flaws: identifying limitations and opportunities in vitamin C research. Nutrients 2013; 5:5161-5192
392. Khanna S, Heigel M, Weist J, Gnyawali S, Teplitsky S, Roy S, Sen CK, Rink C. Excessive alpha-tocopherol exacerbates microglial activation and brain injury caused by acute ischemic stroke. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2015; 29:828-836

393. Lubos E, Loscalzo J, Handy DE. Glutathione peroxidase-1 in health and disease: from molecular mechanisms to therapeutic opportunities. Antioxidants & redox signaling 2011; 15:1957-1997
394. Park JG, Yoo JY, Jeong SJ, Choi JH, Lee MR, Lee MN, Hwa Lee J, Kim HC, Jo H, Yu DY, Kang SW, Rhee SG, Lee MH, Oh GT. Peroxiredoxin 2 deficiency exacerbates atherosclerosis in apolipoprotein E-deficient mice. Circulation research 2011; 109:739-749
395. Winter JP, Gong Y, Grant PJ, Wild CP. Glutathione peroxidase 1 genotype is associated with an increased risk of coronary artery disease. Coron Artery Dis 2003; 14:149-153
396. Nemoto M, Nishimura R, Sasaki T, Hiki Y, Miyashita Y, Nishioka M, Fujimoto K, Sakuma T, Ohashi T, Fukuda K, Eto Y, Tajima N. Genetic association of glutathione peroxidase-1 with coronary artery calcification in type 2 diabetes: a case control study with multi-slice computed tomography. Cardiovasc Diabetol 2007; 6:23
397. Hamanishi T, Furuta H, Kato H, Doi A, Tamai M, Shimomura H, Sakagashira S, Nishi M, Sasaki H, Sanke T, Nanjo K. Functional variants in the glutathione peroxidase-1 (GPx-1) gene are associated with increased intima-media thickness of carotid arteries and risk of macrovascular diseases in japanese type 2 diabetic patients. Diabetes 2004; 53:2455-2460
398. Torzewski M, Ochsenhirt V, Kleschyov AL, Oelze M, Daiber A, Li H, Rossmann H, Tsimikas S, Reifenberg K, Cheng F, Lehr HA, Blankenberg S, Forstermann U, Munzel T, Lackner KJ. Deficiency of glutathione peroxidase-1 accelerates the progression of atherosclerosis in apolipoprotein E-deficient mice. Arteriosclerosis, thrombosis, and vascular biology 2007; 27:850-857
399. Lewis P, Stefanovic N, Pete J, Calkin AC, Giunti S, Thallas-Bonke V, Jandeleit-Dahm KA, Allen TJ, Kola I, Cooper ME, de Haan JB. Lack of the antioxidant enzyme glutathione peroxidase-1 accelerates atherosclerosis in diabetic apolipoprotein E-deficient mice. Circulation 2007; 115:2178-2187
400. Guo Z, Ran Q, Roberts LJ, 2nd, Zhou L, Richardson A, Sharan C, Wu D, Yang H. Suppression of atherogenesis by overexpression of glutathione peroxidase-4 in apolipoprotein E-deficient mice. Free Radic Biol Med 2008; 44:343-352
401. Butterfield LH, Merino A, Golub SH, Shau H. From cytoprotection to tumor suppression: the multifactorial role of peroxiredoxins. Antioxidants & redox signaling 1999; 1:385-402
402. Kisucka J, Chauhan AK, Patten IS, Yesilaltay A, Neumann C, Van Etten RA, Krieger M, Wagner DD. Peroxiredoxin1 prevents excessive endothelial activation and early atherosclerosis. Circulation research 2008; 103:598-605
403. Park JG, Oh GT. The role of peroxidases in the pathogenesis of atherosclerosis. BMB Rep 2011; 44:497-505
404. Guo X, Yamada S, Tanimoto A, Ding Y, Wang KY, Shimajiri S, Murata Y, Kimura S, Tasaki T, Nabeshima A, Watanabe T, Kohno K, Sasaguri Y. Overexpression of peroxiredoxin 4 attenuates atherosclerosis in apolipoprotein E knockout mice. Antioxidants & redox signaling 2012; 17:1362-1375
405. Phelan SA, Wang X, Wallbrandt P, Forsman-Semb K, Paigen B. Overexpression of Prdx6 reduces H2O2 but does not prevent diet-induced atherosclerosis in the aortic root. Free Radic Biol Med 2003; 35:1110-1120

406. Fukai T, Ushio-Fukai M. Superoxide dismutases: role in redox signaling, vascular function, and diseases. Antioxidants & redox signaling 2011; 15:1583-1606
407. Shuvalova YA, Kaminnyi AI, Meshkov AN, Shirokov RO, Samko AN. Association between polymorphisms of eNOS and GPx-1 genes, activity of free-radical processes and in-stent restenosis. Mol Cell Biochem 2012; 370:241-249
408. Tribble DL, Gong EL, Leeuwenburgh C, Heinecke JW, Carlson EL, Verstuyft JG, Epstein CJ. Fatty streak formation in fat-fed mice expressing human copper-zinc superoxide dismutase. Arteriosclerosis, thrombosis, and vascular biology 1997; 17:1734-1740
409. Yang H, Roberts LJ, Shi MJ, Zhou LC, Ballard BR, Richardson A, Guo ZM. Retardation of atherosclerosis by overexpression of catalase or both Cu/Zn-superoxide dismutase and catalase in mice lacking apolipoprotein E. Circulation research 2004; 95:1075-1081
410. Ballinger SW, Patterson C, Knight-Lozano CA, Burow DL, Conklin CA, Hu Z, Reuf J, Horaist C, Lebovitz R, Hunter GC, McIntyre K, Runge MS. Mitochondrial integrity and function in atherogenesis. Circulation 2002; 106:544-549
411. Sentman ML, Brannstrom T, Westerlund S, Laukkanen MO, Yla-Herttuala S, Basu S, Marklund SL. Extracellular superoxide dismutase deficiency and atherosclerosis in mice. Arteriosclerosis, thrombosis, and vascular biology 2001; 21:1477-1482
412. Chen H, Yu M, Li M, Zhao R, Zhu Q, Zhou W, Lu M, Lu Y, Zheng T, Jiang J, Zhao W, Xiang K, Jia W, Liu L. Polymorphic variations in manganese superoxide dismutase (MnSOD), glutathione peroxidase-1 (GPX1), and catalase (CAT) contribute to elevated plasma triglyceride levels in Chinese patients with type 2 diabetes or diabetic cardiovascular disease. Mol Cell Biochem 2012; 363:85-91
413. Santl Letonja M, Letonja M, Ikolajevic-Starcevic JN, Petrovic D. Association of manganese superoxide dismutase and glutathione S-transferases genotypes with carotid atherosclerosis in patients with diabetes mellitus type 2. Int Angiol 2012; 31:33-41
414. Stafforini DM. Biology of platelet-activating factor acetylhydrolase (PAF-AH, lipoprotein associated phospholipase A2). Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2009; 23:73-83
415. Karabina SA, Liapikos TA, Grekas G, Goudevenos J, Tselepis AD. Distribution of PAF-acetylhydrolase activity in human plasma low-density lipoprotein subfractions. Biochimica et biophysica acta 1994; 1213:34-38
416. Stremler KE, Stafforini DM, Prescott SM, Zimmerman GA, McIntyre TM. An oxidized derivative of phosphatidylcholine is a substrate for the platelet-activating factor acetylhydrolase from human plasma. The Journal of biological chemistry 1989; 264:5331-5334
417. Kriska T, Marathe GK, Schmidt JC, McIntyre TM, Girotti AW. Phospholipase action of platelet-activating factor acetylhydrolase, but not paraoxonase-1, on long fatty acyl chain phospholipid hydroperoxides. The Journal of biological chemistry 2007; 282:100-108
418. Stafforini DM, Sheller JR, Blackwell TS, Sapirstein A, Yull FE, McIntyre TM, Bonventre JV, Prescott SM, Roberts LJ, 2nd. Release of free F2-isoprostanes from esterified phospholipids is catalyzed by intracellular and plasma platelet-activating factor acetylhydrolases. The Journal of biological chemistry 2006; 281:4616-4623

419. Zalewski A, Macphee C. Role of lipoprotein-associated phospholipase A2 in atherosclerosis: biology, epidemiology, and possible therapeutic target. Arteriosclerosis, thrombosis, and vascular biology 2005; 25:923-931
420. Cai A, Zheng D, Qiu R, Mai W, Zhou Y. Lipoprotein-associated phospholipase A2 (Lp-PLA(2)): a novel and promising biomarker for cardiovascular risks assessment. Dis Markers 2013; 34:323-331
421. Stafforini DM, Zimmerman GA. Unraveling the PAF-AH/Lp-PLA2 controversy. J Lipid Res 2014; 55:1811-1814
422. Rosenson RS, Stafforini DM. Modulation of oxidative stress, inflammation, and atherosclerosis by lipoprotein-associated phospholipase A2. J Lipid Res 2012; 53:1767-1782
423. Shimokata K, Yamada Y, Kondo T, Ichihara S, Izawa H, Nagata K, Murohara T, Ohno M, Yokota M. Association of gene polymorphisms with coronary artery disease in individuals with or without nonfamilial hypercholesterolemia. Atherosclerosis 2004; 172:167-173
424. Campo S, Sardo MA, Bitto A, Bonaiuto A, Trimarchi G, Bonaiuto M, Castaldo M, Saitta C, Cristadoro S, Saitta A. Platelet-activating factor acetylhydrolase is not associated with carotid intima-media thickness in hypercholesterolemic Sicilian individuals. Clin Chem 2004; 50:2077-2082
425. Riley RF, Corson MA. Darapladib, a reversible lipoprotein-associated phospholipase A2 inhibitor, for the oral treatment of atherosclerosis and coronary artery disease. IDrugs 2009; 12:648-655
426. O'Donoghue ML, Braunwald E, White HD, Lukas MA, Tarka E, Steg PG, Hochman JS, Bode C, Maggioni AP, Im K, Shannon JB, Davies RY, Murphy SA, Crugnale SE, Wiviott SD, Bonaca MP, Watson DF, Weaver WD, Serruys PW, Cannon CP, Investigators S-T, Steen DL. Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial. JAMA 2014; 312:1006-1015
427. Stability Investigators, White HD, Held C, Stewart R, Tarka E, Brown R, Davies RY, Budaj A, Harrington RA, Steg PG, Ardissino D, Armstrong PW, Avezum A, Aylward PE, Bryce A, Chen H, Chen MF, Corbalan R, Dalby AJ, Danchin N, De Winter RJ, Denchev S, Diaz R, Elisaf M, Flather MD, Goudev AR, Granger CB, Grinfeld L, Hochman JS, Husted S, Kim HS, Koenig W, Linhart A, Lonn E, Lopez-Sendon J, Manolis AJ, Mohler ER, 3rd, Nicolau JC, Pais P, Parkhomenko A, Pedersen TR, Pella D, Ramos-Corrales MA, Ruda M, Sereg M, Siddique S, Sinnaeve P, Smith P, Sritara P, Swart HP, Sy RG, Teramoto T, Tse HF, Watson D, Weaver WD, Weiss R, Viigimaa M, Vinereanu D, Zhu J, Cannon CP, Wallentin L. Darapladib for preventing ischemic events in stable coronary heart disease. The New England journal of medicine 2014; 370:1702-1711
428. Aviram M, Rosenblat M, Bisgaier CL, Newton RS, Primo-Parmo SL, La Du BN. Paraoxonase inhibits high-density lipoprotein oxidation and preserves its functions. A possible peroxidative role for paraoxonase. J Clin Invest 1998; 101:1581-1590
429. Aviram M, Billecke S, Sorenson R, Bisgaier C, Newton R, Rosenblat M, Erogul J, Hsu C, Dunlop C, La Du B. Paraoxonase active site required for protection against LDL oxidation involves its free sulfhydryl group and is different from that required for its

arylesterase/paraoxonase activities: selective action of human paraoxonase allozymes Q and R. Arteriosclerosis, thrombosis, and vascular biology 1998; 18:1617-1624
430. Shih DM, Gu L, Xia YR, Navab M, Li WF, Hama S, Castellani LW, Furlong CE, Costa LG, Fogelman AM, Lusis AJ. Mice lacking serum paraoxonase are susceptible to organophosphate toxicity and atherosclerosis. Nature 1998; 394:284-287
431. Shih DM, Xia YR, Wang XP, Miller E, Castellani LW, Subbanagounder G, Cheroutre H, Faull KF, Berliner JA, Witztum JL, Lusis AJ. Combined serum paraoxonase knockout/apolipoprotein E knockout mice exhibit increased lipoprotein oxidation and atherosclerosis. The Journal of biological chemistry 2000; 275:17527-17535
432. Tward A, Xia YR, Wang XP, Shi YS, Park C, Castellani LW, Lusis AJ, Shih DM. Decreased atherosclerotic lesion formation in human serum paraoxonase transgenic mice. Circulation 2002; 106:484-490
433. Ng CJ, Hama SY, Bourquard N, Navab M, Reddy ST. Adenovirus mediated expression of human paraoxonase 2 protects against the development of atherosclerosis in apolipoprotein E-deficient mice. Molecular genetics and metabolism 2006; 89:368-373
434. Ng CJ, Bourquard N, Hama SY, Shih D, Grijalva VR, Navab M, Fogelman AM, Reddy ST. Adenovirus-mediated expression of human paraoxonase 3 protects against the progression of atherosclerosis in apolipoprotein E-deficient mice. Arteriosclerosis, thrombosis, and vascular biology 2007; 27:1368-1374
435. She ZG, Zheng W, Wei YS, Chen HZ, Wang AB, Li HL, Liu G, Zhang R, Liu JJ, Stallcup WB, Zhou Z, Liu DP, Liang CC. Human paraoxonase gene cluster transgenic overexpression represses atherogenesis and promotes atherosclerotic plaque stability in ApoE-null mice. Circulation research 2009; 104:1160-1168
436. Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, Kuivenhoven JA, Nordestgaard BG, Descamps OS, Steinhagen-Thiessen E, Tybjaerg-Hansen A, Watts GF, Averna M, Boileau C, Boren J, Catapano AL, Defesche JC, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Ray KK, Stalenhoef AF, Stroes E, Taskinen MR, Wiegman A, Wiklund O, Chapman MJ, European Atherosclerosis Society Consensus Panel on Familial H. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. European heart journal 2014; 35:2146-2157
437. Hopkins PN, Toth PP, Ballantyne CM, Rader DJ. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. Journal of clinical lipidology 2011; 5:S9-17
438. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, Wiegman A, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Kovanen PT, Boileau C, Averna M, Boren J, Bruckert E, Catapano AL, Kuivenhoven JA, Pajukanta P, Ray K, Stalenhoef AF, Stroes E, Taskinen MR, Tybjaerg-Hansen A. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. European heart journal 2013; 34:3478-3490a

439. Khera AV, Won HH, Peloso GM, Lawson KS, Bartz TM, Deng X, van Leeuwen EM, Natarajan P, Emdin CA, Bick AG, Morrison AC, Brody JA, Gupta N, Nomura A, Kessler T, Duga S, Bis JC, van Duijn CM, Cupples LA, Psaty B, Rader DJ, Danesh J, Schunkert H, McPherson R, Farrall M, Watkins H, Lander E, Wilson JG, Correa A, Boerwinkle E, Merlini PA, Ardissino D, Saleheen D, Gabriel S, Kathiresan S. Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia. J Am Coll Cardiol 2016; 67:2578-2589
440. Kathiresan S, Consortium MIG. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. Nat Genet 2009; 41:334-341
441. Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, Ingelsson E, Saleheen D, Erdmann J, Goldstein BA, Stirrups K, Konig IR, Cazier JB, Johansson A, Hall AS, Lee JY, Willer CJ, Chambers JC, Esko T, Folkersen L, Goel A, Grundberg E, Havulinna AS, Ho WK, Hopewell JC, Eriksson N, Kleber ME, Kristiansson K, Lundmark P, Lyytikainen LP, Rafelt S, Shungin D, Strawbridge RJ, Thorleifsson G, Tikkanen E, Van Zuydam N, Voight BF, Waite LL, Zhang W, Ziegler A, Absher D, Altshuler D, Balmforth AJ, Barroso I, Braund PS, Burgdorf C, Claudi-Boehm S, Cox D, Dimitriou M, Do R, Doney AS, El Mokhtari N, Eriksson P, Fischer K, Fontanillas P, Franco-Cereceda A, Gigante B, Groop L, Gustafsson S, Hager J, Hallmans G, Han BG, Hunt SE, Kang HM, Illig T, Kessler T, Knowles JW, Kolovou G, Kuusisto J, Langenberg C, Langford C, Leander K, Lokki ML, Lundmark A, McCarthy MI, Meisinger C, Melander O, Mihailov E, Maouche S, Morris AD, Muller-Nurasyid M, Nikus K, Peden JF, Rayner NW, Rasheed A, Rosinger S, Rubin D, Rumpf MP, Schafer A, Sivananthan M, Song C, Stewart AF, Tan ST, Thorgeirsson G, van der Schoot CE, Wagner PJ, Wells GA, Wild PS, Yang TP, Amouyel P, Arveiler D, Basart H, Boehnke M, Boerwinkle E, Brambilla P, Cambien F, Cupples AL, de Faire U, Dehghan A, Diemert P, Epstein SE, Evans A, Ferrario MM, Ferrieres J, Gauguier D, Go AS, Goodall AH, Gudnason V, Hazen SL, Holm H, Iribarren C, Jang Y, Kahonen M, Kee F, Kim HS, Klopp N, Koenig W, Kratzer W, Kuulasmaa K, Laakso M, Laaksonen R, Lee JY, Lind L, Ouwehand WH, Parish S, Park JE, Pedersen NL, Peters A, Quertermous T, Rader DJ, Salomaa V, Schadt E, Shah SH, Sinisalo J, Stark K, Stefansson K, Tregouet DA, Virtamo J, Wallentin L, Wareham N, Zimmermann ME, Nieminen MS, Hengstenberg C, Sandhu MS, Pastinen T, Syvanen AC, Hovingh GK, Dedoussis G, Franks PW, Lehtimaki T, Metspalu A, Zalloua PA, Siegbahn A, Schreiber S, Ripatti S, Blankenberg SS, Perola M, Clarke R, Boehm BO, O'Donnell C, Reilly MP, Marz W, Collins R, Kathiresan S, Hamsten A, Kooner JS, Thorsteinsdottir U, Danesh J, Palmer CN, Roberts R, Watkins H, Schunkert H, Samani NJ. Large-scale association analysis identifies new risk loci for coronary artery disease. Nat Genet 2013; 45:25-33
442. Kathiresan S, Melander O, Guiducci C, Surti A, Burtt NP, Rieder MJ, Cooper GM, Roos C, Voight BF, Havulinna AS, Wahlstrand B, Hedner T, Corella D, Tai ES, Ordovas JM, Berglund G, Vartiainen E, Jousilahti P, Hedblad B, Taskinen MR, Newton-Cheh C, Salomaa V, Peltonen L, Groop L, Altshuler DM, Orho-Melander M. Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. Nat Genet 2008; 40:189-197

443. Rader DJ. Human genetics of atherothrombotic disease and its risk factors. Arteriosclerosis, thrombosis, and vascular biology 2015; 35:741-747
444. Cohen JC, Boerwinkle E, Mosley TH, Jr., Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. The New England journal of medicine 2006; 354:1264-1272
445. Horton JD, Cohen JC, Hobbs HH. PCSK9: a convertase that coordinates LDL catabolism. J Lipid Res 2009; 50 Suppl:S172-177
446. Maron DJ, Fazio S, Linton MF. Current perspectives on statins. Circulation 2000; 101:207-213
447. Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. J Am Med Assoc 1975; 231:360–381
448. Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. Journal of the American College of Cardiology 1986; 8:1245-1255
449. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984; 251:365-374
450. Scandinavian, Simvastatin, Survival, Study, Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the scandinavian simvastatin survival study (4S). Lancet 1994; 344:1383-1389
451. McKenney JR, EM. Statins. In: Ballantyne CM, ed. Clinical Lipidology, a companion to Braunwald's Heart Disease. Vol Second Edition: Elsevier Saunders; 2015:227-256.
452. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010; 376:1670-1681
453. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, Braunwald E, Sabatine MS. Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis. JAMA 2016; 316:1289-1297
454. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR, Committee FS, Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med 2017; 376:1713-1722
455. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM, Committees OO, Investigators. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med 2018; 379:2097-2107
456. Sampson UK, Fazio S, Linton MF. Residual cardiovascular risk despite optimal LDL cholesterol reduction with statins: the evidence, etiology, and therapeutic challenges. Current atherosclerosis reports 2012; 14:1-10
457. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J,

Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ, Group CT. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. The New England journal of medicine 2017; 377:1119-1131

458. Bohula EA, Giugliano RP, Leiter LA, Verma S, Park JG, Sever PS, Lira Pineda A, Honarpour N, Wang H, Murphy SA, Keech A, Pedersen TR, Sabatine MS. Inflammatory and Cholesterol Risk in the FOURIER Trial. Circulation 2018; 138:131-140
459. Diffenderfer MR, Schaefer EJ. The composition and metabolism of large and small LDL. Current opinion in lipidology 2014; 25:221-226
460. Sachdeva A, Cannon CP, Deedwania PC, Labresh KA, Smith SC, Jr., Dai D, Hernandez A, Fonarow GC. Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in Get With The Guidelines. American heart journal 2009; 157:111-117 e112
461. Krauss RM. Low-density lipoprotein subclasses and risk of coronary artery disease. Curr Opin Lipidol 1991; 2:248-252
462. Hirayama S, Miida T. Small dense LDL: An emerging risk factor for cardiovascular disease. Clin Chim Acta 2012; 414:215-224
463. Sninsky JJ, Rowland CM, Baca AM, Caulfield MP, Superko HR. Classification of LDL phenotypes by 4 methods of determining lipoprotein particle size. Journal of investigative medicine : the official publication of the American Federation for Clinical Research 2013; 61:942-949
464. Tribble DL, Rizzo M, Chait A, Lewis DM, Blanche PJ, Krauss RM. Enhanced oxidative susceptibility and reduced antioxidant content of metabolic precursors of small, dense low-density lipoproteins. The American journal of medicine 2001; 110:103-110
465. Hurt-Camejo E, Camejo G, Rosengren B, Lopez F, Wiklund O, Bondjers G. Differential uptake of proteoglycan-selected subfractions of low density lipoprotein by human macrophages. J Lipid Res 1990; 31:1387-1398
466. Young SG. Recent progress in understanding apolipoprotein B. Circulation 1990; 82:1574-1594
467. Sniderman AD, De Graaf J, Couture P. Low-density lipoprotein-lowering strategies: target versus maximalist versus population percentile. Current opinion in cardiology 2012; 27:405-411
468. Sniderman AD, Lamarche B, Contois JH, de Graaf J. Discordance analysis and the Gordian Knot of LDL and non-HDL cholesterol versus apoB. Current opinion in lipidology 2014; 25:461-467
469. National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report.[see comment]. Circulation 2002; 106:3143-3421
470. Grundy SM, Cleeman JI, Merz CN, Brewer HB, Jr., Clark LT, Hunninghake DB, Pasternak RC, Smith SC, Jr., Stone NJ, National Heart L, Blood I, American College of Cardiology F, American Heart A. Implications of recent clinical trials for the National

Cholesterol Education Program Adult Treatment Panel III guidelines.[erratum appears in Circulation. 2004 Aug 10;110(6):763]. Circulation 2004; 110:227-239
471. Sniderman AD, Williams K, Contois JH, Monroe HM, McQueen MJ, de Graaf J, Furberg CD. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. Circulation Cardiovascular quality and outcomes 2011; 4:337-345
472. Contois JH, McConnell JP, Sethi AA, Csako G, Devaraj S, Hoefner DM, Warnick GR. Apolipoprotein B and cardiovascular disease risk: position statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. Clin Chem 2009; 55:407-419
473. Cromwell WC, Otvos JD, Keyes MJ, Pencina MJ, Sullivan L, Vasan RS, Wilson PW, D'Agostino RB. LDL Particle Number and Risk of Future Cardiovascular Disease in the Framingham Offspring Study - Implications for LDL Management. Journal of clinical lipidology 2007; 1:583-592
474. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, Collins R, Thompson SG, Danesh J. Major lipids, apolipoproteins, and risk of vascular disease. JAMA 2009; 302:1993-2000
475. Otvos JD, Mora S, Shalaurova I, Greenland P, Mackey RH, Goff DC, Jr. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. Journal of clinical lipidology 2011; 5:105-113
476. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Jr., Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Jr., Tomaselli GF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 129:S1-45
477. Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, McKenney JM, Grundy SM, Gill EA, Wild RA, Wilson DP, Brown WV. National lipid association recommendations for patient-centered management of dyslipidemia: part 1--full report. Journal of clinical lipidology 2015; 9:129-169
478. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, Grunberger G, Guerin CK, Bell DSH, Mechanick JI, Pessah-Pollack R, Wyne K, Smith D, Brinton EA, Fazio S, Davidson M, Zangeneh F, Bush MA. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE - EXECUTIVE SUMMARYComplete Appendix to Guidelines available at http://journals.aace.com/. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2017; 23:479-497
479. Authors/Task Force M, Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Z, Riccardi G,

Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis 2016; 253:281-344

480. Genest J, McPherson R, Frohlich J, Anderson T, Campbell N, Carpentier A, Couture P, Dufour R, Fodor G, Francis GA, Grover S, Gupta M, Hegele RA, Lau DC, Leiter L, Lewis GF, Lonn E, Mancini GB, Ng D, Pearson GJ, Sniderman A, Stone JA, Ur E. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. The Canadian journal of cardiology 2009; 25:567-579
481. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Jr., Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;
482. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM, Investigators I-I. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. The New England journal of medicine 2015; 372:2387-2397
483. Koschinsky MLB, MB, Marcovina, SM. Lipoprotein(a). In: Ballantyne CM, ed. Clinical Lipidology, a companion to Braunwald's Heart Disease. Vol Second Edition: Elsevier Saunders; 2015:109-127.
484. Rader DJ, Mann WA, Cain W, Kraft HG, Usher D, Zech LA, Hoeg JM, Davignon J, Lupien P, Grossman M, et al. The low density lipoprotein receptor is not required for normal catabolism of Lp(a) in humans. J Clin Invest 1995; 95:1403-1408
485. Rader DJ, Cain W, Ikewaki K, Talley G, Zech LA, Usher D, Brewer HB, Jr. The inverse association of plasma lipoprotein(a) concentrations with apolipoprotein(a) isoform size is not due to differences in Lp(a) catabolism but to differences in production rate. J Clin Invest 1994; 93:2758-2763
486. Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH. Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. J Clin Invest 1992; 90:52-60
487. Moliterno DJ, Jokinen EV, Miserez AR, Lange RA, Willard JE, Boerwinkle E, Hillis LD, Hobbs HH. No association between plasma lipoprotein(a) concentrations and the presence or absence of coronary atherosclerosis in African-Americans. Arteriosclerosis, thrombosis, and vascular biology 1995; 15:850-855
488. Paultre F, Pearson TA, Weil HF, Tuck CH, Myerson M, Rubin J, Francis CK, Marx HF, Philbin EF, Reed RG, Berglund L. High levels of Lp(a) with a small apo(a) isoform are

associated with coronary artery disease in African American and white men. Arteriosclerosis, thrombosis, and vascular biology 2000; 20:2619-2624
489. Virani SS, Brautbar A, Davis BC, Nambi V, Hoogeveen RC, Sharrett AR, Coresh J, Mosley TH, Morrisett JD, Catellier DJ, Folsom AR, Boerwinkle E, Ballantyne CM. Associations between lipoprotein(a) levels and cardiovascular outcomes in black and white subjects: the Atherosclerosis Risk in Communities (ARIC) Study. Circulation 2012; 125:241-249
490. Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, Marcovina SM, Collins R, Thompson SG, Danesh J. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA 2009; 302:412-423
491. Luke MM, Kane JP, Liu DM, Rowland CM, Shiffman D, Cassano J, Catanese JJ, Pullinger CR, Leong DU, Arellano AR, Tong CH, Movsesyan I, Naya-Vigne J, Noordhof C, Feric NT, Malloy MJ, Topol EJ, Koschinsky ML, Devlin JJ, Ellis SG. A polymorphism in the protease-like domain of apolipoprotein(a) is associated with severe coronary artery disease. Arteriosclerosis, thrombosis, and vascular biology 2007; 27:2030-2036
492. Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, Parish S, Barlera S, Franzosi MG, Rust S, Bennett D, Silveira A, Malarstig A, Green FR, Lathrop M, Gigante B, Leander K, de Faire U, Seedorf U, Hamsten A, Collins R, Watkins H, Farrall M. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. The New England journal of medicine 2009; 361:2518-2528
493. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA 2009; 301:2331-2339
494. Linton MF, Farese RV, Jr., Chiesa G, Grass DS, Chin P, Hammer RE, Hobbs HH, Young SG. Transgenic mice expressing high plasma concentrations of human apolipoprotein B100 and lipoprotein(a). J Clin Invest 1993; 92:3029-3037
495. Schneider M, Witztum JL, Young SG, Ludwig EH, Miller ER, Tsimikas S, Curtiss LK, Marcovina SM, Taylor JM, Lawn RM, Innerarity TL, Pitas RE. High-level lipoprotein [a] expression in transgenic mice: evidence for oxidized phospholipids in lipoprotein [a] but not in low density lipoproteins. J Lipid Res 2005; 46:769-778
496. Tsimikas S, Clopton P, Brilakis ES, Marcovina SM, Khera A, Miller ER, de Lemos JA, Witztum JL. Relationship of oxidized phospholipids on apolipoprotein B-100 particles to race/ethnicity, apolipoprotein(a) isoform size, and cardiovascular risk factors: results from the Dallas Heart Study. Circulation 2009; 119:1711-1719
497. Tsimikas S, Mallat Z, Talmud PJ, Kastelein JJ, Wareham NJ, Sandhu MS, Miller ER, Benessiano J, Tedgui A, Witztum JL, Khaw KT, Boekholdt SM. Oxidation-specific biomarkers, lipoprotein(a), and risk of fatal and nonfatal coronary events. J Am Coll Cardiol 2010; 56:946-955
498. Maher VM, Brown BG, Marcovina SM, Hillger LA, Zhao XQ, Albers JJ. Effects of lowering elevated LDL cholesterol on the cardiovascular risk of lipoprotein(a). Jama 1995; 274:1771-1774
499. Khera AV, Everett BM, Caulfield MP, Hantash FM, Wohlgemuth J, Ridker PM, Mora S. Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an

analysis from the JUPITER Trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). Circulation 2014; 129:635-642
500. Kronenberg F. Lipoprotein(a): there's life in the old dog yet. Circulation 2014; 129:619-621
501. Catapano AL, Reiner Z, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman M, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D. ESC/EAS Guidelines for the management of dyslipidaemias The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis 2011; 217:3-46
502. Tsimikas S, Viney NJ, Hughes SG, Singleton W, Graham MJ, Baker BF, Burkey JL, Yang Q, Marcovina SM, Geary RS, Crooke RM, Witztum JL. Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study. Lancet 2015;
503. Abumrad N, el-Maghrabi M, Amri E, Lopez E, Grimaldi P. Cloning of a rat adipocyte membrane protein implicated in binding or transport of long-chain fatty acids that is induced during preadipocyte differentiation. Homology with human CD36. The Journal of biological chemistry 1993; 268:17665-17668
504. Cartwright I, Plonne D, Higgins J. Intracellular events in the assembly of chylomicrons in rabbit enterocytes. J Lipid Res 2000; 41:1728-1739
505. Mansbach C, 2nd, Gorelick F. Development and physiological regulation of intestinal lipid absorption. II. Dietary lipid absorption, complex lipid synthesis, and the intracellular packaging and secretion of chylomicrons. Am J Physiol Gastrointest Liver Physiol 2007; 293:G645-650
506. Mu H, Hoy CE. The digestion of dietary triacylglycerols. Prog Lipid Res 2004; 43:105-133
507. Phan C, Tso P. Intestinal lipid absorption and transport. Front Biosci 2001; 6:D299-319
508. Iqbal J, Hussain M. Intestinal lipid absorption. Am J Physiol Endocrinol Metab 2009; 296:E1183-1194
509. Pan X, Hussain M. Gut triglyceride production. Biochimica et biophysica acta 2012; 1821:727-735
510. Abumrad NA, Davidson NO. Role of the gut in lipid homeostasis. Physiological reviews 2012; 92:1061-1085
511. Prabhudas M, Bowdish D, Drickamer K, Febbraio M, Herz J, Kobzik L, Krieger M, Loike J, Means T, Moestrup S, Post S, Sawamura T, Silverstein S, Wang X, El Khoury J. Standardizing scavenger receptor nomenclature. J Immunol 2014; 192:1997-2006
512. Storch J, Thumser A. Tissue-specific functions in the fatty acid-binding protein family. The Journal of biological chemistry 2010; 285:32679-32683
513. Mansbach C, 2nd, Siddiqi S. The biogenesis of chylomicrons. Annual review of physiology 2010; 72:315-333
514. Glatz J, Luiken J. Dynamic role of the transmembrane glycoprotein CD36 (SR-B2) in cellular fatty acid uptake and utilization. J Lipid Res 2018; 59:1084-1093
515. Adeli K, Lewis G. Intestinal lipoprotein overproduction in insulin-resistant states. Current opinion in lipidology 2008; 19:221-228

516. Hussain M, Leung T, Zhou L, Abu-Merhi S. Regulating intestinal function to reduce atherogenic lipoproteins. Clin Lipidol 2013; 8
517. Shakir K, Sundaram S, Margolis S. Lipid synthesis in isolated intestinal cells. J Lipid Res 1978; 19:433-442
518. Hamilton R. Synthesis and secretion of plasma lipoproteins. Adv Exp Med Biol 1972; 26:7-24
519. Davidson N, Shelness G. APOLIPOPROTEIN B: mRNA editing, lipoprotein assembly, and presecretory degradation. Annu Rev Nutr 2000; 20:169-193
520. Anant S, Davidson N. Molecular mechanisms of apolipoprotein B mRNA editing. Current opinion in lipidology 2001; 12:159-165
521. Kumar N, Mansbach C, 2nd. Prechylomicron transport vesicle: isolation and partial characterization. Am J Physiol 1999; 276:G378-386
522. Levy E, Stan S, Delvin E, Menard D, Shoulders C, Garofalo C, Slight I, Seidman E, Mayer G, Bendayan M. Localization of microsomal triglyceride transfer protein in the Golgi: possible role in the assembly of chylomicrons. The Journal of biological chemistry 2002; 277:16470-16477
523. Chen Z, Davidson N. IRE1a-XBP1s induces PDI expression to increase MTP activity for hepatic VLDL assembly and lipid homeostasis. Cell Metab 2012; 16:473-486
524. Liang S, Wu X, Fisher E, Ginsberg H. The amino-terminal domain of apolipoprotein B does not undergo retrograde translocation from the endoplasmic reticulum to the cytosol. Proteasomal degradation of nascent apolipoprotein B begins at the carboxyl terminus of the protein, while apolipoprotein B is still in its original translocon. The Journal of biological chemistry 2000; 275:32003-32010
525. Kane J, Havel R. Disorders of the biogenesis and secretion of lipoproteins containing the B apolipoproteins. In: Scriver C, Beaudet A, Sly W, Valle D, eds. The Metabolic Basis of Inherited Disease, 6th Edition. New York, NY: McGraw-Hill; 1989:1139-1164.
526. Wetterau JR, Lin MC, Jamil H. Microsomal triglyceride transfer protein. Biochim Biophys Acta 1997; 1345:136-150
527. Hussain M. A proposed model for the assembly of chylomicrons. Atherosclerosis 2000; 148:1-15
528. Yamaguchi J, Conlon D, Liang J, Fisher E, Ginsberg H. Translocation efficiency of apolipoprotein B is determined by the presence of b-sheet domains, not pause transfer sequences. The Journal of biological chemistry 2006; 281:27063-27071
529. Shoulders C, Stephens D, Jones B. The intracellular transport of chylomicrons requires the small GTPase, Sar1b. Current opinion in lipidology 2004; 15:191-197
530. Siddiqi S, Mahan J, Siddiqi S, Gorelick F, Mansbach C, 2nd. Vesicle-associated membrane protein 7 is expressed in intestinal ER. J Cell Sci 2006; 119:943-950
531. Siddiqi S, Saleem U, Abumrad N, Davidson N, Storch J, Siddiqi S, Mansbach C, 2nd. A novel multiprotein complex is required to generate the prechylomicron transport vesicle from intestinal ER. J Lipid Res 2010; 51:1918-1928
532. Berriot-Varoqueaux N, Dannoura A, Moreau A, Verthier N, Sassolas A, Cadiot G, Lachaux A, Munck A, Schmitz J, Aggerbeck L, Samson-Bouma M. Apolipoprotein B48 glycosylation in abetalipoproteinemia and Anderson's disease. Gastroenterology 2001; 121:1101-1108

533. Siddiqi S, Siddiqi S, Mahan J, Peggs K, Gorelick F, Mansbach C, 2nd. The identification of a novel endoplasmic reticulum to Golgi SNARE complex used by the prechylomicron transport vesicle. The Journal of biological chemistry 2006; 281:20974-20982
534. Jones B, Jones E, Bonney S, Patel H, Mensenkamp A, Eichenbaum-Voline S, Rudling M, Myrdal U, Annesi G, Naik S, Meadows N, Quattrone A, Islam S, Naoumova R, Angelin B, Infante R, Levy E, Roy C, Freemont P, Scott J, Shoulders C. Mutations in a Sar1 GTPase of COPII vesicles are associated with lipid absorption disorders. Nat Genet 2003; 34:29-31
535. Sabesin S, Clark S, Holt P. Ultrastructural features of regional differences in chylomicron secretion by rat intestine. Experimental and molecular pathology 1977; 26:277-289
536. Shen B, Scanu A, Kezdy F. Structure of human serum lipoproteins inferred from compositional analysis. Proceedings of the National Academy of Sciences of the United States of America 1977; 74:837-841
537. Mead J. Lipid Metabolism. Annual review of biochemistry 1963; 32:241-268
538. Sane A, Sinnett D, Delvin E, Bendayan M, Marcil V, Menard D, Beaulieu J, Levy E. Localization and role of NPC1L1 in cholesterol absorption in human intestine. J Lipid Res 2006; 47:2112-2120
539. Stange E, Dietschy J. Cholesterol synthesis and low density lipoprotein uptake are regulated independently in rat small intestinal epithelium. Proc Nat Acad Sci, USA 1983; 80:5739-5743
540. Le May C, Berger J, Lespine A, Pillot B, Prieur X, Letessier E, Hussain M, Collet X, Cariou B, Costet P. Transintestinal Cholesterol Excretion Is an Active Metabolic Process Modulated by PCSK9 and Statin Involving ABCB1. Arteriosclerosis, thrombosis, and vascular biology 2013; 33:1484-1493
541. Tomkin G, Owens D. The chylomicron: relationship to atherosclerosis. International journal of vascular medicine 2012; 2012:784536
542. Brinton E. Management of Hypertriglyceridemia for Prevention of Atherosclerotic Cardiovascular Disease. Cardiology clinics 2015; 33:309-323
543. Thiam A, Farese R, Jr., Walther T. The biophysics and cell biology of lipid droplets. Nat Rev Mol Cell Biol 2013; 14:775-786
544. Demignot S, Beilstein F, Morel E. Triglyceride-rich lipoproteins and cytosolic lipid droplets in enterocytes: key players in intestinal physiology and metabolic disorders. Biochimie 2014; 96:48-55
545. Lehner R, Lian J, Quiroga A. Lumenal lipid metabolism: implications for lipoprotein assembly. Arteriosclerosis, thrombosis, and vascular biology 2012; 32:1087-1093
546. van der Veen J, van Dijk T, Vrins C, van Meer H, Havinga R, Bijsterveld K, Tietge U, Groen A, Kuipers F. Activation of the liver X receptor stimulates trans-intestinal excretion of plasma cholesterol. The Journal of biological chemistry 2009; 284:19211-19219
547. Temel R, Brown J. A new model of reverse cholesterol transport: enTICEing strategies to stimulate intestinal cholesterol excretion. Trends in pharmacological sciences 2015; 36:440-451
548. Miller M, Stone N, Ballantyne C, Bittner V, Criqui M, Ginsberg H, Goldberg A, Howard W, Jacobson M, Kris-Etherton P, Lennie T, Levi M, Mazzone T, Pennathur S, American Heart Association Clinical Lipidology T, Prevention Committee of the Council on Nutrition

PA, Metabolism, Council on Arteriosclerosis T, Vascular B, Council on Cardiovascular N, Council on the Kidney in Cardiovascular D. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2011; 123:2292-2333
549. Christian J, Bourgeois N, Snipes R, Lowe K. Prevalence of severe (500 to 2,000 mg/dl) hypertriglyceridemia in United States adults. The American journal of cardiology 2011; 107:891-897
550. Ford E, Li C, Zhao G, Pearson W, Mokdad A. Hypertriglyceridemia and its pharmacologic treatment among US adults. Archives of internal medicine 2009; 169:572-578
551. Maki K, Bays H, Dicklin M. Treatment options for the management of hypertriglyceridemia: strategies based on the best-available evidence. Journal of clinical lipidology 2012; 6:413-426
552. Carroll M, Lacher D, Sorlie P, Cleeman J, Gordon D, Wolz M, Grundy S, Johnson C. Trends in serum lipids and lipoproteins of adults, 1960-2002. JAMA 2005; 294:1773-1781
553. Flegal K, Carroll M, Ogden C, Johnson C. Prevalence and trends in obesity among US adults, 1999-2000. JAMA 2002; 288:1723-1727
554. Yuan G, Al-Shali K, Hegele R. Hypertriglyceridemia: its etiology, effects and treatment. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2007; 176:1113-1120
555. Austin M, Hokanson J, Edwards K. Hypertriglyceridemia as a cardiovascular risk factor. The American journal of cardiology 1998; 81:7B-12B
556. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt S, Khaw K, Gudnason V. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation 2007; 115:450-458
557. Castelli W. The triglyceride issue: a view from Framingham. American heart journal 1986; 112:432-437
558. Rhoads G, Blackwelder W, Stemmermann G, Hayashi T, Kagan A. Coronary risk factors and autopsy findings in Japanese-American men. Laboratory investigation; a journal of technical methods and pathology 1978; 38:304-311
559. Robertson T, Kato H, Gordon T, Kagan A, Rhoads G, Land C, Worth R, Belsky J, Dock D, Miyanishi M, Kawamoto S. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Coronary heart disease risk factors in Japan and Hawaii. The American journal of cardiology 1977; 39:244-249
560. Yano K, Rhoads G, Kagan A, Tillotson J. Dietary intake and the risk of coronary heart disease in Japanese men living in Hawaii. Am J Clin Nutr 1978; 31:1270-1279
561. Hulley S, Rosenman R, Bawol R, Brand R. Epidemiology as a guide to clinical decisions. The association between triglyceride and coronary heart disease. The New England journal of medicine 1980; 302:1383-1389
562. Lindkvist B, Appelros S, Regner S, Manjer J. A prospective cohort study on risk of acute pancreatitis related to serum triglycerides, cholesterol and fasting glucose.

Pancreatology : official journal of the International Association of Pancreatology 2012; 12:317-324
563. Murphy M, Sheng X, MacDonald T, Wei L. Hypertriglyceridemia and acute pancreatitis. JAMA internal medicine 2013; 173:162-164
564. Preiss D, Tikkanen M, Welsh P, Ford I, Lovato L, Elam M, LaRosa J, DeMicco DA, Colhoun H, Goldenberg I, Murphy M, MacDonald T, Pedersen T, Keech A, Ridker P, Kjekshus J, Sattar N, McMurray J. Lipid-modifying therapies and risk of pancreatitis: a meta-analysis. JAMA 2012; 308:804-811
565. Sandhu S, Al-Sarraf A, Taraboanta C, Frohlich J, Francis G. Incidence of pancreatitis, secondary causes, and treatment of patients referred to a specialty lipid clinic with severe hypertriglyceridemia: a retrospective cohort study. Lipids in health and disease 2011; 10:157
566. Jacobs D, Jr., Barrett-Connor E. Retest reliability of plasma cholesterol and triglyceride. The Lipid Research Clinics Prevalence Study. American journal of epidemiology 1982; 116:878-885
567. NIH Consensus conference. Triglyceride, high-density lipoprotein, and coronary heart disease. NIH Consensus Development Panel on Triglyceride, High-Density Lipoprotein, and Coronary Heart Disease. JAMA 1993; 269:505-510
568. Miller M. Chapter 9. High-density lipoprotein cholesterol and triglycerides in coronary heart disease risk assessment. In: Ballantyne C, ed. Clinical lipidology: A companion to Braunwald's Heart Disease, Second Edition. Philadelphia: Elsevier Saunders; 2015:100-108.
569. Pejic R, Lee D. Hypertriglyceridemia. Journal of the American Board of Family Medicine : JABFM 2006; 19:310-316
570. Talayero B, Sacks F. The role of triglycerides in atherosclerosis. Current cardiology reports 2011; 13:544-552
571. Katcher H, Hill A, Lanford J, Yoo J, Kris-Etherton P. Lifestyle approaches and dietary strategies to lower LDL-cholesterol and triglycerides and raise HDL-cholesterol. Endocrinology and metabolism clinics of North America 2009; 38:45-78
572. Brunner D, Altman S, Loebl K, Schwartz S, Levin S. Serum cholesterol and triglycerides in patients suffering from ischemic heart disease and in healthy subjects. Atherosclerosis 1977; 28:197-204
573. Castelli W, Doyle J, Gordon T, Hames C, Hjortland M, Hulley S, Kagan A, Zukel W. HDL cholesterol and other lipids in coronary heart disease. The cooperative lipoprotein phenotyping study. Circulation 1977; 55:767-772
574. Fager G, Wiklund O, Olofsson S, Wilhelmsen L, Bondjers G. Multivariate analyses of serum apolipoproteins and risk factors in relation to acute myocardial infarction. Arteriosclerosis 1981; 1:273-279
575. Gotto A, Gorry G, Thompson J, Cole J, Trost R, Yeshurun D, DeBakey M. Relationship between plasma lipid concentrations and coronary artery disease in 496 patients. Circulation 1977; 56:875-883
576. Hamsten A, Walldius G, Dahlen G, Johansson B, De Faire U. Serum lipoproteins and apolipoproteins in young male survivors of myocardial infarction. Atherosclerosis 1986; 59:223-235

577. Kukita H, Imamura Y, Hamada M, Joh T, Kokubu T. Plasma lipids and lipoproteins in Japanese male patients with coronary artery disease and in their relatives. Atherosclerosis 1982; 42:21-29
578. Scott D, Gotto A, Cole J, Gorry G. Plasma lipids as collateral risk factors in coronary artery disease--a study of 371 males with chest pain. Journal of chronic diseases 1978; 31:337-345
579. Assmann G, Cullen P, Schulte H. The Munster Heart Study (PROCAM). Results of follow-up at 8 years. European heart journal 1998; 19 Suppl A:A2-A11
580. Miller M, Cannon C, Murphy S, Qin J, Ray K, Braunwald E, Investigators PI-T. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. J Am Coll Cardiol 2008; 51:724-730
581. Do R, Willer CJ, Schmidt EM, Sengupta S, Gao C, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, Beckmann JS, Bragg-Gresham JL, Chang HY, Demirkan A, Den Hertog HM, Donnelly LA, Ehret GB, Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkila K, Hypponen E, Isaacs A, Jackson AU, Johansson A, Johnson T, Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lyytikainen LP, Magnusson PK, Mangino M, Mihailov E, Montasser ME, Muller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD, Perola M, Petersen AK, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ, Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G, Dimitriou M, Doney AS, Doring A, Elliott P, Epstein SE, Eyjolfsson GI, Gigante B, Goodarzi MO, Grallert H, Gravito ML, Groves CJ, Hallmans G, Hartikainen AL, Hayward C, Hernandez D, Hicks AA, Holm H, Hung YJ, Illig T, Jones MR, Kaleebu P, Kastelein JJ, Khaw KT, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimaki T, Lin SY, Lindstrom J, Loos RJ, Mach F, McArdle WL, Meisinger C, Mitchell BD, Muller G, Nagaraja R, Narisu N, Nieminen TV, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stancakova A, Stirrups K, Swift AJ, Tiret L, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N, Wijmenga C, Wild SH, Willemsen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen YD, Collins FS, Cooper RS, Danesh J, Dedoussis G, de Faire U, Feranil AB, Ferrieres J, Ferrucci L, Freimer NB, Gieger C, Groop LC, Gudnason V, Gyllensten U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Hveem K, Iribarren C, Jarvelin MR, Jula A, Kahonen M, Kaprio J, Kesaniemi A, Kivimaki M, Kooner JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L, Lindgren CM, Martin NG, Marz W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L, Morris AD, Munroe PB, Njolstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R, Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PE, Sheu WH, Shuldiner AR, Siegbahn A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli

E, Tuomilehto J, Uusitupa M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolffenbuttel BH, Altshuler D, Ordovas JM, Boerwinkle E, Palmer CN, Thorsteinsdottir U, Chasman DI, Rotter JI, Franks PW, Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P, Mohlke KL, Ingelsson E, Abecasis GR, Daly MJ, Neale BM, Kathiresan S. Common variants associated with plasma triglycerides and risk for coronary artery disease. Nature genetics 2013; 45:1345-1352

582. Holmes MV, Asselbergs FW, Palmer TM, Drenos F, Lanktree MB, Nelson CP, Dale CE, Padmanabhan S, Finan C, Swerdlow DI, Tragante V, van Iperen EP, Sivapalaratnam S, Shah S, Elbers CC, Shah T, Engmann J, Giambartolomei C, White J, Zabaneh D, Sofat R, McLachlan S, Doevendans PA, Balmforth AJ, Hall AS, North KE, Almoguera B, Hoogeveen RC, Cushman M, Fornage M, Patel SR, Redline S, Siscovick DS, Tsai MY, Karczewski KJ, Hofker MH, Verschuren WM, Bots ML, van der Schouw YT, Melander O, Dominiczak AF, Morris R, Ben-Shlomo Y, Price J, Kumari M, Baumert J, Peters A, Thorand B, Koenig W, Gaunt TR, Humphries SE, Clarke R, Watkins H, Farrall M, Wilson JG, Rich SS, de Bakker PI, Lange LA, Davey Smith G, Reiner AP, Talmud PJ, Kivimaki M, Lawlor DA, Dudbridge F, Samani NJ, Keating BJ, Hingorani AD, Casas JP. Mendelian randomization of blood lipids for coronary heart disease. European heart journal 2015; 36:539-550
583. Thomsen M, Varbo A, Tybjaerg-Hansen A, Nordestgaard BG. Low nonfasting triglycerides and reduced all-cause mortality: a mendelian randomization study. Clinical chemistry 2014; 60:737-746
584. Baigent C, Keech A, Kearney P, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R, Cholesterol Treatment Trialists C. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005; 366:1267-1278
585. Patel A, Barzi F, Jamrozik K, Lam T, Ueshima H, Whitlock G, Woodward M, Asia Pacific Cohort Studies C. Serum triglycerides as a risk factor for cardiovascular diseases in the Asia-Pacific region. Circulation 2004; 110:2678-2686
586. Sacks F, Tonkin A, Craven T, Pfeffer M, Shepherd J, Keech A, Furberg C, Braunwald E. Coronary heart disease in patients with low LDL-cholesterol: benefit of pravastatin in diabetics and enhanced role for HDL-cholesterol and triglycerides as risk factors. Circulation 2002; 105:1424-1428
587. Jun M, Foote C, Lv J, Neal B, Patel A, Nicholls S, Grobbee D, Cass A, Chalmers J, Perkovic V. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet 2010; 375:1875-1884
588. Hokanson J, Austin M. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996; 3:213-219
589. Desnuelle P, Savary P. Specificities of Lipases. J Lipid Res 1963; 4:369-384
590. Brewer H, Jr. Hypertriglyceridemia: changes in the plasma lipoproteins associated with an increased risk of cardiovascular disease. The American journal of cardiology 1999; 83:3F-12F

591. Zheng C, Khoo C, Furtado J, Sacks F. Apolipoprotein C-III and the metabolic basis for hypertriglyceridemia and the dense low-density lipoprotein phenotype. Circulation 2010; 121:1722-1734
592. Ooi T, Ooi D. The atherogenic significance of an elevated plasma triglyceride level. Critical Rev Clin Lab Sci 1998; 35:489-516
593. Nordestgaards B. The vascular endothelial barrier-selective retention of lipoproteins. Current opinion in lipidology 1996; 7:269–273
594. Zilversmit D. A proposal linking atherogenesis to the interaction of endothelial lipoprotein lipase with triglyceride-rich lipoproteins. Circulation research 1973; 33:633-638
595. Mamo J, Proctor S, Smith D. Retention of chylomicron remnants by arterial tissue; importance of an efficient clearance mechanism from plasma. Atherosclerosis 1998; 141 Suppl 1:S63-S69
596. Rutledge J, Mullick A, Gardner G, Goldberg IJ. Direct visualization of lipid deposition and reverse lipid transport in a perfused artery : roles of VLDL and HDL. Circulation research 2000; 86:768-773
597. Van Eck M, Zimmermann R, Groot P, Zechner R, Van Berkel T. Role of macrophage-derived lipoprotein lipase in lipoprotein metabolism and atherosclerosis. Arteriosclerosis, thrombosis, and vascular biology 2000; 20:E53-62
598. Mahley RW, Huang Y, Rall SC, Jr. Pathogenesis of type III hyperlipoproteinemia (dysbetalipoproteinemia). Questions, quandaries, and paradoxes. J Lipid Res 1999; 40:1933-1949
599. Mahley R, Ji Z. Remnant lipoprotein metabolism: key pathways involving cell-surface heparan sulfate proteoglycans and apolipoprotein E. J Lipid Res 1999; 40:1-16
600. Mahley R, Weisgraber K, Farese R. Disorders of lipid metabolism. Williams textbook of endocrinology. Vol 91998:1099-1119.
601. Abou Ziki MD, Strulovici-Barel Y, Hackett NR, Rodriguez-Flores JL, Mezey JG, Salit J, Radisch S, Hollmann C, Chouchane L, Malek J, Zirie MA, Jayyuosi A, Gotto AM, Jr., Crystal RG. Prevalence of the apolipoprotein E Arg145Cys dyslipidemia at-risk polymorphism in African-derived populations. The American journal of cardiology 2014; 113:302-308
602. de Villiers WJ, van der Westhuyzen DR, Coetzee GA, Henderson HE, Marais AD. The apolipoprotein E2 (Arg145Cys) mutation causes autosomal dominant type III hyperlipoproteinemia with incomplete penetrance. Arteriosclerosis, thrombosis, and vascular biology 1997; 17:865-872
603. Schaefer E, Gregg R, Ghiselli G, Forte T, Ordovas J, Zech L, Brewer H, Jr. Familial apolipoprotein E deficiency. J Clin Invest 1986; 78:1206-1219
604. Lada A, Rudel L, St Clair R. Effects of LDL enriched with different dietary fatty acids on cholesteryl ester accumulation and turnover in THP-1 macrophages. J Lipid Res 2003; 44:770-779
605. Lada AT, Willingham MC, St. Clair R. Triglyceride depletion in THP-1 cells alters cholesteryl ester physical state and cholesterol efflux. J Lipid Res 2002; 43:618-628
606. Rothblat G, Bamberger M, Phillips M. Reverse cholesterol transport. Methods in Enzymology 1986; 129:628-644

607. Ullery-Ricewick J, Cox B, Griffin E, Jerome W. Triglyceride alters lysosomal cholesteryl ester metabolism in cholesteryl-ester laden macrophage foam cells. J Lipid Res 2009; 50:2014-2026
608. Hardy S, Langelier Y, Prentki M. Oleate activates phosphatidylinositol 3-kinase and promotes proliferation and reduces apoptosis of MDA-MB-231 breast cancer cells, whereas palmitate has opposite effects. Cancer research 2000; 60:6353-6358
609. Maedler K, Spinas G, Dyntar D, Moritz W, Kaiser N, Donath M. Distinct effects of saturated and monounsaturated fatty acids on beta-cell turnover and function. Diabetes 2001; 50:69-76
610. Paumen M, Ishida Y, Muramatsu M, Yamamoto M, Honjo T. Inhibition of carnitine palmitoyltransferase I augments sphingolipid synthesis and palmitate-induced apoptosis. The Journal of biological chemistry 1997; 272:3324-3329
611. Chang W, Lin J, Dong J, Li D. Pyroptosis: an inflammatory cell death implicates in atherosclerosis. Medical hypotheses 2013; 81:484-486
612. Tabas I. Apoptosis and plaque destabilization in atherosclerosis: the role of macrophage apoptosis induced by cholesterol. Cell Death and Differentiation 2004; 11:S12-S16
613. Leitinger N, Schulman I. Phenotypic polarization of macrophages in atherosclerosis. Arteriosclerosis, thrombosis, and vascular biology 2013; 33:1120-1126
614. Hansson G. Immune mechanisms in plaque formation. Atherosclerosis rev 1991; 23:169-176
615. Yla-Herttuala S, Lipton B, Rosenfeld M, Goldberg I, Steinberg D, Witztum J. Macrophages and smooth muscle cells express lipoprotein lipase in human and rabbit atherosclerotic lesions. Proceedings of the National Academy of Sciences of the United States of America 1991; 88:10143-10147
616. Zhang W, Schwartz E, Wang Y, Attrep J, Li Z, Reaven P. Elevated concentrations of nonesterified fatty acids increase monocyte expression of CD11b and adhesion to endothelial cells. Arteriosclerosis, thrombosis, and vascular biology 2006; 26:514-519
617. Chung B, Segrest J, Smith K, Griffin F, Brouillette C. Lipolytic surface remnants of triglyceride-rich lipoproteins are cytotoxic to macrophages but not in the presence of high density lipoprotein. J Clin Invest 1989; 83:1363-1374
618. Kume N, Cybulsky M, Gimbrone M, Jr. Lysophosphatidylcholine, a component of atherogenic lipoproteins, induces mononuclear leukocyte adhesion molecules in cultured human and rabbit arterial endothelial cells. J Clin Invest 1992; 90:1138-1144
619. Wang MD, Kiss RS, Franklin V, McBride HM, Whitman SC, Marcel YL. Different cellular traffic of LDL-cholesterol and acetylated LDL-cholesterol leads to distinct reverse cholesterol transport pathways. J Lipid Res 2007; 48:633-645
620. Wehinger A, Tancevski I, Schgoer W, Eller P, Hochegger K, Morak M, Hermetter A, Ritsch A, Patsch J, Foeger B. Phospholipid transfer protein augments apoptosis in THP-1-derived macrophages induced by lipolyzed hypertriglyceridemic plasma. Arteriosclerosis, thrombosis, and vascular biology 2007; 27:908-815
621. Benlian P, De Gennes JL, Foubert L, Zhang H, Gagne SE, Hayden M. Premature atherosclerosis in patients with familial chylomicronemia caused by mutations in the lipoprotein lipase gene. The New England journal of medicine 1996; 335:848-854

622. Clee S, Bissada N, Miao F, Miao L, Marais A, Henderson H, Steures P, McManus J, McManus B, LeBoeuf R, Kastelein J, Hayden M. Plasma and vessel wall lipoprotein lipase have different roles in atherosclerosis. J Lipid Res 2000; 41:521-531
623. de Souza R, Mente A, Maroleanu A, Cozma A, Ha V, Kishibe T, Uleryk E, Budylowski P, Schunemann H, Beyene J, Anand S. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. Bmj 2015; 351:h3978
624. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. PLoS medicine 2010; 7:e1000252
625. Hooper L, Martin N, Abdelhamid A, Davey Smith G. Reduction in saturated fat intake for cardiovascular disease. The Cochrane database of systematic reviews 2015; 6:CD011737
626. Jakobsen M, O'Reilly E, Heitmann B, Pereira M, Balter K, Fraser G, Goldbourt U, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett W, Ascherio A. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. Am J Clin Nutr 2009; 89:1425-1432
627. Li Y, Hruby A, Bernstein A, Ley S, Wang D, Chiuve S, Sampson L, Rexrode K, Rimm E, Willett W, Hu F. Saturated Fats Compared With Unsaturated Fats and Sources of Carbohydrates in Relation to Risk of Coronary Heart Disease: A Prospective Cohort Study. J Am Coll Cardiol 2015; 66:1538-1548
628. Yamagishi K, Nettleton JA, Folsom AR, Investigators AS. Plasma fatty acid composition and incident heart failure in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. American heart journal 2008; 156:965-974
629. Stampfer M, Hu F, Manson J, Rimm E, Willett W. Primary prevention of coronary heart disease in women through diet and lifestyle. The New England journal of medicine 2000; 343:16-22
630. Hu F, Willett W. Diet and coronary heart disease: findings from the Nurses' Health Study and Health Professionals' Follow-up Study. The journal of nutrition, health & aging 2001; 5:132-138
631. Mozaffarian D, Wu J. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol 2011; 58:2047-2067
632. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT, Jr., Juliano RA, Jiao L, Granowitz C, Tardif JC, Ballantyne CM, Investigators R-I. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. The New England journal of medicine 2018;
633. Maki K, Lawless A, Kelley K, Kaden V, Geiger C, Dicklin M. Corn oil improves the plasma lipoprotein lipid profile compared with extra-virgin olive oil consumption in men and women with elevated cholesterol: results from a randomized controlled feeding trial. Journal of clinical lipidology 2015; 9:49-57
634. Wagner K, Tomasch R, Elmadfa I. Impact of diets containing corn oil or olive/sunflower oil mixture on the human plasma and lipoprotein lipid metabolism. European journal of nutrition 2001; 40:161-167

635. Lichtenstein A, Ausman L, Carrasco W, Jenner J, Gualtieri L, Goldin B, Ordovas J, Schaefer E. Effects of canola, corn, and olive oils on fasting and postprandial plasma lipoproteins in humans as part of a National Cholesterol Education Program Step 2 diet. Arterioscler Thromb 1993; 13:1533-1542
636. Micha R, Mozaffarian D. Trans fatty acids: effects on metabolic syndrome, heart disease and diabetes. Nature reviews Endocrinology 2009; 5:335-344
637. Wang Q, Imamura F, Lemaitre R, Rimm E, Wang M, King I, Song X, Siscovick D, Mozaffarian D. Plasma phospholipid trans-fatty acids levels, cardiovascular diseases, and total mortality: the cardiovascular health study. Journal of the American Heart Association 2014; 3
638. Jacobson T, Maki K, Orringer C, Jones P, Kris-Etherton P, Sikand G, Forge R, Daniels S, Wilson D, Morris P, Wild R, Grundy S, Daviglus M, Ferdinand K, Vijay K, Deedwania P, Aberg J, Liao K, McKenney J, Ross J, Braun L, Ito M, Bolick J, Dicklin M, Kirkpatrick C, Rhodes K, Smith N, Blackett P, DeFerranti S, Gidding S, Davey R-E, McCrindle B, McNeal C, Urbina E, Dayspring T, Underberg J, Lopez J, Pirzada A, Roderguez C, Fichtenbaum C, Gallant J, Horberg M, Longenecker C, Myerson M, Overton E, Coblyn J, Curtis J, Plutzky J, Solomon D, Bays H, Brown W. National lipid association recommendations for patient-centered management of dyslipidemia: part 2. Journal of clinical lipidology 2015; In Press
639. Bates S, Murphy P, Feng Z, Kanazawa T, Getz G. Very low density lipoproteins promote triglyceride accumulation in macrophages. Arteriosclerosis 1984; 4:103-114
640. Lindqvist P, Ostlund-Lindqvist AM, Witztum JL, Steinberg D, Little JA. The role of lipoprotein lipase in the metabolism of triglyceride-rich lipoproteins by macrophages. J Biol Chem 1983; 258:9086-9092
641. Gianturco S, Ramprasad M, Lin A, Song R, Bradley W. Cellular binding site and membrane binding proteins for triglyceride-rich lipoproteins in human monocyte-macrophages and THP-1 monocytic cells. J Lipid Res 1994; 35:1674-1687
642. Evans A, Sawyez C, Wolfe B, Connelly P, Maquire G, Huff M. Evidence that cholesteryl ester and triglyceride accumulation in J774 macrophages induced by very low density lipoprotein subfractions occurs by different mechanisms. J Lipid Res 1993; 34:703-717
643. Tabas I, Myers J, Innerarity T, Xu X, Arnold J, Maxfield F. The influence of particle size and multiple apoprotein E-receptor interactions on the endocytic targeting of b-VLDL in mouse. J Cell Biol 1991; 115:1547-1560
644. Brown W, Levy R, Fredrickson D. Studies of the proteins in human plasma very low density lipoproteins. The Journal of biological chemistry 1969; 244:5687-5694
645. Brown W, Baginsky M. Inhibition of lipoprotein lipase by an apoprotein of human very low density lipoprotein. Biochem Biophys Res Commun 1972; 46:375-382
646. Windler E, Havel R. Inhibitory effects of C apolipoproteins from rats and humans on the uptake of triglyceride-rich lipoproteins and their remnants by the perfused rat liver. J Lipid Res 1985; 26:556-565
647. Ginsberg H, Le N, Goldberg I, Gibson J, Rubinstein A, Wang-Iverson P, Norum R, Brown W. Apolipoprotein B metabolism in subjects with deficiency of apolipoproteins CIII and AI. Evidence that apolipoprotein CIII inhibits catabolism of triglyceride-rich lipoproteins by lipoprotein lipase in vivo. J Clin Invest 1986; 78:1287-1295

648. Ito Y, Azrolan N, O'Connell A, Walsh A, Breslow J. Hypertriglyceridemia as a result of human apo CIII gene expression in transgenic mice. Science 1990; 249:790-793
649. Pollin T, Damcott C, Shen H, Ott SH, Shelton J, Horenstein R, Post W, McLenithan J, Bielak L, Peyser P, Mitchell B, Miller M, O'Connell J, Shuldiner A. A null mutation in human APOC3 confers a favorable plasma lipid profile and apparent cardioprotection. Science 2008; 322:1702-1705
650. Bochem A, van Capelleveen J, Dallinga-Thie G, Schimmel A, Motazacker M, Tietjen I, Singaraja R, Hayden M, Kastelein J, Stroes E, Hovingh G. Two novel mutations in apolipoprotein C3 underlie atheroprotective lipid profiles in families. Clinical genetics 2014; 85:433-440
651. Crosby J, Peloso G, Auer P, Crosslin D, Stitziel N, Lange L, Lu Y, Tang Z, Zhang H, Hindy G, Masca N, Stirrups K, Kanoni S, Do R, Jun G, Hu Y, Kang H, Xue C, Goel A, Farrall M, Duga S, Merlini P, Asselta R, Girelli D, Olivieri O, Martinelli N, Yin W, Reilly D, Speliotes E, Fox C, Hveem K, Holmen O, Nikpay M, Farlow D, Assimes T, Franceschini N, Robinson J, North K, Martin L, Gupta N, Escher S, Jansson J, Van Zuydam N, Palmer C, Wareham N, Koch W, Meitinger T, Peters A, Lieb W, Erbel R, Konig I, Kruppa J, Degenhardt F, Gottesman O, Bottinger E, O'Donnell C, Psaty B, Ballantyne C, Abecasis G, Ordovas J, Melander O, Watkins H, Orho-Melander M, Ardissino D, Loos R, McPherson R, Willer C, Erdmann J, Hall A, Samani N, Deloukas P, Schunkert H, Wilson J, Kooperberg C, Rich S, Tracy R, Lin D, Gabriel S, Nickerson D, Jarvik G, Cupples L, Reiner A, Boerwinkle E, Kathiresan S, Institute THWGotESPNHLB. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. The New England journal of medicine 2014; 371:22-31
652. Jorgensen A, Frikke-Schmidt R, Nordestgaard B, Tybjaerg-Hansen A. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. The New England journal of medicine 2014; 371:32-41
653. Graham M, Lee R, Bell T, 3rd, Fu W, Mullick A, Alexander V, Singleton W, Viney N, Geary R, Su J, Baker B, Burkey J, Crooke S, Crooke R. Antisense oligonucleotide inhibition of apolipoprotein C-III reduces plasma triglycerides in rodents, nonhuman primates, and humans. Circulation research 2013; 112:1479-1490
654. Digenio A, Dunbar RL, Alexander VJ, Hompesch M, Morrow L, Lee RG, Graham MJ, Hughes SG, Yu R, Singleton W, Baker BF, Bhanot S, Crooke RM. Antisense-Mediated Lowering of Plasma Apolipoprotein C-III by Volanesorsen Improves Dyslipidemia and Insulin Sensitivity in Type 2 Diabetes. Diabetes care 2016; 39:1408-1415
655. Pechlaner R, Tsimikas S, Yin X, Willeit P, Baig F, Santer P, Oberhollenzer F, Egger G, Witztum JL, Alexander VJ, Willeit J, Kiechl S, Mayr M. Very-Low-Density Lipoprotein-Associated Apolipoproteins Predict Cardiovascular Events and Are Lowered by Inhibition of APOC-III. Journal of the American College of Cardiology 2017; 69:789-800
656. Kawakami A, Aikawa M, Alcaide P, Luscinskas F, Libby P, Sacks F. Apolipoprotein CIII induces expression of vascular cell adhesion molecule-1 in vascular endothelial cells and increases adhesion of monocytic cells. Circulation 2006; 114:681-687
657. Kawakami A, Osaka M, Tani M, Azuma H, Sacks F, Shimokado K, Yoshida M. Apolipoprotein CIII links hyperlipidemia with vascular endothelial cell dysfunction. Circulation 2008; 118:731-742

658. Hiukka A, Stahlman M, Pettersson C, Levin M, Adiels M, Teneberg S, Leinonen E, Hulten L, Wiklund O, Oresic M, Olofsson S, Taskinen M, Ekroos K, Boren J. ApoCIII-enriched LDL in type 2 diabetes displays altered lipid composition, increased susceptibility for sphingomyelinase, and increased binding to biglycan. Diabetes 2009; 58:2018-2026
659. Georgieva A, Cate H, Keulen E, van Oerle R, Govers-Riemslag J, Hamulyak K, van der Kallen C, Van Greevenbroek M, De Bruin T. Prothrombotic markers in familial combined hyperlipidemia: evidence of endothelial cell activation and relation to metabolic syndrome. Atherosclerosis 2004; 175:345-351
660. Sutherland J, McKinley B, Eckel R. The metabolic syndrome and inflammation. Metabolic syndrome and related disorders 2004; 2:82-104
661. Norata G, Grigore L, Raselli S, Redaelli L, Hamsten A, Maggi F, Eriksson P, Catapano A. Post-prandial endothelial dysfunction in hypertriglyceridemic subjects: molecular mechanisms and gene expression studies. Atherosclerosis 2007; 193:321-327
662. Berglund L, Brunzell J, Goldberg A, Goldberg I, Sacks F, Murad M, Stalenhoef A, Endocrine s. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. The Journal of clinical endocrinology and metabolism 2012; 97:2969-2989
663. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Circulation 2002; 106:3143-3421
664. Brunzell J, Davidson M, Furberg C, Goldberg R, Howard B, Stein J, Witztum J, American Diabetes A, American College of Cardiology F. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. Diabetes Care 2008; 31:811-822
665. Manninen V, Tenkanen L, Koskinen P, Huttunen J, Manttari M, Heinonen O, Frick M. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. Circulation 1992; 85:37-45
666. Rubins H, Robins S, Collins D, Fye C, Anderson J, Elam M, Faas F, Linares E, Schaefer E, Schectman G, Wilt T, Wittes J. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. The New England journal of medicine 1999; 341:410-418
667. Robins S, Collins D, Wittes J, Papademetriou V, Deedwania P, Schaefer E, McNamara J, Kashyap M, Hershman J, Wexler L, Rubins H, Trial V-HSGVAH-DLI. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. JAMA 2001; 285:1585-1591
668. Ginsberg H, Elam M, Lovato L, Crouse J, 3rd, Leiter L, Linz P, Friedewald W, Buse J, Gerstein H, Probstfield J, Grimm R, Ismail-Beigi F, Bigger J, Goff D, Jr., Cushman W, Simons-Morton D, Byington R. Effects of combination lipid therapy in type 2 diabetes mellitus. The New England journal of medicine 2010; 362:1563-1574
669. Keech A, Simes R, Barter P, Best J, Scott R, Taskinen M, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesaniemi Y, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting

M, Ehnholm C, Laakso M, investigators Fs. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005; 366:1849-1861
670. Barter P, Rye K. Is there a role for fibrates in the management of dyslipidemia in the metabolic syndrome? Arteriosclerosis, thrombosis, and vascular biology 2008; 28:39-46
671. Elam M, Lovato L, Ginsberg H. Role of fibrates in cardiovascular disease prevention, the ACCORD-Lipid perspective. Current opinion in lipidology 2011; 22:55-61
672. Freeman M, Walford G. Chapter 41. Lipoprotein metabolism and the treatment of lipid disorders. In: Jameson J, De Groot L, eds. Endocrinology, adult and pediatric, Seventh Edition2015.
673. Branchi A, Fiorenza A, Rovellini A, Torri A, Muzio F, Macor S, Sommariva D. Lowering effects of four different statins on serum triglyceride level. European journal of clinical pharmacology 1999; 55:499-502
674. Guyton JR, Slee AE, Anderson T, Fleg JL, Goldberg RB, Kashyap ML, Marcovina SM, Nash SD, O'Brien KD, Weintraub WS, Xu P, Zhao XQ, Boden WE. Relationship of lipoproteins to cardiovascular events: the AIM-HIGH Trial (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes). J Am Coll Cardiol 2013; 62:1580-1584
675. Kris-Etherton P, Harris W, Appel L, American Heart Association. Nutrition C. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation 2002; 106:2747-2757
676. Harris W. n-3 fatty acids and serum lipoproteins: human studies. Am J Clin Nutr 1997; 65:1645S-1654S
677. Lungershausen Y, Abbey M, Nestel P, Howe P. Reduction of blood pressure and plasma triglycerides by omega-3 fatty acids in treated hypertensives. Journal of hypertension 1994; 12:1041-1045
678. Jacobson T. Role of n-3 fatty acids in the treatment of hypertriglyceridemia and cardiovascular disease. Am J Clin Nutr 2008; 87:1981S-1990S
679. Kotwal S, Jun M, Sullivan D, Perkovic V, Neal B. Omega 3 Fatty acids and cardiovascular outcomes: systematic review and meta-analysis. Circulation Cardiovascular quality and outcomes 2012; 5:808-818
680. Bhatt DL, Steg PG, Brinton EA, Jacobson TA, Miller M, Tardif JC, Ketchum SB, Doyle RT, Jr., Murphy SA, Soni PN, Braeckman RA, Juliano RA, Ballantyne CM, Investigators R-I. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial. Clin Cardiol 2017; 40:138-148
681. Prasad K. Flaxseed and cardiovascular health. Journal of cardiovascular pharmacology 2009; 54:369-377
682. Brenna J, Salem N, Jr., Sinclair A, Cunnane S, International Society for the Study of Fatty A, Lipids I. alpha-Linolenic acid supplementation and conversion to n-3 long-chain polyunsaturated fatty acids in humans. Prostaglandins, leukotrienes, and essential fatty acids 2009; 80:85-91
683. Goldberg I, Eckel R, McPherson R. Triglycerides and heart disease: still a hypothesis? Arteriosclerosis, thrombosis, and vascular biology 2011; 31:1716-1725

684. Freedman D, Gruchow H, Anderson A, Rimm A, Barboriak JJ. Relation of triglyceride levels to coronary artery disease: the Milwaukee Cardiovascular Data Registry. American journal of epidemiology 1988; 127:1118-1130
685. Rosenson RS, Brewer HB, Jr., Davidson WS, Fayad ZA, Fuster V, Goldstein J, Hellerstein M, Jiang XC, Phillips MC, Rader DJ, Remaley AT, Rothblat GH, Tall AR, Yvan-Charvet L. Cholesterol efflux and atheroprotection: advancing the concept of reverse cholesterol transport. Circulation 2012; 125:1905-1919
686. Barter PJ, Rye KA. Molecular mechanisms of reverse cholesterol transport. Current opinion in lipidology 1996; 7:82-87
687. von Eckardstein A, Nofer JR, Assmann G. High density lipoproteins and arteriosclerosis. Role of cholesterol efflux and reverse cholesterol transport. Arteriosclerosis, thrombosis, and vascular biology 2001; 21:13-27
688. Glomset JA, Janssen ET, Kennedy R, Dobbins J. Role of plasma lecithin:cholesterol acyltransferase in the metabolism of high density lipoproteins. J Lipid Res 1966; 7:638-648
689. Wang N, Tall AR. Regulation and mechanisms of ATP-binding cassette transporter A1-mediated cellular cholesterol efflux. Arteriosclerosis, thrombosis, and vascular biology 2003; 23:1178-1184
690. Wang N, Lan D, Chen W, Matsuura F, Tall AR. ATP-binding cassette transporters G1 and G4 mediate cellular cholesterol efflux to high-density lipoproteins. Proceedings of the National Academy of Sciences of the United States of America 2004; 101:9774-9779
691. Tarling EJ, Edwards PA. Intracellular Localization of Endogenous Mouse ABCG1 Is Mimicked by Both ABCG1-L550 and ABCG1-P550-Brief Report. Arterioscler Thromb Vasc Biol 2016; 36:1323-1327
692. Tarling EJ, Edwards PA. ATP binding cassette transporter G1 (ABCG1) is an intracellular sterol transporter. Proceedings of the National Academy of Sciences of the United States of America 2011; 108:19719-19724
693. Acton SL, Scherer PE, Lodish HF, Krieger M. Expression cloning of SR-BI, a CD36-related class B scavenger receptor. The Journal of biological chemistry 1994; 269:21003-21009
694. Acton S, Rigotti A, Landschulz KT, Xu S, Hobbs HH, Krieger M. Identification of scavenger receptor SR-BI as a high density lipoprotein receptor. Science 1996; 271:518-520
695. Adorni MP, Zimetti F, Billheimer JT, Wang N, Rader DJ, Phillips MC, Rothblat GH. The roles of different pathways in the release of cholesterol from macrophages. J Lipid Res 2007; 48:2453-2462
696. de La Llera-Moya M, Connelly MA, Drazul D, Klein SM, Favari E, Yancey PG, Williams DL, Rothblat GH. Scavenger receptor class B type I affects cholesterol homeostasis by magnifying cholesterol flux between cells and HDL. J Lipid Res 2001; 42:1969-1978
697. Yancey PG, de la Llera-Moya M, Swarnakar S, Monza P, Klein S, Connelly M, Johnson W, Williams D, Rothblat GH. High density lipoprotein phospholipid composition is a major determinant of the bi-directional flux and net movement of cellular free cholesterol mediated by scavenger receptor BI. The Journal of biological chemistry 2000; 275:36596-35604

698. Kellner-Weibel G, de La Llera-Moya M, Connelly MA, Stoudt G, Christian AE, Haynes MP, Williams DL, Rothblat GH. Expression of scavenger receptor BI in COS-7 cells alters cholesterol content and distribution. Biochemistry 2000; 39:221-229
699. Jahani M, Lacko AG. A study of the interaction of lecithin: cholesterol acyltransferase with subfractions of high density lipoproteins. J Lipid Res 1981; 22:1102-1110
700. Calabresi L, Franceschini G. Lecithin:cholesterol acyltransferase, high-density lipoproteins, and atheroprotection in humans. Trends in cardiovascular medicine 2010; 20:50-53
701. Lewis GF, Rader DJ. New insights into the regulation of HDL metabolism and reverse cholesterol transport. Circulation research 2005; 96:1221-1232
702. Barter P, Rye KA. Cholesteryl ester transfer protein: its role in plasma lipid transport. Clinical and experimental pharmacology & physiology 1994; 21:663-672
703. Rohrl C, Stangl H. HDL endocytosis and resecretion. Biochim Biophys Acta 2013; 1831:1626-1633
704. Zanoni P, Velagapudi S, Yalcinkaya M, Rohrer L, von Eckardstein A. Endocytosis of lipoproteins. Atherosclerosis 2018; 275:273-295
705. Pagler TA, Rhode S, Neuhofer A, Laggner H, Strobl W, Hinterndorfer C, Volf I, Pavelka M, Eckhardt ER, van der Westhuyzen DR, Schutz GJ, Stangl H. SR-BI-mediated high density lipoprotein (HDL) endocytosis leads to HDL resecretion facilitating cholesterol efflux. J Biol Chem 2006; 281:11193-11204
706. Sun B, Eckhardt ER, Shetty S, van der Westhuyzen DR, Webb NR. Quantitative analysis of SR-BI-dependent HDL retroendocytosis in hepatocytes and fibroblasts. J Lipid Res 2006; 47:1700-1713
707. Brundert M, Heeren J, Merkel M, Carambia A, Herkel J, Groitl P, Dobner T, Ramakrishnan R, Moore KJ, Rinninger F. Scavenger receptor CD36 mediates uptake of high density lipoproteins in mice and by cultured cells. J Lipid Res 2011; 52:745-758
708. Malaval C, Laffargue M, Barbaras R, Rolland C, Peres C, Champagne E, Perret B, Terce F, Collet X, Martinez LO. RhoA/ROCK I signalling downstream of the P2Y13 ADP-receptor controls HDL endocytosis in human hepatocytes. Cellular signalling 2009; 21:120-127
709. Cardouat G, Duparc T, Fried S, Perret B, Najib S, Martinez LO. Ectopic adenine nucleotide translocase activity controls extracellular ADP levels and regulates the F1-ATPase-mediated HDL endocytosis pathway on hepatocytes. Biochim Biophys Acta Mol Cell Biol Lipids 2017; 1862:832-841
710. Nijstad N, Gautier T, Briand F, Rader DJ, Tietge UJ. Biliary sterol secretion is required for functional in vivo reverse cholesterol transport in mice. Gastroenterology 2011; 140:1043-1051
711. van der Velde AE, Brufau G, Groen AK. Transintestinal cholesterol efflux. Current opinion in lipidology 2010; 21:167-171
712. Castelli WP. Epidemiology of coronary heart disease: the Framingham study. The American journal of medicine 1984; 76:4-12
713. Gofman JW, Young W, Tandy R. Ischemic heart disease, atherosclerosis, and longevity. Circulation 1966; 34:679-697

714. Miller GJ, Miller NE. Plasma-high-density-lipoprotein concentration and development of ischaemic heart-disease. Lancet 1975; 1:16-19
715. Rhoads GG, Gulbrandsen CL, Kagan A. Serum lipoproteins and coronary heart disease in a population study of Hawaii Japanese men. The New England journal of medicine 1976; 294:293-298
716. Pearson TA, Bulkley BH, Achuff SC, Kwiterovich PO, Gordis L. The association of low levels of HDL cholesterol and arteriographically defined coronary artery disease. American journal of epidemiology 1979; 109:285-295
717. Nofer JR, Tepel M, Kehrel B, Walter M, Seedorf U, Assmann G, Zidek W. High density lipoproteins enhance the Na+/H+ antiport in human platelets. Thrombosis and haemostasis 1996; 75:635-641
718. Goldbourt U, Yaari S, Medalie JH. Isolated low HDL cholesterol as a risk factor for coronary heart disease mortality. A 21-year follow-up of 8000 men. Arteriosclerosis, thrombosis, and vascular biology 1997; 17:107-113
719. Abbott RD, Wilson PW, Kannel WB, Castelli WP. High density lipoprotein cholesterol, total cholesterol screening, and myocardial infarction. The Framingham Study. Arteriosclerosis 1988; 8:207-211
720. Miller M, Mead LA, Kwiterovich PO, Jr., Pearson TA. Dyslipidemias with desirable plasma total cholesterol levels and angiographically demonstrated coronary artery disease. The American journal of cardiology 1990; 65:1-5
721. Ginsburg GS, Safran C, Pasternak RC. Frequency of low serum high-density lipoprotein cholesterol levels in hospitalized patients with "desirable" total cholesterol levels. The American journal of cardiology 1991; 68:187-192
722. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, Jacobs DR, Jr., Bangdiwala S, Tyroler HA. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989; 79:8-15
723. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. The New England journal of medicine 1987; 317:1237-1245
724. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM, Jr. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998; 279:1615-1622
725. Olsson AG, Schwartz GG, Szarek M, Sasiela WJ, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A. High-density lipoprotein, but not low-density lipoprotein cholesterol levels influence short-term prognosis after acute coronary syndrome: results from the MIRACL trial. European heart journal 2005; 26:890-896
726. Ray KK, Cannon CP, Cairns R, Morrow DA, Ridker PM, Braunwald E. Prognostic utility of apoB/AI, total cholesterol/HDL, non-HDL cholesterol, or hs-CRP as predictors of clinical risk in patients receiving statin therapy after acute coronary syndromes: results

from PROVE IT-TIMI 22. Arteriosclerosis, thrombosis, and vascular biology 2009; 29:424-430
727. Ballantyne CM, Herd JA, Ferlic LL, Dunn JK, Farmer JA, Jones PH, Schein JR, Gotto AM, Jr. Influence of low HDL on progression of coronary artery disease and response to fluvastatin therapy. Circulation 1999; 99:736-743
728. Tardif JC, Gregoire J, L'Allier PL, Ibrahim R, Lesperance J, Heinonen TM, Kouz S, Berry C, Basser R, Lavoie MA, Guertin MC, Rodes-Cabau J, Effect of r HDLoA-S, Efficacy I. Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial. JAMA 2007; 297:1675-1682
729. Plump AS, Scott CJ, Breslow JL. Human apolipoprotein A-I gene expression increases high density lipoprotein and suppresses atherosclerosis in the apolipoprotein E-deficient mouse. Proceedings of the National Academy of Sciences of the United States of America 1994; 91:9607-9611
730. Rubin EM, Krauss RM, Spangler EA, Verstuyft JG, Clift SM. Inhibition of early atherogenesis in transgenic mice by human apolipoprotein AI. Nature 1991; 353:265-267
731. Badimon JJ, Badimon L, Fuster V. Regression of atherosclerotic lesions by high density lipoprotein plasma fraction in the cholesterol-fed rabbit. J Clin Invest 1990; 85:1234-1241
732. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. The New England journal of medicine 2011; 365:2255-2267
733. Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, Wallendszus K, Craig M, Jiang L, Collins R, Armitage J. Effects of extended-release niacin with laropiprant in high-risk patients. The New England journal of medicine 2014; 371:203-212
734. Song WL, FitzGerald GA. Niacin, an old drug with a new twist. J Lipid Res 2013; 54:2586-2594
735. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B, Investigators I. Effects of torcetrapib in patients at high risk for coronary events. The New England journal of medicine 2007; 357:2109-2122
736. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJ, Mundl H, Nicholls SJ, Shah PK, Tardif JC, Wright RS, dal OI. Effects of dalcetrapib in patients with a recent acute coronary syndrome. The New England journal of medicine 2012; 367:2089-2099
737. HPS3/TIMI55–REVEAL Collaborative Group, Bowman L, Hopewell JC, Chen F, Wallendszus K, Stevens W, Collins R, Wiviott SD, Cannon CP, Braunwald E, Sammons E, Landray MJ. Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease. The New England journal of medicine 2017; 377:1217-1227
738. Tall AR, Rader DJ. Trials and Tribulations of CETP Inhibitors. Circulation research 2018; 122:106-112
739. Nicholls SJ, Andrews J, Kastelein JJP, Merkely B, Nissen SE, Ray KK, Schwartz GG, Worthley SG, Keyserling C, Dasseux JL, Griffith L, Kim SW, Janssan A, Di Giovanni G,

Pisaniello AD, Scherer DJ, Psaltis PJ, Butters J. Effect of Serial Infusions of CER-001, a Pre-beta High-Density Lipoprotein Mimetic, on Coronary Atherosclerosis in Patients Following Acute Coronary Syndromes in the CER-001 Atherosclerosis Regression Acute Coronary Syndrome Trial: A Randomized Clinical Trial. JAMA Cardiol 2018; 3:815-822
740. Nicholls SJ, Puri R, Ballantyne CM, Jukema JW, Kastelein JJP, Koenig W, Wright RS, Kallend D, Wijngaard P, Borgman M, Wolski K, Nissen SE. Effect of Infusion of High-Density Lipoprotein Mimetic Containing Recombinant Apolipoprotein A-I Milano on Coronary Disease in Patients With an Acute Coronary Syndrome in the MILANO-PILOT Trial: A Randomized Clinical Trial. JAMA Cardiol 2018; 3:806-814
741. Bisoendial RJ, Hovingh GK, Levels JH, Lerch PG, Andresen I, Hayden MR, Kastelein JJ, Stroes ES. Restoration of endothelial function by increasing high-density lipoprotein in subjects with isolated low high-density lipoprotein. Circulation 2003; 107:2944-2948
742. Karalis I, Jukema JW. HDL Mimetics Infusion and Regression of Atherosclerosis: Is It Still Considered a Valid Therapeutic Option? Curr Cardiol Rep 2018; 20:66
743. Rohatgi A, Khera A, Berry JD, Givens EG, Ayers CR, Wedin KE, Neeland IJ, Yuhanna IS, Rader DR, de Lemos JA, Shaul PW. HDL cholesterol efflux capacity and incident cardiovascular events. The New England journal of medicine 2014; 371:2383-2393
744. Saleheen D, Scott R, Javad S, Zhao W, Rodrigues A, Picataggi A, Lukmanova D, Mucksavage ML, Luben R, Billheimer J, Kastelein JJ, Boekholdt SM, Khaw KT, Wareham N, Rader DJ. Association of HDL cholesterol efflux capacity with incident coronary heart disease events: a prospective case-control study. The lancet Diabetes & endocrinology 2015; 3:507-513
745. Zerrad-Saadi A, Therond P, Chantepie S, Couturier M, Rye KA, Chapman MJ, Kontush A. HDL3-mediated inactivation of LDL-associated phospholipid hydroperoxides is determined by the redox status of apolipoprotein A-I and HDL particle surface lipid rigidity: relevance to inflammation and atherogenesis. Arteriosclerosis, thrombosis, and vascular biology 2009; 29:2169-2175
746. Khera AV, Cuchel M, de la Llera-Moya M, Rodrigues A, Burke MF, Jafri K, French BC, Phillips JA, Mucksavage ML, Wilensky RL, Mohler ER, Rothblat GH, Rader DJ. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. The New England journal of medicine 2011; 364:127-135
747. Sirtori CR, Calabresi L, Franceschini G, Baldassarre D, Amato M, Johansson J, Salvetti M, Monteduro C, Zulli R, Muiesan ML, Agabiti-Rosei E. Cardiovascular status of carriers of the apolipoprotein A-I(Milano) mutant: the Limone sul Garda study. Circulation 2001; 103:1949-1954
748. Hovingh GK, Brownlie A, Bisoendial RJ, Dube MP, Levels JH, Petersen W, Dullaart RP, Stroes ES, Zwinderman AH, de Groot E, Hayden MR, Kuivenhoven JA, Kastelein JJ. A novel apoA-I mutation (L178P) leads to endothelial dysfunction, increased arterial wall thickness, and premature coronary artery disease. J Am Coll Cardiol 2004; 44:1429-1435
749. Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, Eaton GM, Lauer MA, Sheldon WS, Grines CL, Halpern S, Crowe T, Blankenship JC, Kerensky R. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA 2003; 290:2292-2300

750. Johannsen TH, Frikke-Schmidt R, Schou J, Nordestgaard BG, Tybjaerg-Hansen A. Genetic inhibition of CETP, ischemic vascular disease and mortality, and possible adverse effects. J Am Coll Cardiol 2012; 60:2041-2048
751. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Holm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, Konig IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schafer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet 2012; 380:572-580
752. Li XM, Tang WH, Mosior MK, Huang Y, Wu Y, Matter W, Gao V, Schmitt D, Didonato JA, Fisher EA, Smith JD, Hazen SL. Paradoxical association of enhanced cholesterol efflux with increased incident cardiovascular risks. Arteriosclerosis, thrombosis, and vascular biology 2013; 33:1696-1705
753. Day N, Oakes S, Luben R, Khaw KT, Bingham S, Welch A, Wareham N. EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. British journal of cancer 1999; 80 Suppl 1:95-103
754. Jeyarajah EJ, Cromwell WC, Otvos JD. Lipoprotein particle analysis by nuclear magnetic resonance spectroscopy. Clinics in laboratory medicine 2006; 26:847-870
755. Hutchins PM, Ronsein GE, Monette JS, Pamir N, Wimberger J, He Y, Anantharamaiah GM, Kim DS, Ranchalis JE, Jarvik GP, Vaisar T, Heinecke JW. Quantification of HDL particle concentration by calibrated ion mobility analysis. Clin Chem 2014; 60:1393-1401
756. Mackey RH, Greenland P, Goff DC, Jr., Lloyd-Jones D, Sibley CT, Mora S. High-density lipoprotein cholesterol and particle concentrations, carotid atherosclerosis, and coronary events: MESA (multi-ethnic study of atherosclerosis). J Am Coll Cardiol 2012; 60:508-516
757. El Harchaoui K, Arsenault BJ, Franssen R, Despres JP, Hovingh GK, Stroes ES, Otvos JD, Wareham NJ, Kastelein JJ, Khaw KT, Boekholdt SM. High-density lipoprotein particle size and concentration and coronary risk. Annals of internal medicine 2009; 150:84-93

758. Virani SS, Catellier DJ, Pompeii LA, Nambi V, Hoogeveen RC, Wasserman BA, Coresh J, Mosley TH, Otvos JD, Sharrett AR, Boerwinkle E, Ballantyne CM. Relation of cholesterol and lipoprotein parameters with carotid artery plaque characteristics: the Atherosclerosis Risk in Communities (ARIC) carotid MRI study. Atherosclerosis 2011; 219:596-602
759. de la Llera-Moya M, Drazul-Schrader D, Asztalos BF, Cuchel M, Rader DJ, Rothblat GH. The ability to promote efflux via ABCA1 determines the capacity of serum specimens with similar high-density lipoprotein cholesterol to remove cholesterol from macrophages. Arteriosclerosis, thrombosis, and vascular biology 2010; 30:796-801
760. Havel RJ, Eder HA, Bragdon JH. The distribution and chemical composition of ultracentrifugally separated lipoproteins in human serum. J Clin Invest 1955; 34:1345-1353
761. Gofman JW, Lindgren FT, Elliott H. Ultracentrifugal studies of lipoproteins of human serum. The Journal of biological chemistry 1949; 179:973-979
762. Rothblat GH, Phillips MC. High-density lipoprotein heterogeneity and function in reverse cholesterol transport. Current opinion in lipidology 2010; 21:229-238
763. Cheung MC, Albers JJ. Characterization of lipoprotein particles isolated by immunoaffinity chromatography. Particles containing A-I and A-II and particles containing A-I but no A-II. The Journal of biological chemistry 1984; 259:12201-12209
764. James RW, Hochstrasser D, Tissot JD, Funk M, Appel R, Barja F, Pellegrini C, Muller AF, Pometta D. Protein heterogeneity of lipoprotein particles containing apolipoprotein A-I without apolipoprotein A-II and apolipoprotein A-I with apolipoprotein A-II isolated from human plasma. J Lipid Res 1988; 29:1557-1571
765. Kuklenyik Z, Jones JI, Gardner MS, Schieltz DM, Parks BA, Toth CA, Rees JC, Andrews ML, Carter K, Lehtikoski AK, McWilliams LG, Williamson YM, Bierbaum KP, Pirkle JL, Barr JR. Core lipid, surface lipid and apolipoprotein composition analysis of lipoprotein particles as a function of particle size in one workflow integrating asymmetric flow field-flow fractionation and liquid chromatography-tandem mass spectrometry. PLoS One 2018; 13:e0194797
766. Castro GR, Fielding CJ. Early incorporation of cell-derived cholesterol into pre-beta-migrating high-density lipoprotein. Biochemistry 1988; 27:25-29
767. Pownall HJ, Ehnholm C. The unique role of apolipoprotein A-I in HDL remodeling and metabolism. Current opinion in lipidology 2006; 17:209-213
768. Wiesner P, Leidl K, Boettcher A, Schmitz G, Liebisch G. Lipid profiling of FPLC-separated lipoprotein fractions by electrospray ionization tandem mass spectrometry. J Lipid Res 2009; 50:574-585
769. Kontush A, Lhomme M, Chapman MJ. Unraveling the complexities of the HDL lipidome. J Lipid Res 2013; 54:2950-2963
770. Shah AS, Tan L, Long JL, Davidson WS. Proteomic diversity of high density lipoproteins: our emerging understanding of its importance in lipid transport and beyond. J Lipid Res 2013; 54:2575-2585
771. Vaisar T, Pennathur S, Green PS, Gharib SA, Hoofnagle AN, Cheung MC, Byun J, Vuletic S, Kassim S, Singh P, Chea H, Knopp RH, Brunzell J, Geary R, Chait A, Zhao XQ, Elkon K, Marcovina S, Ridker P, Oram JF, Heinecke JW. Shotgun proteomics

implicates protease inhibition and complement activation in the antiinflammatory properties of HDL. J Clin Invest 2007; 117:746-756
772. Vickers KC, Palmisano BT, Shoucri BM, Shamburek RD, Remaley AT. MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins. Nature cell biology 2011; 13:423-433
773. Tabet F, Vickers KC, Cuesta Torres LF, Wiese CB, Shoucri BM, Lambert G, Catherinet C, Prado-Lourenco L, Levin MG, Thacker S, Sethupathy P, Barter PJ, Remaley AT, Rye KA. HDL-transferred microRNA-223 regulates ICAM-1 expression in endothelial cells. Nature communications 2014; 5:3292
774. Allen RM, Zhao S, Ramirez Solano MA, Zhu W, Michell DL, Wang Y, Shyr Y, Sethupathy P, Linton MF, Graf GA, Sheng Q, Vickers KC. Bioinformatic analysis of endogenous and exogenous small RNAs on lipoproteins. J Extracell Vesicles 2018; 7:1506198
775. Navab M, Anantharamaiah GM, Reddy ST, Van Lenten BJ, Ansell BJ, Fogelman AM. Mechanisms of disease: proatherogenic HDL--an evolving field. Nature clinical practice Endocrinology & metabolism 2006; 2:504-511
776. Van Lenten BJ, Navab M, Shih D, Fogelman AM, Lusis AJ. The role of high-density lipoproteins in oxidation and inflammation. Trends in cardiovascular medicine 2001; 11:155-161
777. Eren E, Yilmaz N, Aydin O. High Density Lipoprotein and it's Dysfunction. The open biochemistry journal 2012; 6:78-93
778. Toth PP, Barter PJ, Rosenson RS, Boden WE, Chapman MJ, Cuchel M, D'Agostino RB, Sr., Davidson MH, Davidson WS, Heinecke JW, Karas RH, Kontush A, Krauss RM, Miller M, Rader DJ. High-density lipoproteins: a consensus statement from the National Lipid Association. Journal of clinical lipidology 2013; 7:484-525
779. Rached FH, Chapman MJ, Kontush A. HDL particle subpopulations: Focus on biological function. BioFactors 2015; 41:67-77
780. Nofer JR. Signal transduction by HDL: agonists, receptors, and signaling cascades. Handbook of experimental pharmacology 2015; 224:229-256
781. Mendez AJ, Oram JF, Bierman EL. Protein kinase C as a mediator of high density lipoprotein receptor-dependent efflux of intracellular cholesterol. The Journal of biological chemistry 1991; 266:10104-10111
782. Walter M, Reinecke H, Nofer JR, Seedorf U, Assmann G. HDL3 stimulates multiple signaling pathways in human skin fibroblasts. Arteriosclerosis, thrombosis, and vascular biology 1995; 15:1975-1986
783. Yamauchi Y, Hayashi M, Abe-Dohmae S, Yokoyama S. Apolipoprotein A-I activates protein kinase C alpha signaling to phosphorylate and stabilize ATP binding cassette transporter A1 for the high density lipoprotein assembly. The Journal of biological chemistry 2003; 278:47890-47897
784. Yamauchi Y, Chang CC, Hayashi M, Abe-Dohmae S, Reid PC, Chang TY, Yokoyama S. Intracellular cholesterol mobilization involved in the ABCA1/apolipoprotein-mediated assembly of high density lipoprotein in fibroblasts. J Lipid Res 2004; 45:1943-1951
785. Ma L, Dong F, Denis M, Feng Y, Wang MD, Zha X. Ht31, a protein kinase A anchoring inhibitor, induces robust cholesterol efflux and reverses macrophage foam cell formation

through ATP-binding cassette transporter A1. The Journal of biological chemistry 2011; 286:3370-3378
786. See RH, Caday-Malcolm RA, Singaraja RR, Zhou S, Silverston A, Huber MT, Moran J, James ER, Janoo R, Savill JM, Rigot V, Zhang LH, Wang M, Chimini G, Wellington CL, Tafuri SR, Hayden MR. Protein kinase A site-specific phosphorylation regulates ATP-binding cassette A1 (ABCA1)-mediated phospholipid efflux. The Journal of biological chemistry 2002; 277:41835-41842
787. Nofer JR, Remaley AT, Feuerborn R, Wolinnska I, Engel T, von Eckardstein A, Assmann G. Apolipoprotein A-I activates Cdc42 signaling through the ABCA1 transporter. J Lipid Res 2006; 47:794-803
788. Tang C, Vaughan AM, Oram JF. Janus kinase 2 modulates the apolipoprotein interactions with ABCA1 required for removing cellular cholesterol. The Journal of biological chemistry 2004; 279:7622-7628
789. Tang C, Vaughan AM, Anantharamaiah GM, Oram JF. Janus kinase 2 modulates the lipid-removing but not protein-stabilizing interactions of amphipathic helices with ABCA1. J Lipid Res 2006; 47:107-114
790. Liu D, Ji L, Tong X, Pan B, Han JY, Huang Y, Chen YE, Pennathur S, Zhang Y, Zheng L. Human apolipoprotein A-I induces cyclooxygenase-2 expression and prostaglandin I-2 release in endothelial cells through ATP-binding cassette transporter A1. American journal of physiology Cell physiology 2011; 301:C739-748
791. Mineo C, Yuhanna IS, Quon MJ, Shaul PW. High density lipoprotein-induced endothelial nitric-oxide synthase activation is mediated by Akt and MAP kinases. The Journal of biological chemistry 2003; 278:9142-9149
792. Kimura T, Tomura H, Sato K, Ito M, Matsuoka I, Im DS, Kuwabara A, Mogi C, Itoh H, Kurose H, Murakami M, Okajima F. Mechanism and role of high density lipoprotein-induced activation of AMP-activated protein kinase in endothelial cells. The Journal of biological chemistry 2010; 285:4387-4397
793. Tan JT, Prosser HC, Vanags LZ, Monger SA, Ng MK, Bursill CA. High-density lipoproteins augment hypoxia-induced angiogenesis via regulation of post-translational modulation of hypoxia-inducible factor 1alpha. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2014; 28:206-217
794. Zhang Q, Zhang Y, Feng H, Guo R, Jin L, Wan R, Wang L, Chen C, Li S. High density lipoprotein (HDL) promotes glucose uptake in adipocytes and glycogen synthesis in muscle cells. PloS one 2011; 6:e23556
795. Seetharam D, Mineo C, Gormley AK, Gibson LL, Vongpatanasin W, Chambliss KL, Hahner LD, Cummings ML, Kitchens RL, Marcel YL, Rader DJ, Shaul PW. High-density lipoprotein promotes endothelial cell migration and reendothelialization via scavenger receptor-B type I. Circulation research 2006; 98:63-72
796. Zhang QH, Zu XY, Cao RX, Liu JH, Mo ZC, Zeng Y, Li YB, Xiong SL, Liu X, Liao DF, Yi GH. An involvement of SR-B1 mediated PI3K-Akt-eNOS signaling in HDL-induced cyclooxygenase 2 expression and prostacyclin production in endothelial cells. Biochem Biophys Res Commun 2012; 420:17-23
797. Assanasen C, Mineo C, Seetharam D, Yuhanna IS, Marcel YL, Connelly MA, Williams DL, de la Llera-Moya M, Shaul PW, Silver DL. Cholesterol binding, efflux, and a PDZ-

interacting domain of scavenger receptor-BI mediate HDL-initiated signaling. J Clin Invest 2005; 115:969-977
798. Yuhanna IS, Zhu Y, Cox BE, Hahner LD, Osborne-Lawrence S, Lu P, Marcel YL, Anderson RG, Mendelsohn ME, Hobbs HH, Shaul PW. High-density lipoprotein binding to scavenger receptor-BI activates endothelial nitric oxide synthase. Nature medicine 2001; 7:853-857
799. Argraves KM, Gazzolo PJ, Groh EM, Wilkerson BA, Matsuura BS, Twal WO, Hammad SM, Argraves WS. High density lipoprotein-associated sphingosine 1-phosphate promotes endothelial barrier function. The Journal of biological chemistry 2008; 283:25074-25081
800. Matsuo Y, Miura S, Kawamura A, Uehara Y, Rye KA, Saku K. Newly developed reconstituted high-density lipoprotein containing sphingosine-1-phosphate induces endothelial tube formation. Atherosclerosis 2007; 194:159-168
801. Miura S, Fujino M, Matsuo Y, Kawamura A, Tanigawa H, Nishikawa H, Saku K. High density lipoprotein-induced angiogenesis requires the activation of Ras/MAP kinase in human coronary artery endothelial cells. Arteriosclerosis, thrombosis, and vascular biology 2003; 23:802-808
802. Kimura T, Tomura H, Mogi C, Kuwabara A, Damirin A, Ishizuka T, Sekiguchi A, Ishiwara M, Im DS, Sato K, Murakami M, Okajima F. Role of scavenger receptor class B type I and sphingosine 1-phosphate receptors in high density lipoprotein-induced inhibition of adhesion molecule expression in endothelial cells. The Journal of biological chemistry 2006; 281:37457-37467
803. Nofer JR, Levkau B, Wolinska I, Junker R, Fobker M, von Eckardstein A, Seedorf U, Assmann G. Suppression of endothelial cell apoptosis by high density lipoproteins (HDL) and HDL-associated lysosphingolipids. The Journal of biological chemistry 2001; 276:34480-34485
804. Tamama K, Tomura H, Sato K, Malchinkhuu E, Damirin A, Kimura T, Kuwabara A, Murakami M, Okajima F. High-density lipoprotein inhibits migration of vascular smooth muscle cells through its sphingosine 1-phosphate component. Atherosclerosis 2005; 178:19-23
805. Sattler KJ, Elbasan S, Keul P, Elter-Schulz M, Bode C, Graler MH, Brocker-Preuss M, Budde T, Erbel R, Heusch G, Levkau B. Sphingosine 1-phosphate levels in plasma and HDL are altered in coronary artery disease. Basic research in cardiology 2010; 105:821-832
806. Nofer JR, van der Giet M, Tolle M, Wolinska I, von Wnuck Lipinski K, Baba HA, Tietge UJ, Godecke A, Ishii I, Kleuser B, Schafers M, Fobker M, Zidek W, Assmann G, Chun J, Levkau B. HDL induces NO-dependent vasorelaxation via the lysophospholipid receptor S1P3. J Clin Invest 2004; 113:569-581
807. Morel S, Frias MA, Rosker C, James RW, Rohr S, Kwak BR. The natural cardioprotective particle HDL modulates connexin43 gap junction channels. Cardiovascular research 2012; 93:41-49
808. Martinez LO, Jacquet S, Esteve JP, Rolland C, Cabezon E, Champagne E, Pineau T, Georgeaud V, Walker JE, Terce F, Collet X, Perret B, Barbaras R. Ectopic beta-chain of

ATP synthase is an apolipoprotein A-I receptor in hepatic HDL endocytosis. Nature 2003; 421:75-79
809. Sun Y, Ishibashi M, Seimon T, Lee M, Sharma SM, Fitzgerald KA, Samokhin AO, Wang Y, Sayers S, Aikawa M, Jerome WG, Ostrowski MC, Bromme D, Libby P, Tabas IA, Welch CL, Tall AR. Free cholesterol accumulation in macrophage membranes activates Toll-like receptors and p38 mitogen-activated protein kinase and induces cathepsin K. Circulation research 2009; 104:455-465
810. Shaw JA, Bobik A, Murphy A, Kanellakis P, Blombery P, Mukhamedova N, Woollard K, Lyon S, Sviridov D, Dart AM. Infusion of reconstituted high-density lipoprotein leads to acute changes in human atherosclerotic plaque. Circulation research 2008; 103:1084-1091
811. Park SH, Park JH, Kang JS, Kang YH. Involvement of transcription factors in plasma HDL protection against TNF-alpha-induced vascular cell adhesion molecule-1 expression. The international journal of biochemistry & cell biology 2003; 35:168-182
812. McGrath KC, Li XH, Puranik R, Liong EC, Tan JT, Dy VM, DiBartolo BA, Barter PJ, Rye KA, Heather AK. Role of 3beta-hydroxysteroid-delta 24 reductase in mediating antiinflammatory effects of high-density lipoproteins in endothelial cells. Arteriosclerosis, thrombosis, and vascular biology 2009; 29:877-882
813. Norata GD, Callegari E, Marchesi M, Chiesa G, Eriksson P, Catapano AL. High-density lipoproteins induce transforming growth factor-beta2 expression in endothelial cells. Circulation 2005; 111:2805-2811
814. Murphy AJ, Woollard KJ, Hoang A, Mukhamedova N, Stirzaker RA, McCormick SP, Remaley AT, Sviridov D, Chin-Dusting J. High-density lipoprotein reduces the human monocyte inflammatory response. Arteriosclerosis, thrombosis, and vascular biology 2008; 28:2071-2077
815. Bursill CA, Castro ML, Beattie DT, Nakhla S, van der Vorst E, Heather AK, Barter PJ, Rye KA. High-density lipoproteins suppress chemokines and chemokine receptors in vitro and in vivo. Arteriosclerosis, thrombosis, and vascular biology 2010; 30:1773-1778
816. De Nardo D, Labzin LI, Kono H, Seki R, Schmidt SV, Beyer M, Xu D, Zimmer S, Lahrmann C, Schildberg FA, Vogelhuber J, Kraut M, Ulas T, Kerksiek A, Krebs W, Bode N, Grebe A, Fitzgerald ML, Hernandez NJ, Williams BR, Knolle P, Kneilling M, Rocken M, Lutjohann D, Wright SD, Schultze JL, Latz E. High-density lipoprotein mediates anti-inflammatory reprogramming of macrophages via the transcriptional regulator ATF3. Nat Immunol 2014; 15:152-160
817. Vaughan AM, Tang C, Oram JF. ABCA1 mutants reveal an interdependency between lipid export function, apoA-I binding activity, and Janus kinase 2 activation. J Lipid Res 2009; 50:285-292
818. Yvan-Charvet L, Welch C, Pagler TA, Ranalletta M, Lamkanfi M, Han S, Ishibashi M, Li R, Wang N, Tall AR. Increased inflammatory gene expression in ABC transporter-deficient macrophages: free cholesterol accumulation, increased signaling via toll-like receptors, and neutrophil infiltration of atherosclerotic lesions. Circulation 2008; 118:1837-1847
819. Tolle M, Pawlak A, Schuchardt M, Kawamura A, Tietge UJ, Lorkowski S, Keul P, Assmann G, Chun J, Levkau B, van der Giet M, Nofer JR. HDL-associated

lysosphingolipids inhibit NAD(P)H oxidase-dependent monocyte chemoattractant protein-1 production. Arteriosclerosis, thrombosis, and vascular biology 2008; 28:1542-1548
820. Yvan-Charvet L, Pagler T, Gautier EL, Avagyan S, Siry RL, Han S, Welch CL, Wang N, Randolph GJ, Snoeck HW, Tall AR. ATP-binding cassette transporters and HDL suppress hematopoietic stem cell proliferation. Science 2010; 328:1689-1693
821. Wilhelm AJ, Zabalawi M, Grayson JM, Weant AE, Major AS, Owen J, Bharadwaj M, Walzem R, Chan L, Oka K, Thomas MJ, Sorci-Thomas MG. Apolipoprotein A-I and its role in lymphocyte cholesterol homeostasis and autoimmunity. Arteriosclerosis, thrombosis, and vascular biology 2009; 29:843-849
822. Wilhelm AJ, Zabalawi M, Owen JS, Shah D, Grayson JM, Major AS, Bhat S, Gibbs DP, Jr., Thomas MJ, Sorci-Thomas MG. Apolipoprotein A-I modulates regulatory T cells in autoimmune LDLr-/-, ApoA-I-/- mice. The Journal of biological chemistry 2010; 285:36158-36169
823. Yu BL, Wang SH, Peng DQ, Zhao SP. HDL and immunomodulation: an emerging role of HDL against atherosclerosis. Immunology and cell biology 2010; 88:285-290
824. Hyka N, Dayer JM, Modoux C, Kohno T, Edwards CK, 3rd, Roux-Lombard P, Burger D. Apolipoprotein A-I inhibits the production of interleukin-1beta and tumor necrosis factor-alpha by blocking contact-mediated activation of monocytes by T lymphocytes. Blood 2001; 97:2381-2389
825. Westerterp M, Gourion-Arsiquaud S, Murphy AJ, Shih A, Cremers S, Levine RL, Tall AR, Yvan-Charvet L. Regulation of hematopoietic stem and progenitor cell mobilization by cholesterol efflux pathways. Cell stem cell 2012; 11:195-206
826. Murphy AJ, Bijl N, Yvan-Charvet L, Welch CB, Bhagwat N, Reheman A, Wang Y, Shaw JA, Levine RL, Ni H, Tall AR, Wang N. Cholesterol efflux in megakaryocyte progenitors suppresses platelet production and thrombocytosis. Nature medicine 2013; 19:586-594
827. Naqvi TZ, Shah PK, Ivey PA, Molloy MD, Thomas AM, Panicker S, Ahmed A, Cercek B, Kaul S. Evidence that high-density lipoprotein cholesterol is an independent predictor of acute platelet-dependent thrombus formation. The American journal of cardiology 1999; 84:1011-1017
828. Calkin AC, Drew BG, Ono A, Duffy SJ, Gordon MV, Schoenwaelder SM, Sviridov D, Cooper ME, Kingwell BA, Jackson SP. Reconstituted high-density lipoprotein attenuates platelet function in individuals with type 2 diabetes mellitus by promoting cholesterol efflux. Circulation 2009; 120:2095-2104
829. Brodde MF, Korporaal SJ, Herminghaus G, Fobker M, Van Berkel TJ, Tietge UJ, Robenek H, Van Eck M, Kehrel BE, Nofer JR. Native high-density lipoproteins inhibit platelet activation via scavenger receptor BI: role of negatively charged phospholipids. Atherosclerosis 2011; 215:374-382
830. Nofer JR, Brodde MF, Kehrel BE. High-density lipoproteins, platelets and the pathogenesis of atherosclerosis. Clinical and experimental pharmacology & physiology 2010; 37:726-735
831. Li D, Weng S, Yang B, Zander DS, Saldeen T, Nichols WW, Khan S, Mehta JL. Inhibition of arterial thrombus formation by ApoA1 Milano. Arteriosclerosis, thrombosis, and vascular biology 1999; 19:378-383

832. Carson SD. Plasma high density lipoproteins inhibit the activation of coagulation factor X by factor VIIa and tissue factor. FEBS letters 1981; 132:37-40
833. Sugatani J, Miwa M, Komiyama Y, Ito S. High-density lipoprotein inhibits the synthesis of platelet-activating factor in human vascular endothelial cells. Journal of lipid mediators and cell signalling 1996; 13:73-88
834. Viswambharan H, Ming XF, Zhu S, Hubsch A, Lerch P, Vergeres G, Rusconi S, Yang Z. Reconstituted high-density lipoprotein inhibits thrombin-induced endothelial tissue factor expression through inhibition of RhoA and stimulation of phosphatidylinositol 3-kinase but not Akt/endothelial nitric oxide synthase. Circulation research 2004; 94:918-925
835. Epand RM, Stafford A, Leon B, Lock PE, Tytler EM, Segrest JP, Anantharamaiah GM. HDL and apolipoprotein A-I protect erythrocytes against the generation of procoagulant activity. Arterioscler Thromb 1994; 14:1775-1783
836. Ramet ME, Ramet M, Lu Q, Nickerson M, Savolainen MJ, Malzone A, Karas RH. High-density lipoprotein increases the abundance of eNOS protein in human vascular endothelial cells by increasing its half-life. J Am Coll Cardiol 2003; 41:2288-2297
837. Terasaka N, Yu S, Yvan-Charvet L, Wang N, Mzhavia N, Langlois R, Pagler T, Li R, Welch CL, Goldberg IJ, Tall AR. ABCG1 and HDL protect against endothelial dysfunction in mice fed a high-cholesterol diet. J Clin Invest 2008; 118:3701-3713
838. Annema W, von Eckardstein A. High-density lipoproteins. Multifunctional but vulnerable protections from atherosclerosis. Circulation journal : official journal of the Japanese Circulation Society 2013; 77:2432-2448
839. de Souza JA, Vindis C, Negre-Salvayre A, Rye KA, Couturier M, Therond P, Chantepie S, Salvayre R, Chapman MJ, Kontush A. Small, dense HDL 3 particles attenuate apoptosis in endothelial cells: pivotal role of apolipoprotein A-I. Journal of cellular and molecular medicine 2010; 14:608-620
840. Riwanto M, Rohrer L, Roschitzki B, Besler C, Mocharla P, Mueller M, Perisa D, Heinrich K, Altwegg L, von Eckardstein A, Luscher TF, Landmesser U. Altered activation of endothelial anti- and proapoptotic pathways by high-density lipoprotein from patients with coronary artery disease: role of high-density lipoprotein-proteome remodeling. Circulation 2013; 127:891-904
841. Suc I, Escargueil-Blanc I, Troly M, Salvayre R, Negre-Salvayre A. HDL and ApoA prevent cell death of endothelial cells induced by oxidized LDL. Arteriosclerosis, thrombosis, and vascular biology 1997; 17:2158-2166
842. Sugano M, Tsuchida K, Makino N. High-density lipoproteins protect endothelial cells from tumor necrosis factor-alpha-induced apoptosis. Biochem Biophys Res Commun 2000; 272:872-876
843. Christoffersen C, Obinata H, Kumaraswamy SB, Galvani S, Ahnstrom J, Sevvana M, Egerer-Sieber C, Muller YA, Hla T, Nielsen LB, Dahlback B. Endothelium-protective sphingosine-1-phosphate provided by HDL-associated apolipoprotein M. Proceedings of the National Academy of Sciences of the United States of America 2011; 108:9613-9618
844. Navab M, Ananthramaiah GM, Reddy ST, Van Lenten BJ, Ansell BJ, Fonarow GC, Vahabzadeh K, Hama S, Hough G, Kamranpour N, Berliner JA, Lusis AJ, Fogelman AM. The oxidation hypothesis of atherogenesis: the role of oxidized phospholipids and HDL. J Lipid Res 2004; 45:993-1007

845. Navab M, Hama SY, Cooke CJ, Anantharamaiah GM, Chaddha M, Jin L, Subbanagounder G, Faull KF, Reddy ST, Miller NE, Fogelman AM. Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein: step 1. J Lipid Res 2000; 41:1481-1494
846. Navab M, Hama SY, Anantharamaiah GM, Hassan K, Hough GP, Watson AD, Reddy ST, Sevanian A, Fonarow GC, Fogelman AM. Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein: steps 2 and 3. J Lipid Res 2000; 41:1495-1508
847. Vohl MC, Neville TA, Kumarathasan R, Braschi S, Sparks DL. A novel lecithin-cholesterol acyltransferase antioxidant activity prevents the formation of oxidized lipids during lipoprotein oxidation. Biochemistry 1999; 38:5976-5981
848. Watson AD, Navab M, Hama SY, Sevanian A, Prescott SM, Stafforini DM, McIntyre TM, Du BN, Fogelman AM, Berliner JA. Effect of platelet activating factor-acetylhydrolase on the formation and action of minimally oxidized low density lipoprotein. J Clin Invest 1995; 95:774-782
849. Noto H, Hara M, Karasawa K, Iso ON, Satoh H, Togo M, Hashimoto Y, Yamada Y, Kosaka T, Kawamura M, Kimura S, Tsukamoto K. Human plasma platelet-activating factor acetylhydrolase binds to all the murine lipoproteins, conferring protection against oxidative stress. Arteriosclerosis, thrombosis, and vascular biology 2003; 23:829-835
850. Garner B, Waldeck AR, Witting PK, Rye KA, Stocker R. Oxidation of high density lipoproteins. II. Evidence for direct reduction of lipid hydroperoxides by methionine residues of apolipoproteins AI and AII. The Journal of biological chemistry 1998; 273:6088-6095
851. Bashtovyy D, Jones MK, Anantharamaiah GM, Segrest JP. Sequence conservation of apolipoprotein A-I affords novel insights into HDL structure-function. J Lipid Res 2011; 52:435-450
852. Kontush A, Chantepie S, Chapman MJ. Small, dense HDL particles exert potent protection of atherogenic LDL against oxidative stress. Arteriosclerosis, thrombosis, and vascular biology 2003; 23:1881-1888
853. Kumpula LS, Kumpula JM, Taskinen MR, Jauhiainen M, Kaski K, Ala-Korpela M. Reconsideration of hydrophobic lipid distributions in lipoprotein particles. Chemistry and physics of lipids 2008; 155:57-62
854. Christison J, Karjalainen A, Brauman J, Bygrave F, Stocker R. Rapid reduction and removal of HDL- but not LDL-associated cholesteryl ester hydroperoxides by rat liver perfused in situ. The Biochemical journal 1996; 314 (Pt 3):739-742
855. Mertens A, Verhamme P, Bielicki JK, Phillips MC, Quarck R, Verreth W, Stengel D, Ninio E, Navab M, Mackness B, Mackness M, Holvoet P. Increased low-density lipoprotein oxidation and impaired high-density lipoprotein antioxidant defense are associated with increased macrophage homing and atherosclerosis in dyslipidemic obese mice: LCAT gene transfer decreases atherosclerosis. Circulation 2003; 107:1640-1646
856. Rallidis LS, Tellis CC, Lekakis J, Rizos I, Varounis C, Charalampopoulos A, Zolindaki M, Dagres N, Anastasiou-Nana M, Tselepis AD. Lipoprotein-associated phospholipase A(2) bound on high-density lipoprotein is associated with lower risk for cardiac death in stable

coronary artery disease patients: a 3-year follow-up. J Am Coll Cardiol 2012; 60:2053-2060
857. Wu A, Hinds CJ, Thiemermann C. High-density lipoproteins in sepsis and septic shock: metabolism, actions, and therapeutic applications. Shock 2004; 21:210-221
858. Wurfel MM, Kunitake ST, Lichenstein H, Kane JP, Wright SD. Lipopolysaccharide (LPS)-binding protein is carried on lipoproteins and acts as a cofactor in the neutralization of LPS. The Journal of experimental medicine 1994; 180:1025-1035
859. Levine DM, Parker TS, Donnelly TM, Walsh A, Rubin AL. In vivo protection against endotoxin by plasma high density lipoprotein. Proceedings of the National Academy of Sciences of the United States of America 1993; 90:12040-12044
860. Hajduk SL, Moore DR, Vasudevacharya J, Siqueira H, Torri AF, Tytler EM, Esko JD. Lysis of Trypanosoma brucei by a toxic subspecies of human high density lipoprotein. The Journal of biological chemistry 1989; 264:5210-5217
861. Perez-Morga D, Vanhollebeke B, Paturiaux-Hanocq F, Nolan DP, Lins L, Homble F, Vanhamme L, Tebabi P, Pays A, Poelvoorde P, Jacquet A, Brasseur R, Pays E. Apolipoprotein L-I promotes trypanosome lysis by forming pores in lysosomal membranes. Science 2005; 309:469-472
862. Lecordier L, Vanhollebeke B, Poelvoorde P, Tebabi P, Paturiaux-Hanocq F, Andris F, Lins L, Pays E. C-terminal mutants of apolipoprotein L-I efficiently kill both Trypanosoma brucei brucei and Trypanosoma brucei rhodesiense. PLoS pathogens 2009; 5:e1000685
863. Patel PJ, Khera AV, Wilensky RL, Rader DJ. Anti-oxidative and cholesterol efflux capacities of high-density lipoprotein are reduced in ischaemic cardiomyopathy. European journal of heart failure 2013; 15:1215-1219
864. Patel PJ, Khera AV, Jafri K, Wilensky RL, Rader DJ. The anti-oxidative capacity of high-density lipoprotein is reduced in acute coronary syndrome but not in stable coronary artery disease. J Am Coll Cardiol 2011; 58:2068-2075
865. Smith JD. Dysfunctional HDL as a diagnostic and therapeutic target. Arteriosclerosis, thrombosis, and vascular biology 2010; 30:151-155
866. Li C, Gu Q. Protective effect of paraoxonase 1 of high-density lipoprotein in type 2 diabetic patients with nephropathy. Nephrology 2009; 14:514-520
867. Nobecourt E, Jacqueminet S, Hansel B, Chantepie S, Grimaldi A, Chapman MJ, Kontush A. Defective antioxidative activity of small dense HDL3 particles in type 2 diabetes: relationship to elevated oxidative stress and hyperglycaemia. Diabetologia 2005; 48:529-538
868. Ferretti G, Bacchetti T, Busni D, Rabini RA, Curatola G. Protective effect of paraoxonase activity in high-density lipoproteins against erythrocyte membranes peroxidation: a comparison between healthy subjects and type 1 diabetic patients. The Journal of clinical endocrinology and metabolism 2004; 89:2957-2962
869. Watanabe J, Charles-Schoeman C, Miao Y, Elashoff D, Lee YY, Katselis G, Lee TD, Reddy ST. Proteomic profiling following immunoaffinity capture of high-density lipoprotein: association of acute-phase proteins and complement factors with proinflammatory high-density lipoprotein in rheumatoid arthritis. Arthritis and rheumatism 2012; 64:1828-1837

870. Charles-Schoeman C, Watanabe J, Lee YY, Furst DE, Amjadi S, Elashoff D, Park G, McMahon M, Paulus HE, Fogelman AM, Reddy ST. Abnormal function of high-density lipoprotein is associated with poor disease control and an altered protein cargo in rheumatoid arthritis. Arthritis and rheumatism 2009; 60:2870-2879
871. Kontush A, de Faria EC, Chantepie S, Chapman MJ. Antioxidative activity of HDL particle subspecies is impaired in hyperalphalipoproteinemia: relevance of enzymatic and physicochemical properties. Arteriosclerosis, thrombosis, and vascular biology 2004; 24:526-533
872. Van Lenten BJ, Hama SY, de Beer FC, Stafforini DM, McIntyre TM, Prescott SM, La Du BN, Fogelman AM, Navab M. Anti-inflammatory HDL becomes pro-inflammatory during the acute phase response. Loss of protective effect of HDL against LDL oxidation in aortic wall cell cocultures. J Clin Invest 1995; 96:2758-2767
873. Ansell BJ, Navab M, Hama S, Kamranpour N, Fonarow G, Hough G, Rahmani S, Mottahedeh R, Dave R, Reddy ST, Fogelman AM. Inflammatory/antiinflammatory properties of high-density lipoprotein distinguish patients from control subjects better than high-density lipoprotein cholesterol levels and are favorably affected by simvastatin treatment. Circulation 2003; 108:2751-2756
874. Navab M, Hama SY, Hough GP, Subbanagounder G, Reddy ST, Fogelman AM. A cell-free assay for detecting HDL that is dysfunctional in preventing the formation of or inactivating oxidized phospholipids. J Lipid Res 2001; 42:1308-1317
875. Mastorikou M, Mackness B, Liu Y, Mackness M. Glycation of paraoxonase-1 inhibits its activity and impairs the ability of high-density lipoprotein to metabolize membrane lipid hydroperoxides. Diabetic medicine : a journal of the British Diabetic Association 2008; 25:1049-1055
876. Kalogerakis G, Baker AM, Christov S, Rowley KG, Dwyer K, Winterbourn C, Best JD, Jenkins AJ. Oxidative stress and high-density lipoprotein function in Type I diabetes and end-stage renal disease. Clinical science 2005; 108:497-506
877. Hansel B, Giral P, Nobecourt E, Chantepie S, Bruckert E, Chapman MJ, Kontush A. Metabolic syndrome is associated with elevated oxidative stress and dysfunctional dense high-density lipoprotein particles displaying impaired antioxidative activity. The Journal of clinical endocrinology and metabolism 2004; 89:4963-4971
878. de Souza JA, Vindis C, Hansel B, Negre-Salvayre A, Therond P, Serrano CV, Jr., Chantepie S, Salvayre R, Bruckert E, Chapman MJ, Kontush A. Metabolic syndrome features small, apolipoprotein A-I-poor, triglyceride-rich HDL3 particles with defective anti-apoptotic activity. Atherosclerosis 2008; 197:84-94
879. Xu Y, Jin X, Ping Q, Cheng J, Sun M, Cao F, You W, Yuan D. A novel lipoprotein-mimic nanocarrier composed of the modified protein and lipid for tumor cell targeting delivery. Journal of controlled release : official journal of the Controlled Release Society 2010; 146:299-308
880. Morgantini C, Natali A, Boldrini B, Imaizumi S, Navab M, Fogelman AM, Ferrannini E, Reddy ST. Anti-inflammatory and antioxidant properties of HDLs are impaired in type 2 diabetes. Diabetes 2011; 60:2617-2623
881. Gowri MS, Van der Westhuyzen DR, Bridges SR, Anderson JW. Decreased protection by HDL from poorly controlled type 2 diabetic subjects against LDL oxidation may Be

due to the abnormal composition of HDL. Arteriosclerosis, thrombosis, and vascular biology 1999; 19:2226-2233
882. Vaziri ND, Moradi H, Pahl MV, Fogelman AM, Navab M. In vitro stimulation of HDL anti-inflammatory activity and inhibition of LDL pro-inflammatory activity in the plasma of patients with end-stage renal disease by an apoA-1 mimetic peptide. Kidney international 2009; 76:437-444
883. Moradi H, Pahl MV, Elahimehr R, Vaziri ND. Impaired antioxidant activity of high-density lipoprotein in chronic kidney disease. Translational research : the journal of laboratory and clinical medicine 2009; 153:77-85
884. McMahon M, Grossman J, FitzGerald J, Dahlin-Lee E, Wallace DJ, Thong BY, Badsha H, Kalunian K, Charles C, Navab M, Fogelman AM, Hahn BH. Proinflammatory high-density lipoprotein as a biomarker for atherosclerosis in patients with systemic lupus erythematosus and rheumatoid arthritis. Arthritis and rheumatism 2006; 54:2541-2549
885. Charles-Schoeman C, Lee YY, Grijalva V, Amjadi S, FitzGerald J, Ranganath VK, Taylor M, McMahon M, Paulus HE, Reddy ST. Cholesterol efflux by high density lipoproteins is impaired in patients with active rheumatoid arthritis. Annals of the rheumatic diseases 2012; 71:1157-1162
886. Tan KC, Chow WS, Lam JC, Lam B, Wong WK, Tam S, Ip MS. HDL dysfunction in obstructive sleep apnea. Atherosclerosis 2006; 184:377-382
887. Sorrentino SA, Besler C, Rohrer L, Meyer M, Heinrich K, Bahlmann FH, Mueller M, Horvath T, Doerries C, Heinemann M, Flemmer S, Markowski A, Manes C, Bahr MJ, Haller H, von Eckardstein A, Drexler H, Landmesser U. Endothelial-vasoprotective effects of high-density lipoprotein are impaired in patients with type 2 diabetes mellitus but are improved after extended-release niacin therapy. Circulation 2010; 121:110-122
888. Persegol L, Verges B, Foissac M, Gambert P, Duvillard L. Inability of HDL from type 2 diabetic patients to counteract the inhibitory effect of oxidised LDL on endothelium-dependent vasorelaxation. Diabetologia 2006; 49:1380-1386
889. Persegol L, Foissac M, Lagrost L, Athias A, Gambert P, Verges B, Duvillard L. HDL particles from type 1 diabetic patients are unable to reverse the inhibitory effect of oxidised LDL on endothelium-dependent vasorelaxation. Diabetologia 2007; 50:2384-2387
890. Speer T, Rohrer L, Blyszczuk P, Shroff R, Kuschnerus K, Krankel N, Kania G, Zewinger S, Akhmedov A, Shi Y, Martin T, Perisa D, Winnik S, Muller MF, Sester U, Wernicke G, Jung A, Gutteck U, Eriksson U, Geisel J, Deanfield J, von Eckardstein A, Luscher TF, Fliser D, Bahlmann FH, Landmesser U. Abnormal high-density lipoprotein induces endothelial dysfunction via activation of Toll-like receptor-2. Immunity 2013; 38:754-768
891. Charakida M, Besler C, Batuca JR, Sangle S, Marques S, Sousa M, Wang G, Tousoulis D, Delgado Alves J, Loukogeorgakis SP, Mackworth-Young C, D'Cruz D, Luscher T, Landmesser U, Deanfield JE. Vascular abnormalities, paraoxonase activity, and dysfunctional HDL in primary antiphospholipid syndrome. JAMA 2009; 302:1210-1217
892. Holven KB, Aukrust P, Retterstol K, Otterdal K, Bjerkeli V, Ose L, Nenseter MS, Halvorsen B. The antiatherogenic function of HDL is impaired in hyperhomocysteinemic subjects. J Nutr 2008; 138:2070-2075

893. Annema W, Nijstad N, Tolle M, de Boer JF, Buijs RV, Heeringa P, van der Giet M, Tietge UJ. Myeloperoxidase and serum amyloid A contribute to impaired in vivo reverse cholesterol transport during the acute phase response but not group IIA secretory phospholipase A(2). J Lipid Res 2010; 51:743-754
894. Holzer M, Wolf P, Curcic S, Birner-Gruenberger R, Weger W, Inzinger M, El-Gamal D, Wadsack C, Heinemann A, Marsche G. Psoriasis alters HDL composition and cholesterol efflux capacity. J Lipid Res 2012; 53:1618-1624
895. Ronda N, Favari E, Borghi MO, Ingegnoli F, Gerosa M, Chighizola C, Zimetti F, Adorni MP, Bernini F, Meroni PL. Impaired serum cholesterol efflux capacity in rheumatoid arthritis and systemic lupus erythematosus. Annals of the rheumatic diseases 2014; 73:609-615
896. Vivekanandan-Giri A, Slocum JL, Byun J, Tang C, Sands RL, Gillespie BW, Heinecke JW, Saran R, Kaplan MJ, Pennathur S. High density lipoprotein is targeted for oxidation by myeloperoxidase in rheumatoid arthritis. Annals of the rheumatic diseases 2013; 72:1725-1731
897. Yamamoto S, Yancey PG, Ikizler A, Jerome WG, Kaseda R, Cox B, Bian A, Shintani A, Fogo AB, Linton MF, Fazio S, Kon V. Dysfunctional High-Density Lipoprotein in Patients on Chronic Hemodialysis. Journal of the American College of Cardiology 2012; 60:2372-2379
898. Holzer M, Birner-Gruenberger R, Stojakovic T, El-Gamal D, Binder V, Wadsack C, Heinemann A, Marsche G. Uremia Alters HDL Composition and Function. J Am Soc Nephrol 2011; 22:1631-1641
899. Cavallero E, Brites F, Delfly B, Nicolaiew N, Decossin C, Degeitere C, Fruchart JC, Wikinski R, Jacotot B, Castro G. Abnormal Reverse Cholesterol Transport in Controlled Type-Ii Diabetic-Patients - Studies on Fasting and Postprandial Lpa-I Particles. Arterioscl Throm Vas 1995; 15:2130-2135
900. Zhou HL, Tan KCB, Shiu SWM, Wong Y. Increased serum advanced glycation end products are associated with impairment in HDL antioxidative capacity in diabetic nephropathy. Nephrol Dial Transpl 2008; 23:927-933
901. Besler C, Heinrich K, Rohrer L, Doerries C, Riwanto M, Shih DM, Chroni A, Yonekawa K, Stein S, Schaefer N, Mueller M, Akhmedov A, Daniil G, Manes C, Templin C, Wyss C, Maier W, Tanner FC, Matter CM, Corti R, Furlong C, Lusis AJ, von Eckardstein A, Fogelman AM, Luscher TF, Landmesser U. Mechanisms underlying adverse effects of HDL on eNOS-activating pathways in patients with coronary artery disease. J Clin Invest 2011; 121:2693-2708