IMMUNE SYSTEM EFFECTS ON THE ENDOCRINE SYSTEM

Georgios Boutzios, MD, PhD Consultant in Endocrinology, Department of Pathophysiology, Laiko University Hospital, Athens, Greece, email: gboutzios@gmail.com

Gregory Kaltsas, MD, FRCP Associate Professor of Medicine, Department of Pathophysiology, Laiko University Hospital, Athens 115 27, Greece, email: mailto:gkaltsas@endo.gr

Revised March 2015

ABSTRACT

The majority of the effects of the immune on the endocrine system are mediated by a number of chemokines, the most important of which are the cytokines. Cytokines are produced by different types of cells, and exhibit less restricted tissue specificity than hormones. More than 100 different type of cytokines have been identified up to now that can influence the activation, growth and differentiation of several target cells and serve as molecular messengers between cells, exhibiting either a pro- or an anti-inflammatory effect. Structurally, cytokines can be divided into the following groups: the 4α helix family members [interleukin 2, interferon gamma, and interleukin (IL) -10], IL-1 and IL-17 family, and chemokines.
Cytokines are mainly produced from immune cells, but are also secreted by the thyroid follicular cells as well as by inflammatory cells leading to euthyroid sick syndrome (ESS), amiodarone induced thyroid disease, postpartum thyroiditis, Hashimoto thyroiditis and Graves' disease. In diabetes mellitus (DM), an interplay between inflammatory and metabolic abnormalities leads to tissue damage. Diabetes Mellitus type 1 (DM1) is mediated by cellular immune reactions, and islet autoantibodies constitute robust predictors of the risk of progression towards DM1. In contrast, obesity is strongly related to Diabetes Mellitus type 2 (DM2) mainly through inducing insulin resistance which is the impaired ability of insulin to effectively induce glucose uptake by cells. The immune system has also the ability to affect the balance of bone resorption and formation by inducing osteoclast differentiation. In addition to osteoblasts, receptor activator of nuclear factor kappa-B ligand is also produced by monocytes, neutrophils, and lymphocytes, which leads to activation of osteoclasts leading to oosteoporosis.
The hypothalamo-pituitary-adrenal axis (HPA-axis) is activated in states of inflammation or infection. This activation is mediated by the inflammatory cytokines tumor necrosis factor-α (TNF-α), IL-1, and IL-6, which are secreted in tandem in response to various infectious and non-infectious stimuli. In the autonomic nervous system, catecholamines have been found to stimulate IL-6 secretion through a beta-adrenergic mechanism showing the immune effects on endocrine system.

INTRODUCTION

The mammalian immune system is composed of the innate and adaptive branches that integrate to mount sophisticated responses to combat invading pathogens, while preserving homeostasis at various sites colonized by various pathogens [1]. In order to preserve this

homeostatic environment a close interrelation between the immune and endocrine system has evolved. The majority of the effects of the immune on the endocrine system are mediated by a number of chemokines the most important of which are the cytokines [1]. Cytokines are small soluble glycosylated proteins that can theoretically be secreted by all cells of the human body, confer cellular resistance and mediate communication between immune and non-immune cells. These compounds are produced by different types of cells, such as glial cells, macrophages, neutrophils, lymphocytes, adipocytes and others, and exhibit less restricted tissue specificity than hormones [1, 2]. More than 100 different type of cytokines have been identified up to now that can influence the activation, growth and differentiation of several target cells and serve as molecular messengers between cells, exhibiting either a pro- or an anti-inflammatory effect. Structurally, cytokines can be divided into 4 groups: the 4α helix family members (interleukin 2 [IL-2], interferon gamma [IFN-γ], and IL-10), IL-1 and IL-17 family, and chemokines. However, a more helpful division is according to their functional grouping into those involved in Th1 responses (cell-mediated immunity) and those involved in Th2 responses (humoral immunity) [3]. Cytokines, such as interleukin-1 beta (IL-1β), IL-6 and IL-8 are pro-inflammatory mediators, inducing a systemic inflammatory response reflected by increased levels of soluble interleukin-2 receptor (sIL-2R), neopterin or tumor necrosis factor-alpha (TNF-α); TNF-α has multiple functions in the development of the immune system as not only serves as the pro-inflammatory cytokine but also modulates the adaptive immune responses. Other cytokines, such as IL-10, and interleukin-1 beta receptor antagonist (IL-1RA) are also involved in systemic inflammation [3]. The IL-10 family of cytokines consists of nine related molecules with differences of sequence homology. IL-10 family members can be sub-divided into three groups with different biological functions: 1) the immune-regulatory cytokine IL-10 itself; 2) the IL-20 subfamily: IL-19, IL-20, IL-22, IL-24, and IL-26 which play a role in host-defense mechanisms against bacteria and fungi; and 3) the type III interferons: IL-28α, IL-28β, and IL-29 which induce antiviral responses [4, 5]. More recent data have shown that IL-33 can prevent the development of experimental cerebral malaria by orchestrating a protective immune response via innate lymphoid cells 2 (ILC2), M2 macrophages and regulatory T cells [6].
This chapter will focus on the interactions of cytokines on different endocrine systems.

IMMUNE SYSTEM AND THYROID DISEASE

Cytokines are mainly produced from immune cells, but are also secreted by the thyroid follicular cells as well as by inflammatory cells [7]. Cytokines up-regulate the inflammatory reaction through stimulation of T and B lymphocytes, resulting in antibody production and tissue injury, and thus play a crucial role in autoimmune thyroid diseases [7, 8].

Euthyroid Sick Syndrome

The term "Euthyroid Sick Syndrome" (ESS) has been used for more than thirty years to describe a pattern of thyroid hormone alterations during non-thyroidal illness. Conditions associated with ESS include systemic inflammation, myocardial infarction, starvation, sepsis, surgery, trauma, chronic degenerative diseases, malignancy and every other condition with the clinical manifestation of severe illness. The characteristic laboratory abnormalities of the ESS include low triidothyronine (T3) and/or free T3 (fT3), elevated reverse T3 (rT3), normal or low thyroid stimulating hormone (TSH), and normal or low serum thyroxine (T4) or free T4 (fT4) concentrations. These abnormalities follow the concept that the more severe the illness is the

more extensive the hormonal alterations are and develop as a result of cytokine action on several pathways of thyroid hormonal synthesis and/or degradation. In particular, thyroid hormone changes are the result of suppression of thyrotropin-releasing hormone (TRH) and TSH release, and inhibition of hepatic type-1 5Ά deiodinase (D1) that facilitates conversion of T4 to T3 and of rT3 to diiodothyronine [9]. Thus the cause of the decreased T3 concentration in ESS is decreased T3 production, whereas the cause of the increased rT3 concentration is the result of attenuated degradation. Prolonged and severe illness is marked by a decrease in circulating total T4 along with low T3 and high rT3; furthermore, very low T4 levels carry a poor prognosis and have been associated with an increased mortality rate [9]. Cyttokines including IL-1α, IL-1β, IL-6, interferon-gamma (IFN-γ) TNF-α, and TGF-β2, exert an inhibitory role on sodium–iodine symporter (NIS) protein expression and NIS gene transcription, an intrinsic membrane protein that facilitates the active transport of iodine into the thyroid cell [7, 10, 11]. In addition to the effects on iodide uptake, cytokines have also been shown to decrease thyrocyte growth [12], iodide organification [13, 14], thyroglobulin synthesis [15, 16], and thyroid hormone release in vitro [17].

Cytokines can also affect hepatic deoiodinase type 1 D1 activity (Figure 1). The main role of D1 is to peripherally convert T4 to T3 and rT3 to diiodothyronine. In ESS, there is a decrease in D1 activity leading to decreased T3 and increased rT3 concentrations. However, the exact mechanism of decreased D1 activity in ESS still remains unclear. In vitro studies, evaluating the effects of cytokines IL-1β, IL-6, and TNF-α on D1 levels in rat thyroid FRTL-5 and liver cells, have produced controversial results. The D1 activity in rat thyroid FRTL-5 was inhibited by these cytokines [18], whereas liver D1 activity was surprisingly increased [19].

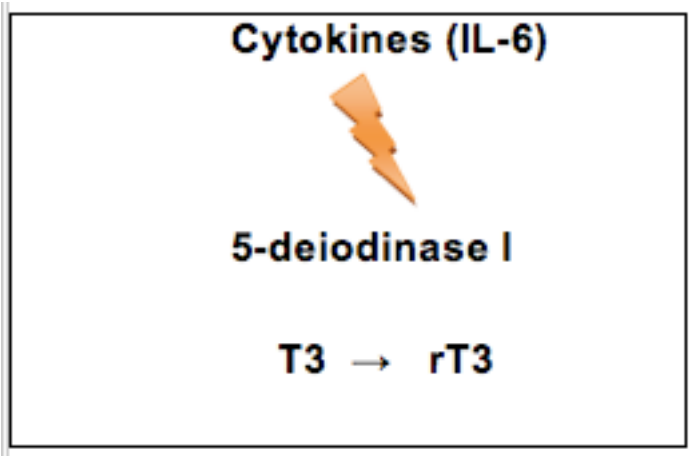

Figure 1. IL-6 inhibition of 5Î„ deiodinase-I resulting in decrease in T3 and increase in rT3 concentration

While the in vitro studies of cytokine effect on D1 activity are controversial, in vivo studies have revealed that cytokines can inhibit D1 activity either directly or indirectly. To delineate the effects of IL-6 on D1 activity, IL-6 knockout mice [20] were used in whom Listeria monocytogenes infection or turpentine injection induced a ESS state. The decrease in serum T3 concentration was attenuated in the IL-6 knockout mice compared to wild-type animals. This was associated with only a modest decrease in hepatic D1 activity (compared to wild-type animals), implying that IL-6 played a significant role in the pathogenesis of ESS in that model.

In exploring the effects of cytokines on the hypothalamic-pituitary unit, in vitro studies demonstrated that IL-1β and TNF-α can inhibit TSH release from the pituitary through stimulation of K+-mediated release of somatostatin from the hypothalamus (Figure 2) [21]. IL-6 exhibited no effect on TSH secretion or somatostatin release, implying that this cytokine had no direct effect on the hypothalamic-pituitary unit of the thyroid axis [22].

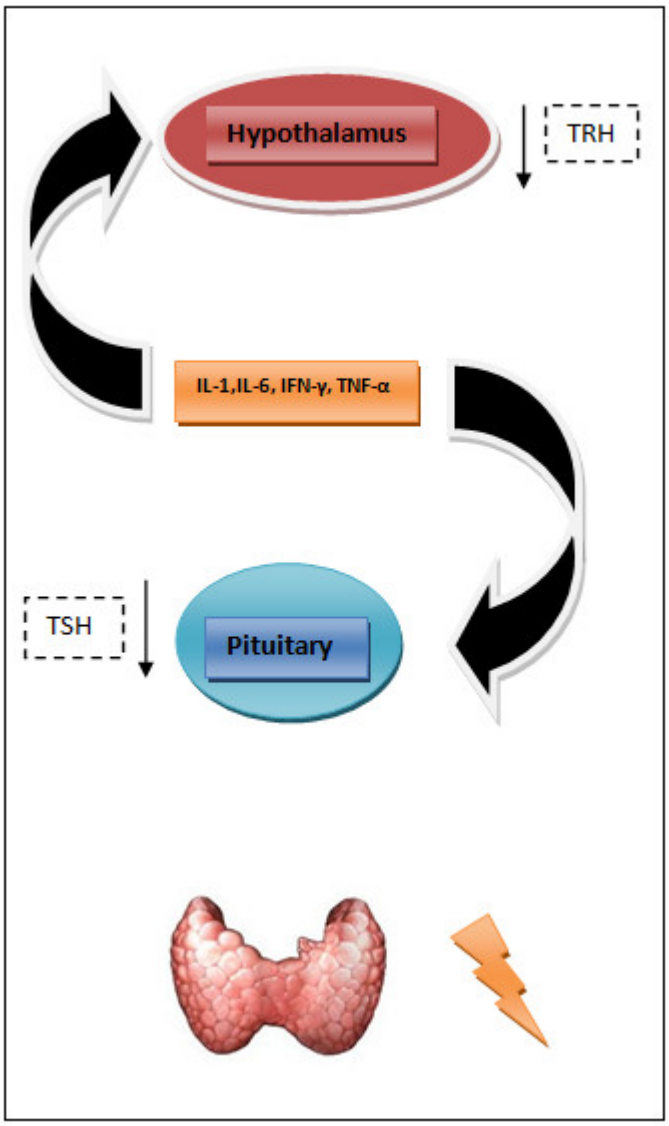

Figure 2. Cytokine-mediated decrease in thyrotropin-releasing hormone (TRH) and TSH secretion

In animal studies, administration of TNF-α to rats had a similar effect [23, 24]. After IL-6 was administered to rats, TSH decreased without any change in hypothalamic pro-TRH mRNA levels, or in stored β-TSH in the pituitary [25]. These data, along with the lack of any IL-6 effect on TSH release in vitro, suggest that the observed decrease of circulating TSH in vivo following IL-6 administration was the result of an indirect rather than a direct action on the TRH-TSH unit.

The central role of cytokines in the pathophysiology of ESS has been further elucidated in studies involving cytokine administration to humans. Following TNF-α administration to healthy volunteers a decrease in serum T3 and an increase in serum rT3 concentration was found [26]. Unlike IL-6, serum TNF-α levels did not correlate with any of the typical thyroid parameters such as low T3, increased rT3, or decreased TSH levels, as seen in ESS [27, 28], suggesting that the changes of thyroid hormonal profile following TNF-α administration might be indirect (i.e. through TNF-α increase in circulating IL-6 levels) rather than direct. Furthermore, both IL-6 and TNF-α can regulate type 2 iodothyronine 5'-deiodinase in the anterior pituitary, affecting TSH release, thus contributing to the development of the non-thyroidal illness syndrome [29, 30]. In addition, TNF-α seems to be the critical cytokine mediating the downstream anti-resorptive effects of TSH on the skeleton [31].

A link between leptin and pro-inflammatory cytokines such as TNF-α leading to the development of ESS, has also been suggested following the finding that TNF-α levels were associated with increased leptin levels in patients with chronic obstructive pulmonary disease [32]. Moreover, serum leptin levels were increased and significantly associated with IL-6 levels and disease activity in men with ankylosing spondylitis [33]. It has been suggested that the primary action of leptin on the hypothalamic-pituitary-thyroid (HPT) axis is alteration of the set point for feedback sensitivity of hypophysiotropic TRH producing neurons in the paraventricular nucleus (PVN) of the hypothalamus to thyroid hormones (mainly T3) through lowering of the set point when leptin levels are suppressed during fasting [34]. Two anatomically distinct and functionally antagonistic populations of neurons in the arcuate nucleus of the hypothalamus, α-melanocortin-stimulating hormone (α-MSH) producing neurons that co-express cocaine and amphetamine-regulated transcript, and neuropeptide Y (NPY)-producing neurons that co-express agouti-related peptide (AGRP), are responsible for the actions of leptin on hypophysiotropic TRH. It is thought that the inhibitory effect of AGRP on TRH gene expression is the result of antagonizing the activating effects of α-MSH at the melanocortin 4 receptor on the surface of hypophysiotropic TRH neurons, whereas the inhibitory effect of NPY occurs by reducing cAMP levels [35]. A direct action of leptin on hypophysiotropic TRH neurons has also been proposed [36]. These data suggest that leptin can act via two different and independent mechanisms (cytokine dependent and directly) in seriously ill patients, affecting the thyroid function as a whole.

Recent data have shown that thyroid hormone replacement therapy significantly increases the remission of ESS in patients with nephrotic syndrome and that ESS also predicts the development of severe neurological deficits following cerebral infarction in patients with large artery atherosclerosis. Euthyroid sick syndrome, was also found to be related to in-hospital and long term mortality in patients with ST segment elevation myocardial infarction (STEMI) undergoing primary percutaneous intervention and may be benefited from adequate replacement [37, 38].

The Role of IL-6 in Amiodarone-Induced Thyroid Disease

Amiodarone, a benzofuran derivative with a similar structure to thyroid hormones, is a highly effective antiarrhythmic agent widely used in the treatment of various types of tachyarrhythmias (supraventricular and ventricular arrhythmias). Amiodarone contains two iodine atoms per molecule which is approximately 37,5% iodine by molecular weight [39].

Administration of amiodarone is associated with complex changes in thyroid physiology. The iodine load results in an inhibition of thyroid hormone synthesis and metabolism, particularly 5'-monodeiodination of T4 to T3. Such alterations occur in all patients and although the majority remain clinically euthyroid, approximately 14% of amiodarone-treated patients develop thyroid dysfunction [39-41]. The relative proportion of patients developing either thyrotoxicosis or hypothyroidism depends on the iodine content of the local diet and pre-existing thyroid autoimmunity. In relatively iodine replete areas, approximately 25% of patients with amiodarone-induced thyroid dysfunction become thyrotoxic, accounting for approximately 3% of amiodarone treated individuals [41]. The pathogenesis of amiodarone-induced thyrotoxicosis (AIT) is complex although two distinct forms, Type 1 and Type 2, are recognized; Type 1 develops in patients with latent thyroid disease, predominantly nodular goiter in whom the amiodarone iodine load triggers increased synthesis of thyroid hormones. Type 2 is the result of a destructive thyroiditis in a previously normal gland, with leakage of preformed thyroid hormones despite a reduction in hormone synthesis [39-42]. A cross-sectional study in patients with AIT revealed that serum IL-6 concentration was elevated in such patients without a goiter or circulating thyroidal autoantibodies (AIT-) compared to patients with AIT in the presence of a goiter or thyroidal autoantibodies (AIT+) [43]. AIT-patients had a very low (<3%) 24-hour thyroidal radioiodine uptake suggesting that a subacute thyroiditis-like mechanism was responsible for the thyrotoxicosis. To determine if plasma IL-6 concentration was elevated in other destructive processes besides AIT, serum IL-6 concentration was measured in patients undergoing fine needle aspiration of the thyroid, percutaneous ethanol injections into thyroid nodules or radioactive iodine treatment. Serum IL-6 concentration increased significantly following any of these procedures, suggesting that IL-6 could be used as a marker of any thyroid destructive processes, regardless of the etiology [44].

Differentiating between the two types of AIT is an essential step in their management as treatment of each type is different [41]. Type 1 usually responds to thionamide therapy that blocks hormone synthesis and perchlorate that blocks active transport of iodine into the thyroid, whereas Type 2 responds to high-dose of corticosteroids [41, 42, 45, 46]. Nevertheless, several studies now suggest that these two types should be treated concomitantly, and thus patients with AIT receive both anti-thyroid drugs and prednisolone. In resistant to medical treatment cases and/or in patients with severe cardiac diseases who cannot interrupt amiiodarone or require quick amiodarone reintroduction, total thyroidectomy may be offered after rapid correction of thyrotoxicosis following combination treatment with thionamides, $KClO_4$, corticosteroids and a short course of iopanoic acid [47].

Postpartum Thyroid Disease

Postpartum thyroiditis (PPT) is characterized by the development of postpartum thyroid dysfunction (PPTD), which may occur up to 12 months after delivery. Postpartum exacerbation of autoimmunity may reflect an imbalance in specific regulatory T(REG) cells, which is caused by the rapid fall in the numbers of these cells after delivery, and is associated with fluctuations in transforming growth factor-beta1 serum levels [48, 49].

Usually the syndrome presents as transient hyperthyroidism (median time of onset, 13 weeks post delivery) followed by transient hypothyroidism (median time of onset, 19 weeks post delivery) and in the majority of patients later restoration of normal thyroid function occurs [50]. A plausible explanation for the development of postpartum thyroiditis is that during pregnancy there is a shift from T-helper 1 (TH1 or Type 1) to T-helper 2 (TH2 or Type 2) cytokine

production, followed by a "rebound" shift back to Type 1 after delivery (Figure 3). Type 1 cytokines (e.g. IL-12, IFN-γ) are pro-inflammatory and have been implicated in the pathogenesis of several autoimmune diseases, whereas Type 2 cytokines (e.g. IL-4, IL-10, IL-13) are anti-inflammatory. The pathogenesis of the disease has an autoimmune basis as thyroid peroxidase (anti-TPO) and thyroglobulin (anti-Tg) antibodies are found in almost all patients although anti-TPOs are those best correlating with the development of PPT. Postpartum thyroiditis occurs in up to 50% of women who are found to have anti-TPO antibodies at the end of the first trimester of gestation (i.e. before thyroid antibody titers start to decline during pregnancy). Furthermore, there is evidence that the TPO antibody titer at 16 weeks of gestation is related to the severity of the PPTD [51]. In addition, the ability to activate complement is also thought to play a role in the development of PPT. Approximately, 30-60% of anti-TPO-positive women in pregnancy subsequently develop PPT [52, 53]. Recent data also suggest that Type 2 cytokine production during pregnancy is teleologically important to ensure that the fetus is not rejected [54, 55], and that the inflammatory/infective processes may alter the balance of Th1 and Th2 cytokines causing a shift toward a Th1 predominance. This initiates and intensifies the cascade of inflammatory cytokine production involved in spontaneous abortion, preterm delivery, and/or preeclampsia (Figure 3) [3].

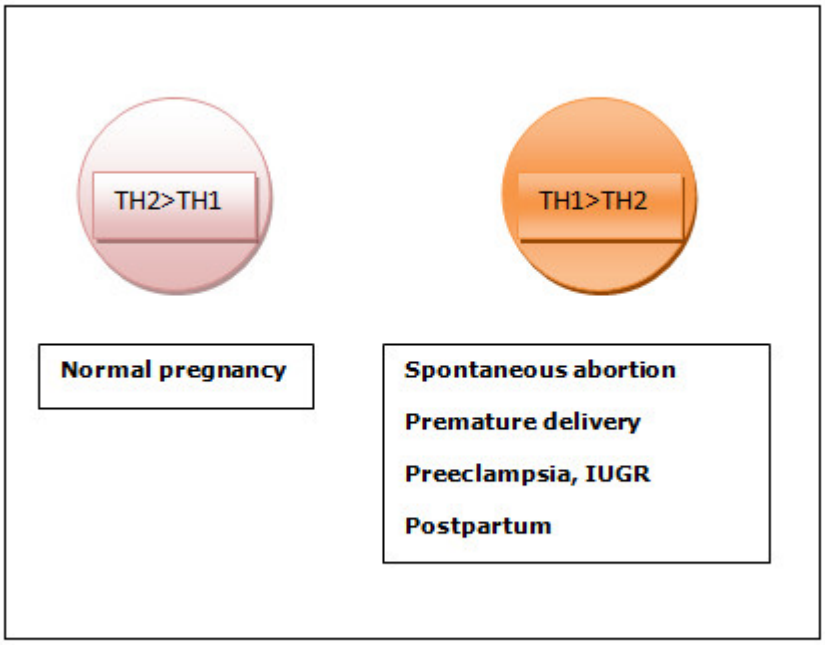

Figure 3. Th1/Th2 balance during pregnancy and postpartum. IUGR: Intrauterine growth retardation

Progesterone has also been shown to affect pregnancy-associated immunomodulation via alteration of the Type 1/Type 2 cytokine balance [56], thus maintaining uterine quiescence. Progesterone esponsiveness requires the expression and functional competence of progesterone receptors (PRs): changes from the PRB to PRA isoform may represent a key step in the mechanism for functional progesterone withdrawal [57]. Progesterone is a potent immunomodulator that alters cytokine secretion of T-cell clones favoring IL-10 production [58].

Progesterone's immunological effects are partially exerted through progesterone-induced blocking factor (PIBF) produced by progesterone-influenced lymphocytes [59, 60]. Progesterone-induced blocking factor has immunomodulating properties that regulate perforin expression by NK cells [60-62]. In addition, PIBF affects Type 1/Type 2 balance via increased IL-3, IL-4, and decreased IL-10 production. Treatment of mice with anti-PIBF antibody resulted in a shift toward Type 1 cytokine production along with increased rates of pregnancy resorption [63]. Additionally, in animal studies, progesterone upregulates Toll-like receptor 4 (TLR-4) expression and suppresses TLR-2 response to infection protecting from pre-term delivery [64]. In addition, progesterone inhibits basal and cytokine-enhanced matrix metalloproteinases (MMP)-1 and MMP-3 expression in cultured human decidual cells [65]. Furthermore, during pregnancy corticotropin-releasing factor (CRF) exerts both anti-inflammatory and pro-inflammatory effects. The anti-inflammatory effect is mediated by the end products of the adaptive response to stress, namely cortisol and catecholamines. The direct pro-inflammatory effect is mediated by the link with corticotropin-releasing factor receptor 1 (CRFR1) which appears to be necessary for the development of local inflammation and is a direct paracrine effect on resident immune cells at the site of inflammation [66].

Hashimoto's Thyroiditis (HT) and Graves' Disease (GD)

Hashimoto's thyroiditis (HT) is the most prevalent autoimmune thyroid disorder; the prevalence of HT confirmed by cytology was found to be 13.4% in consecutive patients who underwent fine-needle aspiration biopsy of thyroid nodules [69]. Cytokines also play a central role in the pathogenesis of common autoimmune thyroid diseases. For reasons that are not clearly delineated, activated T cells invade the thyroid gland and release cytokines, leading to dysregulation of B cells and subsequent production of autoantibodies.

TH1 cells are predominant T cell clones derived from HT patients, whereas TH2 and TH0 cells are predominantly found in patients with GD wherethe secretion of soluble CD23 may participate in B cell activation. Interestingly, anti-TPO and anti-Tg-specific clones derived from HT thyroid tissue produce high levels of IFN-γ, a Type 1 pro-inflammatory cytokine [67]. TH1 cells may also affect autoimmune thyroid disease through induction of thyrocyte apoptosis, which appears to be a major mechanism of thyroid tissue damage, indirectly through IL-1β production by activated macrophages [68]. In addition, thyrocytes themselves can produce inflammatory cytokines such as TNF-α, TGF-β, IL-1, IL-6, and IL-8, which can also cause thyrocyte destruction.

In HT secreted cytokines lead predominantly to a TH1 response as well as to a TH 17 response that has only recently been implicated. Final outcome of HT is thyroid destruction which is mostly a consequence of the apoptotic processes combined with T-cell mediated cytotoxicity [69].

In patients with Graves' disease, the predominant antibodies are directed against the thyroid-stimulating hormone (TSH) receptor (TSH-R). Thyrotrophin receptor antibodies (TRAb) exist as stimulating or blocking antibodies in the serum; however, neutral TRAb are also identified. The clinical features of GD occur when stimulating TRAb predominate [7, 70, 71]. Both in GD and HT, thyroid cells are exposed to complement attack, with subsequent release of prostaglandin E2, IL-1α, and IL-6, which promote infiltration of lymphocytes leading to cell destruction [49]. In GD, inflammatory mediators, such as interleukins and TNF-α, stimulate the production of external thyroid-stimulating antibodies that bind the TSH-R. In thyroid tissue, TH1 recruited lymphocytes may be responsible for enhanced IFN-γ and TNF-α production, which in turn stimulate C-X-C motif chemokine 10 (CXCL10:the prototype of the IFN-γ-

inducible Th1 chemokines) secretion from the thyroid cells, creating an amplification feedback loop, that initiates and perpetuates the autoimmune process [72]. Recent data have shown that TSH exerts an effect on IL-6 production as total fat deposit affects basal and TSH-stimulated IL-6 release from adipose cells in culture. Basal IL-6 release is greater for pre-adipocytes than differentiated adipocytes, whether derived from subcutaneous or omental fat depots, which indicates an effect of adipocyte differentiation on thyroid function [73].

In thyroid-associated ophthalmopathy, fibrocytes which are precursor cells of bone-marrow-derived monocyte lineage expressing the haematopoietic cell antigen CD34 ($CD34^+$ fibrocytes), also express the TSH receptor (TSHR). These cells can also produce several other proteins the expression of which was traditionally thought to be restricted to the thyroid gland. TSHR-expressing fibrocytes in which the receptor is activated by its ligand generate extremely high levels of several inflammatory cytokines. Acting in concert with TSHR, the insulin-like growth factor 1 receptor (IGF-1R) expressed by orbital fibroblasts and fibrocytes may participate in TSHR-dependent cytokine production, as anti-IGF-1R blocking antibodies attenuate these pro-inflammatory TSH actions leading to GD opthalmopathy [74].

THE IMMUNE SYSTEM AND DIABETES MELLITUS

Over recent years our understanding of the etiology of DM1 and DM2 and their vascular complications has widened considerably. In general, an interplay between inflammatory and metabolic abnormalities leads to tissue damage in patients with diabetes. In small and large vessels the earliest indicator of these effects is endothelial dysfunction accompanied by the development of a pro-thrombotic state, whereas in islets and insulin-sensitive tissues, β-cell damage and impaired insulin signaling are the hallmarks of the disease.

Type 1 Diabetes Mellitus

Type 1 diabetes (DM1 or insulin dependent diabetes mellitus) is an autoimmune disease, in which there is progressive and selective destruction of the insulin-producing beta (β) cells in the islets of Langerhans of the pancreas. Similar to diseases such as HT and GD, T cells appear to play a major role in this process. The primary pathogenic process in DM1 is mediated by cellular immune reactions, and islet autoantibodies are robust predictors of the risk of progression towards DM1. Activation of autoimmunity enhances production of pro-inflammatory molecules, which may predict progression to future diabetes [75-77]. Diabetes mellitus is regarded as a multifactorial autoimmune disease and both genetic factors and environmental stimuli are involved in the pathogenic process of disease.

In this concept, MIF (Macrophage migration inhibitory factor), a pro-inflammatory chemokine, produced by β cells may play a role in autoimmune insulinitis and although serum levels are lower in individuals with recent onset DM1, decreased levels are predictive of autoantibody development [78]. Increased interferon-γ-inducible protein 10, a chemo-attractant, and elevated IL-18 levels, which up-regulate synthesis of interferon-γ from T cells, were found in high risk but not low-risk normo-glycemic relatives of patients with DM1 [76]. Levels of the chemokines CCL3 and CCL4 (chemokine C-C motif ligand 3 and 4), which have been associated with experimental insulinitis, were more likely to be elevated in high-risk antibody positive than antibody-negative relatives of patients with DM1 [75]. In addition, a higher

frequency of high-sensitivity C-reactive protein (CRP) levels greater than 0.5 mg/liter were found in children at risk for DM1 [79].

Furthermore, three different mechanisms have been proposed for the pathogenesis of DM1. One mechanism involves molecular mimicry-activated T-cell proliferation. This mechanism is based on the assumption that epitopes of proteins expressed by infectious agents can be shared by unrelated molecules encoded by host genes [80]. A second mechanism triggers molecular mimicry-activated T-cell proliferation is "by stander" T-cell proliferation. This mechanism involves the stimulation of non-antigen-specific T cells by various cytokines during infection simply because they are in the area. The cytokines thought to be involved in this nonspecific stimulation are interferon alpha (IFN-α) and interferon beta (IFN-β) [81]. A third theory involving a superantigen-mediated T-cell proliferation mechanism proposes that auto-reactive T-cells can be inappropriately primed to react against self-structures through an encounter with a superantigen [82].

Type 2 cytokines, appear to be protective against the development of DM2 as it has been shown that the Type 2 cytokine IL-4 protected non obese diabetic (NOD) mice from developing insulinitis or diabetes. The potential role of a Type 2 cytokine deficiency in the pathogenesis of DM1 in humans was also demonstrated in another study involving diabetic siblings. In that study, T-cell clones from normal twins secreted both IFN-γ and IL-4, whereas T-cell clones from diabetic twins secreted only IFN-γ [83]. IFN-γ induced by IL-12 administration prevents the development of diabetes by inhibiting pathogenic IL-17 production in NOD mice [84]. Additionally, a number of studies have shown that TNF-α levels are increased in DM1; TNF-α is involved in the autoimmunity process leading to pancreatic β-cell damage and the induction of DM1 [85, 86]. It has been suggested that TNF-α may eventually be a marker assessing metabolic control in DM1 [86]. Arif et al. have shown that peripheral and islet interleukin-17 pathway activation characterize human autoimmune diabetes and promotes cytokine-mediated β-cell death [87].

Interleukin-6 plays an important role in the pathogenesis of vitiligo-associated DM1 patients and is likely to gain favour as a therapeutic target in these patients [88]. Interleukin 6 (IL-6) may also contribute to DM1 and increased albumin-to-creatinine ratio as well as to poor glycemic control and hyperlipidemia [89]. A recent study has shown that expression of arachidonate 5-lipoxygenase, which encodes enzyme 5-lipoxygenase, and the concentration of the pro-inflammatory cytokine interleukin-1β are increased in peritoneal macrophages and serum from DM1 mice and that leukotriene B4-mediated sterile inflammation promotes susceptibility to sepsis in a mouse model of DM1 [90]. It has been demonstrated that during the natural course of DM1, β- cells would also express Fas by the induction of T cells and inflammatory cytokines leading to subsequent cell death via Fas-Fas Ligand interaction [91].

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (DM2) is one of the most common metabolic disorders worldwide. It is associated with hypercholesterolemia, atherosclerosis, hypertension, kidney disease, and coronary artery disease. Obesity is strongly related to DM2 mainly through inducing insulin resistance (IR) which is the impaired ability of insulin to effectively induce glucose uptake by cells.

The concept that a smoldering inflammatory process is important in the pathogenesis of DM2 [92] has recently attracted much attention and is supported by evidence of inflammation in islets, adipose tissue, liver, and muscle that can provoke IR and β-cell dysfunction[93-95]. Initially nonspecific indicators of inflammation such as white cell count and fibrinogen were found to be predictive of diabetes [96, 97]. Subsequently elevated PAI-1 (Plasminogen activator inhibitor-1), CRP and fibrinogen levels were shown to be independent predictors [98]. These observations are supported by a number of prospective studies, in which tissue plasminogen activator (tPA), another marker of reduced fibrinolysis [8, 99], and von Willebrand factor (vWf), a marker of endothelial injury, were also shown to be predictive [100]. There have been many studies demonstrating an association between CRP and/or IL-6 and incident DM2 that was independent of adiposity or IR [8, 98, 101]. In addition, the early markers of inflammation, MCP-1(Monocyte chemotactic protein-1), IL-8, and interferon-γ-inducible protein-10, were also found to predict the development of DM2 with MCP-1 being independent of traditional risk factors [102]. Restraint stress increases monocyte accumulation, plasma free fatty acids, expression of angiotensinogen and pro-inflammatory cytokines including MCP-1, along with reduced adiponectin levels in patients with IR [103]. The adipose tissue appears to be a major source of circulating IL-6 in humans. Plasma IL-6 concentration correlates well with body mass index (BMI=kg/m^2) [104, 105], and has been found to be elevated in obese people with IR [106].

TNF-α has also received considerable attention with regard to IR and may be a key mediator of its pathogenesis. Adipose tissue expressing TNF-α has been shown to be significantly increased in obese individuals with IR [106, 107], and is thought to play a major role in the pathogenesis of obesity-linked DM2 [108]. Concerning the role of other cytokines in adipose tissue, Pellegrinelli et al demonstrated that the secretome of obese adipocytes decreased the expression of contractile proteins in myotubes consequently inducing atrophy. Using a three-dimensional co-culture of human myotubes and visceral adipose tissue adipocytes these authors demonstrated a decreased expression of genes corresponding to skeletal muscle contractility complex and myogenesis. They also demonstrated an increased secretion by co-cultured cells of cytokines and chemokines with IL-6 and IL-1β as key contributors [109].

TNF-α appears to be an important mediator of IR in obese animals through its overexpression in adipose tissue [110, 111]. At the molecular level, chronic exposure of adipocytes to low doses of TNF-α led to a dramatic decrease in the insulin-stimulated auto-phosphorylation of the insulin receptor and the phosphorylation of insulin receptor substrate 1 (IRS-1) [112]. Furthermore, IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in the presence of TNF-α has been demonstrated. Treatment of cultured murine adipocytes with TNF-α has been shown to induce serine phosphorylation of IRS-1 and convert IRS-1 into an inhibitor of the IR tyrosine kinase activity in vitro [113]. It was concluded that TNF-α plays an inhibitory role on the insulin-stimulated tyrosine kinase phosphorylation cascade. The question of whether TNF-α induces IR directly or indirectly through inhibitors of tyrosine kinase or counter-regulatory hormones on muscle, fat, and liver in vivo needs further investigation. TNF-α has also been shown to down-regulate glucose transporter GLUT4 mRNA levels in adipocyte and myocyte cultures as well [111, 114, 115].

TNF-α may also be playing a role in the hyperlipidemia observed in DM2 as it has been shown to have profound effects on whole body lipid metabolism [116-118]. Circulating triglycerides and very low density lipoproteins in rats and humans are increased after administration of TNF-α [116, 117]. Moreover, an animal study has provided evidence of increased TNF-α levels in animals receiving a high-fat diet [119]. In addition to TNF-α, IL-1 and IFN-γ also stimulate fatty acid synthesis whereas IL-6 influences fat metabolism as well. Several studies have

suggested that certain polymorphisms in the promoter region of the IL-6 gene can affect lipid levels through changes in IL-6 gene transcription and ultimately IL-6 production [120]. IL-6 has been proposed to cause an increase in circulating lipid levels probably through a decrease in peripheral lipoprotein lipase activity [121]. Thus chronic exposure to high IL-6 levels may lead to hyperlipidemia, whereas acute exposure may have the opposite effects on serum lipid levels.

Oxidative stress, as a result of increased cytokine levels in DM2, is also thought to play an important role in activating inflammatory genes [122, 123]. It is possible that oxidative stress markers do not adequately reflect the impact of increased reactive oxygen species (ROS) on β-cells or insulin signaling. Inflammatory, pro-coagulant or endothelial dysfunction markers are more specific because they may be more proximate to the pathophysiology of hyperglycemia [122, 123]. Recently, Hasnain et al showed that islet-endogenous and exogenous IL-22, by regulating oxidative stress pathways, suppresses oxidative and endoplasmic reticulum (ER) stress caused by cytokines or glucolipotoxicity in mouse and human beta cells. In obese mice, antibody neutralization of IL-23 or IL-24 partially reduced β-cell ER stress and improved glucose tolerance, whereas IL-22 administration modulated oxidative stress regulatory genes in islets, suppressed ER stress and inflammation, promoted secretion of high-quality efficacious insulin and fully restored glucose homeostasis followed by restitution of insulin sensitivity [124].

CALCIUM METABOLISM AND THE IMMUNE SYSTEM

Osteoporosis

Osteoporosis is a condition of low bone mass and microarchitectural disruption that results in fractures with minimal trauma. It is more frequent in postmenopausal women and in older men or women due to age-related bone loss. In osteoporosis the balance between bone resorption and bone formation is disrupted with a predominance of bone resorption. The two cells involved in dynamic bone metabolism are osteoblasts, activation of which leads to new bone formation, and osteoclasts which cause old bone reabsorbption. Cytokines have been implicated in the pathogenesis of osteoporosis as osteoblasts produce the cytokines IL-6 and IL-11 [125] whereas cytokines such as IL-1, IL-3, IL-6, IL-11, and TNF-α along with colony stimulating factors are implicated in osteoclast activation [126-128]. On the other hand, only a few cytokines such as IL-17α promote osteogenesis in mesenchymal stem cells. The IL-17α-induced leptin production may provide a key clue to understand a molecular mechanism on the lineage commitment of human bone marrow-derived mesenchymal stem cells (MSCs) into adipocytes or osteoblasts [129].

The immune system has the ability to affect the balance of bone resorption and formation by inducing osteoclast differentiation. In addition to osteoblasts, receptor activator of nuclear factor kappa-B ligand (RANKL) is also produced by monocytes, neutrophils, and lymphocytes, which leads to activation of osteoclasts. These cells produce inflammatory cytokines, such as TNF-α, and ILs (e.g., IL-1, IL-3, IL-6, and IL-17), which may increase osteoclast generation or induce RANKL expression by osteoblasts. Interleukin IL-1 also stimulates TNF receptor associated factor (TRAF6) expression, which leads to pre-osteoclasts differentiation [130]. Other cytokines, such as IL-4, IL- 5, IL-10, IFN-α, IFN-β, and IFN-γ, inhibit osteoclastogenesis

by blocking RANKL signaling. IFN-γ also down-regulates TRAF6, resulting in inhibition of osteoclast formation [131]. In particular, IL-6 plays a major role in osteoclast development and function. Interleukin IL-6 is produced by both stromal cells and osteoblastic cells in response to stimulation by systemic hormones such as parathyroid hormone (PTH), PTH-related peptide (PTH-RP), thyroid hormones and 1,25-dihydroxyvitamin D3. Growth factors involved in bone resorption are transforming growth factor-βeta (TGF-β), and other cytokines such as IL-1 and TNF that increase IL-6 production [132]. Interleukin IL-6 has been shown to stimulate osteoclast formation and bone resorption in fetal mouse bone in vitro [133, 134] and along with IL-1 also stimulates bone resorption in vivo [135]. There is evidence to suggest that IL-6 influences not only immature but mature osteoclasts as well in studies of human osteoclastoma cells that have receptors for IL-6, which stimulates the resorptive activity of these cells [136]. Furthermore, IL-6 has been shown to play a role in the abnormal bone resorption observed in patients with multiple myeloma [137], Paget's disease [138], rheumatoid arthritis [139], and Gorham-Stout disease [140]. Effects of increased osteoclast-induced bone resorption are not solely reserved to IL-6, but to all IL-6 family cytokines,-such as leukemia-inhibitory factor (LIF). It appears that LIF acts on osteoclasts indirectly via stimulating IL-6 release by osteoblasts, resulting in an increase in bone resorption [141].

Furthermore, TNF-α has also been shown to influence bone resorption involved in mainly postmenopausal osteoporosis. One study revealed that augmented production of TNF-α by T-cells following ovariectomy led to increased macrophage stimulating factor (M-CSF) and RANK ligand-induced osteoclastogenesis [142]. Further data on IL-6 and TNF-α knockout mice seem intriguing. It appears that lack of either TNF-α or IL-6 is protective against the development of osteoporosis due to sex-steroid deficiency. It is plausible to consider that TNF-α stimulates IL-6 production, which in turn mediates osteoclast bone resorption. TNF-α stimulates production of IL-6 by several cell types, including bone marrow stromal cells and osteoblasts [143], whereas IL-6 does not seem to affect TNF-α secretion [144]. Therefore, TNF-α may exert some of its actions through IL-6, which may explain why both TNF-α and IL-6 knockout mice show decreased osteoclast-induced bone resorption [144].

Activation of RANKL, produced by either cells of immune system, stromal cells or tumor cells on response to interleukins or parathyroid hormone related protein (PTHrP), represents an important step in understanding the pathohysiology of osteoporosis[130, 145]. RANKL activates osteoclast precursors and subsequent osteolysis, leading to the release of several bone-derived growth factors, including insulin-like growth factor-1 (IGF1), and transforming growth factor-beta (TGF-β) [146]. An abnormal activation of RANKL is induced by several circulating cytokines, such as IL-1α, IL-6, TNF-α and TGF-β (figure 4).

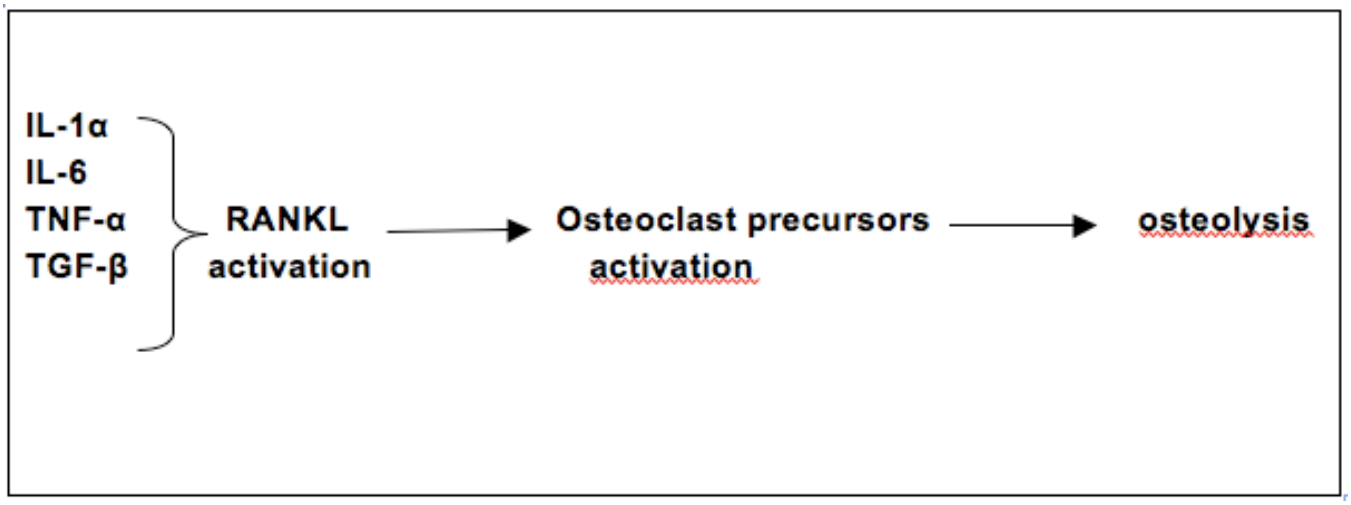

Figure 4. Direct cytokine effects on the bone metabolism leading to osteolysis

In particular, in postmenopausal osteoporosis, there is a dramatic increase in the number of osteoclasts with the decline of circulating estrogens. IL-6 is again thought to play a significant role in the pathogenesis of this process. Estrogens have been shown to inhibit the production of IL-6 from cultured bone marrow stromal and osteoblastic cell lines [147]. The inhibitory effect of estrogen on IL-6 production is mediated through inhibition of IL-6 gene transcription via an estrogen-receptor-mediated effect on the transcriptional activity of the proximal 225-βp sequence of the promoter [148, 149].

Subsequent studies that were conducted to determine if estrogen regulate the production of IL-6, revealed that in murine stromal and osteoblastic cells IL-1 and TNF induced IL-6 production is inhibited by the addition of estrogen and stimulated by estrogen withdrawal [147]. In vivo studies also revealed that the production of IL-6 is increased in cultures of bone marrow cells from OVX mice [148]. This effect is mediated, at least in the mouse, by an indirect effect of estrogen on the transcription activity of the proximal 225-bp sequence of the IL-6 promoter [149, 150]. Interestingly, although studies with human cell lines demonstrated an inhibitory effect of estrogen on human IL-6 promoter [151], three independent groups have failed to demonstrate an inhibitory effect of estrogen on IL-6 production from human bone cells and stromal cells expressing functional estrogen receptors [152-154]. These findings raise the possibility that the production of human IL-6 protein is not increased in conditions of estrogen deficiency. This is further supported by a report that in humans, surgical menopause is not followed by an increase in IL-6, although it causes an increase in soluble IL-6 receptor [155, 156].

Estrogens have also been shown to decrease TNF-α gene expression by blocking Jun NH(2)-terminal kinase (JNK) activity [157]. By blocking JNK, there is decreased phosphorylation of c-Jun and JunD nuclear transcription factors that along with AP-1 help form the initiation complex at the TNF promoter site, resulting in the subsequent inhibition of TNF-α gene transcription. It appears that an intact TNF receptor-I (p55) is necessary for estrogen deficiency-induced osteoporosis as suggested by the maintenance of bone mineral density in p55 knockout mice besides ovariectomy [158]. Ovariectomy in rats also led to a significant increase in IL-1β mRNA and protein levels in the bone marrow and IL-6 and Cox-2 protein levels in tibias [159].

Besides having a direct role on osteoclastogenesis, TNF-α has been shown to inhibit osteoblast differentiation as well. The transcription factor runt-related transcription factor 2 (RUNX2) is a critical regulator of osteoblast differentiation as incubation of fetal calvarial precursor cells with TNF-α led to a 50-90% reduction in the expression of all isoforms of RUNX2 mRNA [160]. TNF-α may also influence other cytokines to mediate osteoclast-induced bone resorption. Interleukin IL-1 plays a role in estrogen deficiency-mediated osteoporosis by stimulating osteoclast activity through direct targeting of mature osteoclasts rather than by stimulating osteoclastogenesis as TNF-α does. A number of studies have shown that TNF-α neutralization blocks IL-1 production, whereas IL-1 neutralization does not block TNF-α. Thus it is likely that increased bone marrow levels of IL-1 observed in ovariectomized mice may be the result of increased TNF-α production. TNF-α, and IL-1 have also been shown to induce production of IL-7 [161]; IL-7 has been shown to influence osteoclastogenesis through T cells by RANK-ligand-dependent and independent mechanisms.

It appears that IL-6 and IL-8 also play a major role in thyrotoxicosis-induced osteoporosis. In addition to the established effects of IL-6 on bone resorption, IL-8 affects bone resorption along with IL-8 receptors being expressed by osteoclasts [162]. Interleukin IL-6 and IL-8, but not IL-1β, IL-11, or TNF-α are increased in patients with thyrotoxicosis due to GD or toxic multinodular goiter [163]. On the contrary, in differentiated thyroid carcinoma with suppressed TSH levels following the exogenous thyroxine administration the levels of IL-1β, TGF-β and TNF are not increased. Nevertheless, it has long been shown that IL-1β, TGF-β, and interferon gamma are anticancer factors able to suppress the proliferation of papillary thyroid carcinoma cells [164, 165]. Similarly, TNF-α has cytostatic affects, and acts as a growth inhibitor of papillary thyroid cancer cell lines [8]. TNF-α elevations due to low TSH signaling in human hyperthyroidism contribute to the bone loss that has traditionally been attributed solely to high thyroid hormone levels [166]. Hyperthyroid mice lacking TSHR had greater bone loss and resorption than hyperthyroid wild-type mice, thereby demonstrating that the absence of TSH signaling contributes to bone loss [167].

Siddiqi A et al. have shown that patients with thyroid carcinoma on TSH suppressive therapy had significantly raised circulating levels of IL-6 and IL-8 compared to controls [163]. In both groups, plasma levels of IL-6 and IL-8 correlated with serum T3 and free T4 concentrations but not with bone turnover markers, namely urinary deoxypyridinoline (Udpd) or bone-specific alkaline phosphatase (b-αLP). Both IL-6 and IL-8 have also been shown to be released by human bone marrow stromal cell cultures containing osteoblast progenitor cells in response to T3 [161]. Therefore, the increased plasma concentrations of IL-6 and IL-8 seen in thyrotoxicosis are most likely caused by T3 stimulation of bone osteoblasts despite the inability of bone markers to correlate with acute changes in thyroid hormone status.
Bone resorption in primary hyperparathyroidism also appears to be mediated by cytokinesl. Cytokines such as IL-6, IL-1β, and TNF-α had been examined with respect to their relationship to biochemical markers of bone turnover in patients with primary hyperparathyroidism, hypoparathyroidism, normal controls, and in patients who had undergone parathyroidectomy. Interleukin IL-6, IL-6 soluble receptor (IL6-sR), and TNF-α were all found to be elevated in patients with primary hyperparathyroidism. In particular, the effects of PTH on bone resorption appear to occur indirectly. PTH binds to high affinity receptors expressed by osteoblasts or osteoblast like cells in bone, and induces these cells to release factors including cytokines that directly modulate the number and/or activity of osteoclasts. Among the cytokines thought to participate in PTH-induced bone resorption, are IL-6 and IL-6sR. Circulating levels of IL-6 and IL-6sR have been shown to be significantly elevated in patients with primary

hyperparathyroidism and correlate with markers of bone resorption [168]. The case for the IL-6/IL-6sR cytokine system playing a role in mediating the catabolic effects of PTH on the skeleton has been further strengthened by the finding that neutralizing IL-6 in vivo attenuates PTH-induced bone resorption in mice [169]. The resorptive response to PTH was also reduced in IL-6 knockout mice [169]. The mechanisms by which IL-6/IL-6sR might participate in the resorptive actions of PTH are not entirely clear. It seems that PTH induces the production of both cytokines in vivo and that in vitro, PTH stimulates IL-6 production by bone cells and IL-6 and IL-6sR by liver cells [170, 171], whereas blocking IL-6 in vivo inhibits PTH-induced bone resorption [169]. In contrast, PTH stimulates the expression of members of the interleukin 6 cytokine superfamily. Although the similarity of gene targets regulated by these cytokines and PTH suggest a synergistic action, the dependence of PTH anabolic action on IL-6 cytokine signaling is unknown. Osteocytic glycoprotein130 is required to maintain PTH1R expression in the osteoblast lineage, and for the stimulation of osteoblast differentiation that occurs in response to PTH [172].

Together both cytokines can stimulate osteoclastogenesis in marrow cultures, and some recent in vitro evidence suggests that IL-6 may act independently of RANKL to induce osteoclastogenesis [173, 174]. Thus, it may be that IL-6 and IL-6sR together are amongst the most direct mediators of PTH-induced osteoclastogenesis. Other evidence suggests that IL-6 can induce RANKL production in bone, so the IL-6/IL-6sR system may lie upstream of RANKL in a cytokine cascade PTH3IL-6/IL-6sR3RANKL [175].

The cytokine that especially correlates with biochemical markers of bone resorption, such as serum deoxypyridinoline, type I collagen carboxyterminal telopeptide, urinary pyridinoline, and urinary deoxypyridinoline, is circulating IL-6. Multiple regression analysis further confirmed that IL-6, and not TNF-α was independently predictive of bone resorption in these patients [168]. Besides having a direct action on bone resorption, IL-6 may also have an indirect action on bone resorption in hyperparathyroidism by its influence on IL-11. Both IL-6 and IL-11 belong to a family of cytokines that shares the use of glycoprotein 130 (gp130) receptor for intracellular signaling [176, 177]. In vitro studies have further established that IL-11 plays a prominent role in bone homeostasis. Like IL-6, IL-11 is also produced by osteoblasts in response to osteotropic factors such as PTH and 1,25$(OH)_2$-vitamin D. In addition, IL-11 has been found to inhibit osteoclast apoptosis and stimulate osteoclast formation [178, 179]. Although PTH stimulates the production of both cytokines by human osteoblast-like cells, IL-6 has been found to be elevated in hyperparathyroidism, while IL-11 levels were significantly reduced. Also, after parathyroidectomy, circulating levels of IL-6 dropped while those of IL-11 increased. When PTH was infused into rodents, there was a significant decline in mean circulating levels of IL-11, whereas IL-6 levels increased. Furthermore, pretreatment of cells with neutralizing serum to IL-6 enhanced PTH-induced IL-11 production, compared with the effect of pretreatment with non-immune sera. These data indicate that IL-6 negatively regulates IL-11 production in vivo and in vitro. Analysis of steady-state mRNA levels in sarcoma osteogenic SaOS-2 cells indicated that this effect is post-transcriptional. Since both IL-6 and IL-11 stimulate osteoclast formation, down-regulation of IL-11 by IL-6 may help modulate the resorptive response to PTH [180]. Additionally, serum 25(OH)-vitamin D was inversely related to IL-6 and TNF-α after accounting for age, gender, season of recruitment, BMI and free body fat indicating the importance of vitamin D levels against systemic inflammation and bone remodeling [181].

Finally, more recent data are paying attention to the role of serum carcinoembryonic antigen (CEA) and monocytes producing cytokines as serum CEA could be serve as a possible biomarker of the risk of incident fracture in postmenopausal Asian women [182]. Monocytes are important to osteoporosis by serving as progenitors of osteoclasts and

produce cytokines for osteoclastogenesis. Liu et al showed that attenuated monocyte apoptosis is a new mechanism for osteoporosis suggested by a transcriptome-wide expression study of monocytes [183].

EFFECTS OF THE IMMUNE SYSTEM ON THE STRESS SYSTEM

The Hypothalamo-Pituitary-Adrenal (HPA) Axis

Acute stress increases the expression of cytokines and other inflammatory-related factors in the central nervous system (CNS), plasma, and endocrine glands. Activation of inflammatory signaling pathways within the HPA axis may play a key role in later stress sensitization. Data on this topic provided a series of experiments that characterize stress effects on members of the IL-1β super-family and other inflammatory-related genes in key structures comprising the HPA axis.[184].

The HPA-axis is activated in states of inflammation or infection. This activation is mediated by the inflammatory cytokines TNF-α, IL-1, and IL-6, which are secreted in tandem in response to various infectious and non-infectious stimuli. The inflammatory cytokines are produced by a variety of cells, including monocytes, macrophages, astrocytes, endothelial cells, and fibroblasts. During inflammatory states, these cytokines activate the HPA-axis through stimulation of the corticotropin-releasing hormone (CRH) neurons of the paraventricular nucleus (PVN) of the hypothalamus [22, 185]. Cytokines influence many neuroendocrine systems, the most prominent of which is the activation of the HPA-axis, resulting in the release of adrenocorticotropic hormone (ACTH) and glucocorticoids [186]. Once present in the bloodstream, these cytokines have also the ability to increase body temperature causing fever and other manifestations of the sickness syndrome [187].

Inflammation-related dysregulation of the HPA axis is central to the course of systemic inflammatory response syndrome or sepsis. The underlying mechanisms, however, are not well understood. Initial activation of adrenocortical hormone production during early sepsis depends on the stimulation of hypothalamus and pituitary mediated by cytokines [188]. The pro-inflammatory cytokine interleukin-1, especially its β form, is probably the most important molecule capable of modulating cerebral functions during systemic and localized inflammation. Systemic IL-β injection activates the neurons involved in the control of autonomic functions, and neutralizing antibodies or IL-1 receptor antagonists are capable of preventing numerous responses during inflammatory stimuli as shown by studies performed in IL-1β deficient mice [189]. Other cytokines implicated in neuroendocrine and febrile responses include TNF-α and IL-6. Like IL-1β, intravenous IL-6 stimulates the hypothalamic-pituitary unit leading to the secretion of cortisol by the adrenal glands, and subsequent termination of the inflammatory cascade [190]. Although all three inflammatory cytokines (IL-1, IL-6 and TNF-α) have the capacity to activate the HPA-axis, it appears that IL-6 is the critical component of this cascade. Studies in rats have demonstrated that immunoneutralization of IL-6 abolishes the effects (as potent activators) of the other two cytokines on the HPA-axis [191]. TNF-α and IL-1 stimulate the production of IL-6 and IL-6 in turn stimulates the HPA-axis. While acute stimulation with IL-6 stimulates the HPA-axis through activation of the hypothalamic CRH neurons, chronic exposure to IL-6 can stimulate directly the corticotroph cells of the pituitary and the adrenal cells Figure 5).

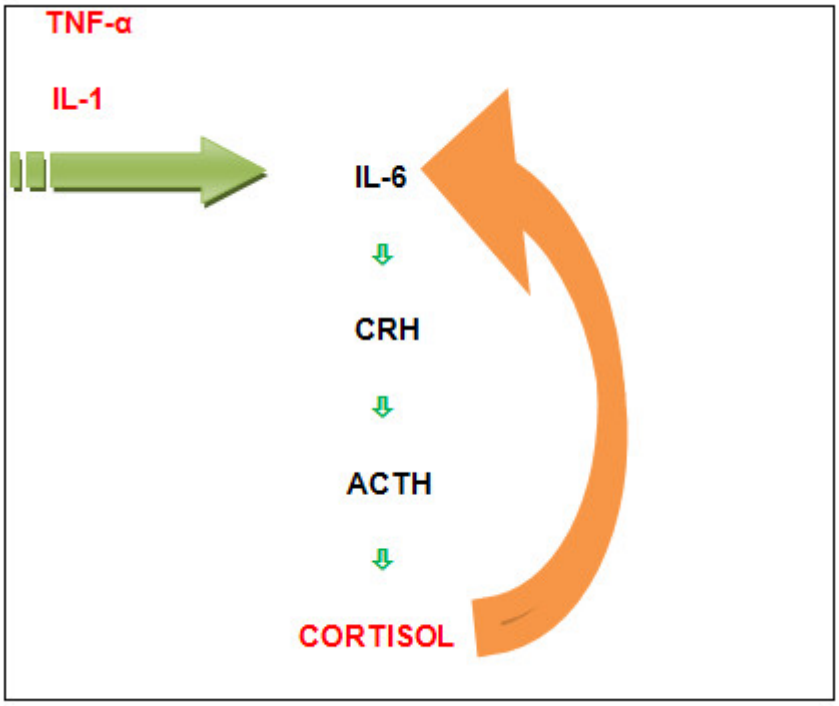

Figure 5. TNF-Î± and IL-1 stimulate the production of IL-6 and IL-6 in turn stimulates the HPA-axis

Glucocorticoids appear to inhibit IL-6 secretion at the transcriptional level through interaction of the ligand-activated glucocorticoid receptor with nuclear factor-Kappa B. This demonstrates that glucocorticoids and IL-6 participate in a feedback loop, in which IL-6 stimulates glucocorticoid release and glucocorticoids subsequently through negative feedback inhibit IL-6 release. This explains the inverse relationship with diurnal variation between circulating IL-6 and glucocorticoid levels [192]. Furthermore, acute hypocortisolism has been shown to result in a four to five fold elevation of circulating IL-6 and TNF-α levels. In a study involving patients with Cushing's disease studied before and after transsphenoidal adenomectomy, cytokines were measured during the hypercortisolemic, hypocortisolemic, and eucortisolemic (while patients were on glucocorticoid replacement) states [193]. When patients were hypocortisolemic, plasma IL-6 concentration increased, while they experienced symptoms of glucocorticoid deficiency, which are part of the "steroid withdrawal syndrome". This syndrome consists of pyrexia, headache, anorexia, nausea, fatigue, malaise, arthralgias, myalgias, and somnolence of variable degree. Interestingly, IL-6 levels did not increase in patients who did not become hypocortisolemic after surgery (and did not develop symptoms consistent with the withdrawal syndrome), indicating that hypocortisolism was necessary for the rise in IL-6. Glucocorticoid replacement was followed by a dramatic decrease of IL-6 levels, which was concomitant with relief of the observed symptoms [193].

Furthermore, increased cortisol turnover is a feature of obese individuals and is exaggerated in upper body (visceral) obesity [194]. Some studies indicate that IL-6 directly stimulates adrenal cortisol release in addition to stimulating hypothalamic CRH and pituitary ACTH release [195-197]. Adipose tissue IL-6 may, therefore, act as a feed-forward regulator of the hypothalamic-pituitary axis function. Cortisol suppression of adipose IL-6 production may serve as a

feedback inhibitor of this regulatory loop. Adrenal cortisol production could be influenced by IL-6 originating from peri-renal adipose tissue that surrounds the adrenal glands. Similar to IL-6, leukemia-inhibitory factor (LIF) can also stimulate the hypothalamic pituitary axis. Leukemia-inhibitory factor is a multifunctional cytokine of the IL-6 cytokine family, sharing the common gp130 receptor subunit together with IL-6, interleukin-11, oncostatin-M, ciliary neurotrophic factor and cardiotrophin-1. Both LIF and its receptor have been found to be expressed in the pituitary gland during development [198]. Furthermore, LIF binding sites (LIFR) have been found in one third of ACTH-positive cells and approximately 20% of growth hormone (GH)-positive cells of the pituitary. In several tissues, LIF, LIFR, and gp130 mRNA expression is stimulated by various inflammatory stimuli, whereas LIF gene expression is negatively regulated by glucocorticoids. LIF stimulates ACTH secretion in vitro and in vivo. Murine corticotroph AtT-20 cells exhibit a 2-4 fold increase in ACTH secretion during incubation with 1 nM LIF for 24 hours. Incubation of AtT-20 cells with CRH results in a 3 to 7 fold rise in ACTH secretion. Combined with LIF, CRH causes a further 2 to 3 fold increase of ACTH secretion in comparison to treatment with CRH alone.

The Autonomic Nervous System

Catecholamines, in particularly norepinephine, preferentially modulate the functions of memory CD8 T cells by inducing inflammatory cytokine production and reducing activation-induced memory CD8 T cell expansion [199]. Catecholamines also have been found to stimulate IL-6 secretion through a beta-adrenergic mechanism in rats [200]. Interleukin 6 (IL-6) has been shown to play a key role in the stress response to exercise in humans as well. In one study involving high-intensity treadmill exercise tests on 15 male volunteers. The study group were divided into three subgroups according to the drug administered (placebo, hydrocortisone and dexamethasone, respectively) given to the volunteers before starting their exercise. Plasma epinephrine and norepinephrine concentrations peaked at 15 minutes after exercise initiation, whereas plasma IL-6 concentrations peaked twice at 15 and at 45 minutes after the onset of the high-intensity treadmill exercise test. There was no difference in either the epinephrine or norepinephrine peaks among the three treatment groups (placebo, hydrocortisone and dexamethasone, respectively) but the net area under the curve for IL-6 was smaller after pretreatment with hydrocortisone or dexamethasone than after pretreatment with placebo. A positive correlation was observed between peak plasma epinephrine and norepinephrine levels and IL-6 plasma levels at 15 minutes [201]. This demonstrates that IL-6 secretion is likely stimulated during exercise by catecholamines, whereas exogenous glucocorticoids attenuate this effect without affecting the catecholamine levels. It has recently, been demonstrated that IL-1 stimulation increases intracellular calcium (iCa^{2+}) in the carotid body glomus cells, releases ATP, and increases the discharge rate of the glossopharyngeal nerve to the carotid sinus. It seems that IL-6 increases intracellular Ca^{2+} concentration and induces catecholamine secretion in rat carotid body glomus cells, a finding which eventually confirms a bidirectional relationship between IL-6 and catecholamines [202].

References

1. Arango Duque, G. and A. Descoteaux, *Macrophage cytokines: involvement in immunity and infectious diseases.* Front Immunol, 2014. **5**: p. 491.

2. Mayer, J., et al., *Inflammatory mediators in human acute pancreatitis: clinical and pathophysiological implications.* Gut, 2000. **47**(4): p. 546-52.

3. Challis, J.R., et al., *Inflammation and pregnancy.* Reprod Sci, 2009. **16**(2): p. 206-15.

4. Hofmann, S.R., et al., *Dynamic CpG-DNA methylation of Il10 and Il19 in CD4+ T lymphocytes and macrophages: effects on tissue-specific gene expression.* Klin Padiatr, 2012. **224**(2): p. 53-60.

5. Ouyang, W., et al., *Regulation and functions of the IL-10 family of cytokines in inflammation and disease.* Annu Rev Immunol, 2011. **29**: p. 71-109.

6. Besnard, A.G., et al., *IL-33-Mediated Protection against Experimental Cerebral Malaria Is Linked to Induction of Type 2 Innate Lymphoid Cells, M2 Macrophages and Regulatory T Cells.* PLoS Pathog, 2015. **11**(2): p. e1004607.

7. Ajjan, R.A., P.F. Watson, and A.P. Weetman, *Cytokines and thyroid function.* Adv Neuroimmunol, 1996. **6**(4): p. 359-86.

8. Lin, J.D., et al., *The roles of cytokines and retinoic acid in the regulation of human thyroid cancer cell growth.* Cytokine, 1998. **10**(7): p. 536-9.

9. Papanicolaou, D.A., *Euthyroid Sick Syndrome and the role of cytokines.* Rev Endocr Metab Disord, 2000. **1**(1-2): p. 43-8.

10. Dohan, O., A. De la Vieja, and N. Carrasco, *Molecular study of the sodium-iodide symporter (NIS): a new field in thyroidology.* Trends Endocrinol Metab, 2000. **11**(3): p. 99-105.

11. Chung, J.K., *Sodium iodide symporter: its role in nuclear medicine.* J Nucl Med, 2002. **43**(9): p. 1188-200.

12. Simons, P.J., F.G. Delemarre, and H.A. Drexhage, *Antigen-presenting dendritic cells as regulators of the growth of thyrocytes: a role of interleukin-1beta and interleukin-6.* Endocrinology, 1998. **139**(7): p. 3148-56.

13. Asakawa, H., et al., *Interferon-gamma reduces the thyroid peroxidase content of cultured human thyrocytes and inhibits its increase induced by thyrotropin.* J Clin Endocrinol Metab, 1992. **74**(6): p. 1331-5.

14. Ashizawa, K., et al., *Interferon-gamma inhibits thyrotropin-induced thyroidal peroxidase gene expression in cultured human thyrocytes.* J Clin Endocrinol Metab, 1989. **69**(2): p. 475-7.

15. Poth, M., Y.C. Tseng, and L. Wartofsky, *Inhibition of TSH activation of human cultured thyroid cells by tumor necrosis factor: an explanation for decreased thyroid function in systemic illness?* Thyroid, 1991. **1**(3): p. 235-40.

16. Yamashita, S., et al., *Interleukin-1 inhibits thyrotrophin-induced human thyroglobulin gene expression.* J Endocrinol, 1989. **122**(1): p. 177-83.

17. Yamazaki, K., et al., *Interleukin-6 (IL-6) inhibits thyroid function in the presence of soluble IL-6 receptor in cultured human thyroid follicles.* Endocrinology, 1996. **137**(11): p. 4857-63.

18. Hashimoto, H., et al., *Effects of tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6 on type I iodothyronine 5'-deiodination in rat thyroid cell line, FRTL-5.* J Interferon Cytokine Res, 1995. **15**(4): p. 367-75.

19. Davies, P.H., M.C. Sheppard, and J.A. Franklyn, *Inflammatory cytokines and type I 5'-deiodinase expression in phi1 rat liver cells.* Mol Cell Endocrinol, 1997. **129**(2): p. 191-8.

20. Boelen, A., et al., *Induced illness in interleukin-6 (IL-6) knock-out mice: a causal role of IL-6 in the development of the low 3,5,3'-triiodothyronine syndrome.* Endocrinology, 1996. **137**(12): p. 5250-4.

21. Wassen, F.W., et al., *Effects of interleukin-1 beta on thyrotropin secretion and thyroid hormone uptake in cultured rat anterior pituitary cells.* Endocrinology, 1996. **137**(5): p. 1591-8.

22. Lyson, K. and S.M. McCann, *The effect of interleukin-6 on pituitary hormone release in vivo and in vitro.* Neuroendocrinology, 1991. **54**(3): p. 262-6.

23. Ozawa, M., et al., *Effects of tumor necrosis factor-alpha/cachectin on thyroid hormone metabolism in mice.* Endocrinology, 1988. **123**(3): p. 1461-7.

24. Pang, X.P., et al., *The mechanism of action of tumour necrosis factor-alpha and interleukin 1 on FRTL-5 rat thyroid cells.* Acta Endocrinol (Copenh), 1990. **123**(2): p. 203-10.

25. van Haasteren, G.A., et al., *Different effects of continuous infusion of interleukin-1 and interleukin-6 on the hypothalamic-hypophysial-thyroid axis.* Endocrinology, 1994. **135**(4): p. 1336-45.

26. van der Poll, T., et al., *Tumor necrosis factor: a putative mediator of the sick euthyroid syndrome in man.* J Clin Endocrinol Metab, 1990. **71**(6): p. 1567-72.

27. Chopra, I.J., S. Sakane, and G.N. Teco, *A study of the serum concentration of tumor necrosis factor-alpha in thyroidal and nonthyroidal illnesses.* J Clin Endocrinol Metab, 1991. **72**(5): p. 1113-6.

28. Girvent, M., et al., *Euthyroid sick syndrome, associated endocrine abnormalities, and outcome in elderly patients undergoing emergency operation.* Surgery, 1998. **123**(5): p. 560-7.

29. Davis, P.J., *Cytokines and growth factors and thyroid hormone.* Curr Opin Endocrinol Diabetes Obes, 2008. **15**(5): p. 428.

30. Baur, A., et al., *Effects of proinflammatory cytokines on anterior pituitary 5'-deiodinase type I and type II.* J Endocrinol, 2000. **167**(3): p. 505-15.

31. Hase, H., et al., *TNFalpha mediates the skeletal effects of thyroid-stimulating hormone.* Proc Natl Acad Sci U S A, 2006. **103**(34): p. 12849-54.

32. Calikoglu, M., et al., *Leptin and TNF-alpha levels in patients with chronic obstructive pulmonary disease and their relationship to nutritional parameters.* Respiration, 2004. **71**(1): p. 45-50.

33. Park, M.C., et al., *Serum leptin levels correlate with interleukin-6 levels and disease activity in patients with ankylosing spondylitis.* Scand J Rheumatol, 2007. **36**(2): p. 101-6.

34. Lechan, R.M. and C. Fekete, *Feedback regulation of thyrotropin-releasing hormone (TRH): mechanisms for the non-thyroidal illness syndrome.* J Endocrinol Invest, 2004. **27**(6 Suppl): p. 105-19.

35. Lechan, R.M. and C. Fekete, *Role of melanocortin signaling in the regulation of the hypothalamic-pituitary-thyroid (HPT) axis.* Peptides, 2006. **27**(2): p. 310-25.

36. Harris, M., et al., *Transcriptional regulation of the thyrotropin-releasing hormone gene by leptin and melanocortin signaling.* J Clin Invest, 2001. **107**(1): p. 111-20.

37. Liu, H., W. Yan, and G. Xu, *Thyroid hormone replacement for nephrotic syndrome patients with euthyroid sick syndrome: a meta-analysis.* Ren Fail, 2014. **36**(9): p. 1360-5.

38. Wu, G.H., et al., *Low T3 syndrome predicts severe neurological deficits of cerebral infarction inpatients with large artery artherosclerosis in internal carotid artery system.* Neuro Endocrinol Lett, 2014. **35**(2): p. 149-53.

39. Harjai, K.J. and A.A. Licata, *Effects of amiodarone on thyroid function.* Ann Intern Med, 1997. **126**(1): p. 63-73.

40. Loh, K.C., *Amiodarone-induced thyroid disorders: a clinical review.* Postgrad Med J, 2000. **76**(893): p. 133-40.

41. Newman, C.M., et al., *Amiodarone and the thyroid: a practical guide to the management of thyroid dysfunction induced by amiodarone therapy.* Heart, 1998. **79**(2): p. 121-7.

42. Martino, E., et al., *The effects of amiodarone on the thyroid.* Endocr Rev, 2001. **22**(2): p. 240-54.

43. Bartalena, L., et al., *Serum interleukin-6 in amiodarone-induced thyrotoxicosis.* J Clin Endocrinol Metab, 1994. **78**(2): p. 423-7.

44. Bartalena, L., et al., *Interleukin-6: a marker of thyroid-destructive processes?* J Clin Endocrinol Metab, 1994. **79**(5): p. 1424-7.

45. Bartalena, L., et al., *Treatment of amiodarone-induced thyrotoxicosis, a difficult challenge: results of a prospective study.* J Clin Endocrinol Metab, 1996. **81**(8): p. 2930-3.

46. Mosher, M.C., *Amiodarone-induced hypothyroidism and other adverse effects.* Dimens Crit Care Nurs, 2011. **30**(2): p. 87-93.

47. Piga, M., et al., *Amiodarone-induced thyrotoxicosis. A review.* Minerva Endocrinol, 2008. **33**(3): p. 213-28.

48. Olivieri, A., et al., *Postpartum thyroiditis is associated with fluctuations in transforming growth factor-beta1 serum levels.* J Clin Endocrinol Metab, 2003. **88**(3): p. 1280-4.

49. Weetman, A.P., G.L. Bennett, and W.L. Wong, *Thyroid follicular cells produce interleukin-8.* J Clin Endocrinol Metab, 1992. **75**(1): p. 328-30.

50. Lazarus, J.H., *The continuing saga of postpartum thyroiditis.* J Clin Endocrinol Metab, 2011. **96**(3): p. 614-6.

51. Premawardhana, L.D., et al., *Postpartum thyroiditis and long-term thyroid status: prognostic influence of thyroid peroxidase antibodies and ultrasound echogenicity.* J Clin Endocrinol Metab, 2000. **85**(1): p. 71-5.

52. Muller, A.F., H.A. Drexhage, and A. Berghout, *Postpartum thyroiditis and autoimmune thyroiditis in women of childbearing age: recent insights and consequences for antenatal and postnatal care.* Endocr Rev, 2001. **22**(5): p. 605-30.

53. Parkes, A.B., et al., *The role of complement in the pathogenesis of postpartum thyroiditis.* J Clin Endocrinol Metab, 1994. **79**(2): p. 395-400.

54. Cross, R.J., J.L. Campbell, and T.L. Roszman, *Potentiation of antibody responsiveness after the transplantation of a syngeneic pituitary gland.* J Neuroimmunol, 1989. **25**(1): p. 29-35.

55. Dardenne, M., et al., *Neuroendocrine control of thymic hormonal production. I. Prolactin stimulates in vivo and in vitro the production of thymulin by human and murine thymic epithelial cells.* Endocrinology, 1989. **125**(1): p. 3-12.

56. Piccinni, M.P., et al., *Progesterone favors the development of human T helper cells producing Th2-type cytokines and promotes both IL-4 production and membrane CD30 expression in established Th1 cell clones.* J Immunol, 1995. **155**(1): p. 128-33.

57. Zakar, T. and F. Hertelendy, *Progesterone withdrawal: key to parturition.* Am J Obstet Gynecol, 2007. **196**(4): p. 289-96.

58. Szekeres-Bartho, J., et al., *Role of progesterone and progestin therapy in threatened abortion and preterm labour.* Front Biosci, 2008. **13**: p. 1981-90.

59. Laskarin, G., et al., *Progesterone directly and indirectly affects perforin expression in cytolytic cells.* Am J Reprod Immunol, 1999. **42**(5): p. 312-20.

60. Szekeres-Bartho, J., et al., *The mechanism of the inhibitory effect of progesterone on lymphocyte cytotoxicity: I. Progesterone-treated lymphocytes release a substance inhibiting cytotoxicity and prostaglandin synthesis.* Am J Reprod Immunol Microbiol, 1985. **9**(1): p. 15-8.

61. Szekeres-Bartho, J., et al., *Immunoregulatory effects of a suppressor factor from healthy pregnant women's lymphocytes after progesterone induction.* Cell Immunol, 1989. **122**(2): p. 281-94.

62. Szekeres-Bartho, J. and T.G. Wegmann, *A progesterone-dependent immunomodulatory protein alters the Th1/Th2 balance.* J Reprod Immunol, 1996. **31**(1-2): p. 81-95.

63. Szekeres-Bartho, J., et al., *Progesterone and non-specific immunologic mechanisms in pregnancy.* Am J Reprod Immunol, 1997. **38**(3): p. 176-82.

64. Elovitz, M.A. and C. Mrinalini, *Can medroxyprogesterone acetate alter Toll-like receptor expression in a mouse model of intrauterine inflammation?* Am J Obstet Gynecol, 2005. **193**(3 Pt 2): p. 1149-55.

65. Oner, C., et al., *Progestin-inflammatory cytokine interactions affect matrix metalloproteinase-1 and -3 expression in term decidual cells: implications for treatment of chorioamnionitis-induced preterm delivery.* J Clin Endocrinol Metab, 2008. **93**(1): p. 252-9.

66. Agelaki, S., et al., *Corticotropin-releasing hormone augments proinflammatory cytokine production from macrophages in vitro and in lipopolysaccharide-induced endotoxin shock in mice.* Infect Immun, 2002. **70**(11): p. 6068-74.

67. Fisfalen, M.E., et al., *Thyrotropin-receptor and thyroid peroxidase-specific T cell clones and their cytokine profile in autoimmune thyroid disease.* J Clin Endocrinol Metab, 1997. **82**(11): p. 3655-63.

68. Meeusen, E.N., R.R. Premier, and M.R. Brandon, *Tissue-specific migration of lymphocytes: a key role for Th1 and Th2 cells?* Immunol Today, 1996. **17**(9): p. 421-4.

69. Zaletel, K. and S. Gaberscek, *Hashimoto's Thyroiditis: From Genes to the Disease.* Curr Genomics, 2011. **12**(8): p. 576-88.

70. Chang, J.W., et al., *Production of multiple cytokines and induction of cachexia in athymic nude mice by a new anaplastic thyroid carcinoma cell line.* J Endocrinol, 2003. **179**(3): p. 387-94.

71. Linkov, F., et al., *Multiplex analysis of cytokines as biomarkers that differentiate benign and malignant thyroid diseases.* Proteomics Clin Appl, 2008. **2**(12): p. 1575-1585.

72. Antonelli, A., et al., *Autoimmune thyroid disorders.* Autoimmun Rev, 2015. **14**(2): p. 174-80.

73. Antunes, T.T., et al., *Interleukin-6 release from human abdominal adipose cells is regulated by thyroid-stimulating hormone: effect of adipocyte differentiation and anatomic depot.* Am J Physiol Endocrinol Metab, 2006. **290**(6): p. E1140-4.

74. Smith, T.J., *TSH-receptor-expressing fibrocytes and thyroid-associated ophthalmopathy.* Nat Rev Endocrinol, 2015. **11**(3): p. 171-181.

75. Hanifi-Moghaddam, P., et al., *Altered chemokine levels in individuals at risk of Type 1 diabetes mellitus.* Diabet Med, 2006. **23**(2): p. 156-63.

76. Nicoletti, F., et al., *Serum levels of the interferon-gamma-inducing cytokine interleukin-18 are increased in individuals at high risk of developing type I diabetes.* Diabetologia, 2001. **44**(3): p. 309-11.

77. Nicoletti, F., et al., *Serum concentrations of the interferon-gamma-inducible chemokine IP-10/CXCL10 are augmented in both newly diagnosed Type I diabetes mellitus patients and subjects at risk of developing the disease.* Diabetologia, 2002. **45**(8): p. 1107-10.

78. Toso, C., et al., *The role of macrophage migration inhibitory factor in mouse islet transplantation.* Transplantation, 2008. **86**(10): p. 1361-9.

79. Chase, H.P., et al., *Elevated C-reactive protein levels in the development of type 1 diabetes.* Diabetes, 2004. **53**(10): p. 2569-73.

80. Atkinson, M.A., et al., *Cellular immunity to a determinant common to glutamate decarboxylase and coxsackie virus in insulin-dependent diabetes.* J Clin Invest, 1994. **94**(5): p. 2125-9.

81. Tough, D.F., P. Borrow, and J. Sprent, *Induction of bystander T cell proliferation by viruses and type I interferon in vivo.* Science, 1996. **272**(5270): p. 1947-50.

82. Katz, J.D., C. Benoist, and D. Mathis, *T helper cell subsets in insulin-dependent diabetes.* Science, 1995. **268**(5214): p. 1185-8.

83. Wilson, S.B., et al., *Extreme Th1 bias of invariant Valpha24JalphaQ T cells in type 1 diabetes.* Nature, 1998. **391**(6663): p. 177-81.

84. Zhang, J., et al., *IFN-gamma induced by IL-12 administration prevents diabetes by inhibiting pathogenic IL-17 production in NOD mice.* J Autoimmun, 2012. **38**(1): p. 20-8.

85. Feugeas, J.P., et al., *Influence of metabolic and genetic factors on tumour necrosis factor-alpha and lymphotoxin-alpha production in insulin-dependent diabetes mellitus.* Diabetes Metab, 1997. **23**(4): p. 295-301.

86. Lechleitner, M., et al., *Relationship of tumor necrosis factor-alpha plasma levels to metabolic control in type 1 diabetes.* Diabetes Care, 1999. **22**(10): p. 1749.

87. Arif, S., et al., *Peripheral and islet interleukin-17 pathway activation characterizes human autoimmune diabetes and promotes cytokine-mediated beta-cell death.* Diabetes, 2011. **60**(8): p. 2112-9.

88. Farhan, J., et al., *Interleukin-6: a possible inflammatory link between vitiligo and type 1 diabetes.* Br J Biomed Sci, 2014. **71**(4): p. 151-7.

89. Ururahy, M.A., et al., *Association of polymorphisms in IL6 gene promoter region with type 1 diabetes and increased albumin-to-creatinine ratio.* Diabetes Metab Res Rev, 2014.

90. Filgueiras, L.R., et al., *Leukotriene B4-mediated sterile inflammation promotes susceptibility to sepsis in a mouse model of type 1 diabetes.* Sci Signal, 2015. **8**(361): p. ra10.

91. Suarez-Pinzon, W., et al., *Beta-cell destruction in NOD mice correlates with Fas (CD95) expression on beta-cells and proinflammatory cytokine expression in islets.* Diabetes, 1999. **48**(1): p. 21-8.

92. Donath, M.Y., et al., *Cytokines and beta-cell biology: from concept to clinical translation.* Endocr Rev, 2008. **29**(3): p. 334-50.

93. Varma, V., et al., *Muscle inflammatory response and insulin resistance: synergistic interaction between macrophages and fatty acids leads to impaired insulin action.* Am J Physiol Endocrinol Metab, 2009. **296**(6): p. E1300-10.

94. Ehses, J.A., et al., *Macrophages, cytokines and beta-cell death in Type 2 diabetes.* Biochem Soc Trans, 2008. **36**(Pt 3): p. 340-2.

95. Shoelson, S.E., J. Lee, and A.B. Goldfine, *Inflammation and insulin resistance.* J Clin Invest, 2006. **116**(7): p. 1793-801.

96. Duncan, B.B., et al., *Factor VIII and other hemostasis variables are related to incident diabetes in adults. The Atherosclerosis Risk in Communities (ARIC) Study.* Diabetes Care, 1999. **22**(5): p. 767-72.

97. Schmidt, M.I., et al., *Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): a cohort study.* Lancet, 1999. **353**(9165): p. 1649-52.

98. Festa, A., et al., *Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study.* Diabetes, 2002. **51**(4): p. 1131-7.

99. Eliasson, M.C., et al., *High levels of tissue plasminogen activator (tPA) antigen precede the development of type 2 diabetes in a longitudinal population study. The Northern Sweden MONICA study.* Cardiovasc Diabetol, 2003. **2**: p. 19.

100. Meigs, J.B., et al., *Hemostatic markers of endothelial dysfunction and risk of incident type 2 diabetes: the Framingham Offspring Study.* Diabetes, 2006. **55**(2): p. 530-7.

101. Lee, C.C., et al., *Association of C-reactive protein with type 2 diabetes: prospective analysis and meta-analysis.* Diabetologia, 2009. **52**(6): p. 1040-7.

102. Herder, C., et al., *Chemokines as risk factors for type 2 diabetes: results from the MONICA/KORA Augsburg study, 1984-2002.* Diabetologia, 2006. **49**(5): p. 921-9.

103. Hayashi, M., et al., *Angiotensin II receptor blocker ameliorates stress-induced adipose tissue inflammation and insulin resistance.* PLoS One, 2014. **9**(12): p. e116163.

104. Vgontzas, A.N., et al., *Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia.* J Clin Endocrinol Metab, 2000. **85**(3): p. 1151-8.

105. Vgontzas, A.N., et al., *Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity.* J Clin Endocrinol Metab, 1997. **82**(5): p. 1313-6.

106. Kern, P.A., et al., *Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance.* Am J Physiol Endocrinol Metab, 2001. **280**(5): p. E745-51.

107. Hotamisligil, G.S., et al., *Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance.* J Clin Invest, 1995. **95**(5): p. 2409-15.

108. Kirwan, J.P., et al., *TNF-alpha is a predictor of insulin resistance in human pregnancy.* Diabetes, 2002. **51**(7): p. 2207-13.

109. Pellegrinelli, V., et al., *Human adipocytes induce inflammation and atrophy in muscle cells during obesity.* Diabetes, 2015.

110. Hofmann, C., et al., *Altered gene expression for tumor necrosis factor-alpha and its receptors during drug and dietary modulation of insulin resistance.* Endocrinology, 1994. **134**(1): p. 264-70.

111. Hotamisligil, G.S., N.S. Shargill, and B.M. Spiegelman, *Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance.* Science, 1993. **259**(5091): p. 87-91.

112. Vilcek, J. and T.H. Lee, *Tumor necrosis factor. New insights into the molecular mechanisms of its multiple actions.* J Biol Chem, 1991. **266**(12): p. 7313-6.

113. Hotamisligil, G.S., et al., *IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance.* Science, 1996. **271**(5249): p. 665-8.

114. Cornelius, P., et al., *Monokine regulation of glucose transporter mRNA in L6 myotubes.* Biochem Biophys Res Commun, 1989. **165**(1): p. 429-36.

115. Stephens, J.M. and P.H. Pekala, *Transcriptional repression of the GLUT4 and C/EBP genes in 3T3-L1 adipocytes by tumor necrosis factor-alpha.* J Biol Chem, 1991. **266**(32): p. 21839-45.

116. Feingold, K.R. and C. Grunfeld, *Role of cytokines in inducing hyperlipidemia.* Diabetes, 1992. **41 Suppl 2**: p. 97-101.

117. Grunfeld, C. and K.R. Feingold, *The metabolic effects of tumor necrosis factor and other cytokines.* Biotherapy, 1991. **3**(2): p. 143-58.

118. Spiegelman, B.M. and G.S. Hotamisligil, *Through thick and thin: wasting, obesity, and TNF alpha.* Cell, 1993. **73**(4): p. 625-7.

119. Margoni, A., et al., *Serum leptin, adiponectin and tumor necrosis factor-alpha in hyperlipidemic rats with/without concomitant diabetes mellitus.* Mol Med, 2011. **17**(1-2): p. 36-40.

120. Fernandez-Real, J.M., et al., *Interleukin-6 gene polymorphism and lipid abnormalities in healthy subjects.* J Clin Endocrinol Metab, 2000. **85**(3): p. 1334-9.

121. Greenberg, A.S., et al., *Interleukin 6 reduces lipoprotein lipase activity in adipose tissue of mice in vivo and in 3T3-L1 adipocytes: a possible role for interleukin 6 in cancer cachexia.* Cancer Res, 1992. **52**(15): p. 4113-6.

122. Meigs, J.B., et al., *Association of oxidative stress, insulin resistance, and diabetes risk phenotypes: the Framingham Offspring Study.* Diabetes Care, 2007. **30**(10): p. 2529-35.

123. Rosen, P., et al., *The role of oxidative stress in the onset and progression of diabetes and its complications: a summary of a Congress Series sponsored by UNESCO-MCBN, the American Diabetes Association and the German Diabetes Society.* Diabetes Metab Res Rev, 2001. **17**(3): p. 189-212.

124. Hasnain, S.Z., et al., *Glycemic control in diabetes is restored by therapeutic manipulation of cytokines that regulate beta cell stress.* Nat Med, 2014. **20**(12): p. 1417-26.

125. Manolagas, S.C. and R.L. Jilka, *Bone marrow, cytokines, and bone remodeling. Emerging insights into the pathophysiology of osteoporosis.* N Engl J Med, 1995. **332**(5): p. 305-11.

126. Girasole, G., et al., *Interleukin-11: a new cytokine critical for osteoclast development.* J Clin Invest, 1994. **93**(4): p. 1516-24.

127. Mundy, G.R., *Cytokines and local factors which affect osteoclast function.* Int J Cell Cloning, 1992. **10**(4): p. 215-22.

128. Horowitz, M.C., et al., *Parathyroid hormone and lipopolysaccharide induce murine osteoblast-like cells to secrete a cytokine indistinguishable from granulocyte-macrophage colony-stimulating factor.* J Clin Invest, 1989. **83**(1): p. 149-57.

129. Noh, H.J., et al., *CHOP down-regulates cFLIP(L) expression by promoting ubiquitin/proteasome-mediated cFLIP(L) degradation.* J Cell Biochem, 2012. **113**(12): p. 3692-700.

130. Blair, H.C. and M. Zaidi, *Osteoclastic differentiation and function regulated by old and new pathways.* Rev Endocr Metab Disord, 2006. **7**(1-2): p. 23-32.

131. Datta, H.K., et al., *The cell biology of bone metabolism.* J Clin Pathol, 2008. **61**(5): p. 577-87.

132. Manolagas, S.C., et al., *Estrogen, cytokines, and the control of osteoclast formation and bone resorption in vitro and in vivo.* Osteoporos Int, 1993. **3 Suppl 1**: p. 114-6.

133. Ishimi, Y., et al., *IL-6 is produced by osteoblasts and induces bone resorption.* J Immunol, 1990. **145**(10): p. 3297-303.

134. Lowik, C.W., et al., *Parathyroid hormone (PTH) and PTH-like protein (PLP) stimulate interleukin-6 production by osteogenic cells: a possible role of interleukin-6 in osteoclastogenesis.* Biochem Biophys Res Commun, 1989. **162**(3): p. 1546-52.

135. Black, K., I.R. Garrett, and G.R. Mundy, *Chinese hamster ovarian cells transfected with the murine interleukin-6 gene cause hypercalcemia as well as cachexia, leukocytosis and thrombocytosis in tumor-bearing nude mice.* Endocrinology, 1991. **128**(5): p. 2657-9.

136. Ohsaki, Y., et al., *Evidence for an autocrine/paracrine role for interleukin-6 in bone resorption by giant cells from giant cell tumors of bone.* Endocrinology, 1992. **131**(5): p. 2229-34.

137. Klein, B., et al., *Murine anti-interleukin-6 monoclonal antibody therapy for a patient with plasma cell leukemia.* Blood, 1991. **78**(5): p. 1198-204.

138. Roodman, G.D., et al., *Interleukin 6. A potential autocrine/paracrine factor in Paget's disease of bone.* J Clin Invest, 1992. **89**(1): p. 46-52.

139. Kotake, S., et al., *Interleukin-6 and soluble interleukin-6 receptors in the synovial fluids from rheumatoid arthritis patients are responsible for osteoclast-like cell formation.* J Bone Miner Res, 1996. **11**(1): p. 88-95.

140. Devlin, R.D., H.G. Bone, 3rd, and G.D. Roodman, *Interleukin-6: a potential mediator of the massive osteolysis in patients with Gorham-Stout disease.* J Clin Endocrinol Metab, 1996. **81**(5): p. 1893-7.

141. Martin, T.J., et al., *Leukaemia inhibitory factor and bone cell function.* Ciba Found Symp, 1992. **167**: p. 141-50; discussion 150-5.

142. Cenci, S., et al., *Estrogen deficiency induces bone loss by enhancing T-cell production of TNF-alpha.* J Clin Invest, 2000. **106**(10): p. 1229-37.

143. van Deventer, S.J., et al., *Experimental endotoxemia in humans: analysis of cytokine release and coagulation, fibrinolytic, and complement pathways.* Blood, 1990. **76**(12): p. 2520-6.

144. Schindler, R., et al., *Correlations and interactions in the production of interleukin-6 (IL-6), IL-1, and tumor necrosis factor (TNF) in human blood mononuclear cells: IL-6 suppresses IL-1 and TNF.* Blood, 1990. **75**(1): p. 40-7.

145. Jules, J., et al., *Molecular basis of requirement of receptor activator of nuclear factor kappaB signaling for interleukin 1-mediated osteoclastogenesis.* J Biol Chem, 2012. **287**(19): p. 15728-38.

146. Van den Berghe, G., et al., *Bone turnover in prolonged critical illness: effect of vitamin D.* J Clin Endocrinol Metab, 2003. **88**(10): p. 4623-32.

147. Girasole, G., et al., *17 beta-estradiol inhibits interleukin-6 production by bone marrow-derived stromal cells and osteoblasts in vitro: a potential mechanism for the antiosteoporotic effect of estrogens.* J Clin Invest, 1992. **89**(3): p. 883-91.

148. Jilka, R.L., et al., *Increased osteoclast development after estrogen loss: mediation by interleukin-6.* Science, 1992. **257**(5066): p. 88-91.

149. Pottratz, S.T., et al., *17 beta-Estradiol inhibits expression of human interleukin-6 promoter-reporter constructs by a receptor-dependent mechanism.* J Clin Invest, 1994. **93**(3): p. 944-50.

150. Ray, A., K.E. Prefontaine, and P. Ray, *Down-modulation of interleukin-6 gene expression by 17 beta-estradiol in the absence of high affinity DNA binding by the estrogen receptor.* J Biol Chem, 1994. **269**(17): p. 12940-6.

151. Stein, B. and M.X. Yang, *Repression of the interleukin-6 promoter by estrogen receptor is mediated by NF-kappa B and C/EBP beta.* Mol Cell Biol, 1995. **15**(9): p. 4971-9.

152. Chaudhary, L.R., T.C. Spelsberg, and B.L. Riggs, *Production of various cytokines by normal human osteoblast-like cells in response to interleukin-1 beta and tumor necrosis factor-alpha: lack of regulation by 17 beta-estradiol.* Endocrinology, 1992. **130**(5): p. 2528-34.

153. Rickard, D., G. Russell, and M. Gowen, *Oestradiol inhibits the release of tumour necrosis factor but not interleukin 6 from adult human osteoblasts in vitro.* Osteoporos Int, 1992. **2**(2): p. 94-102.

154. Rifas, L., et al., *Production of interleukin-6 in human osteoblasts and human bone marrow stromal cells: evidence that induction by interleukin-1 and tumor necrosis factor-alpha is not regulated by ovarian steroids.* Endocrinology, 1995. **136**(9): p. 4056-67.

155. Passeri, G., et al., *Increased interleukin-6 production by murine bone marrow and bone cells after estrogen withdrawal.* Endocrinology, 1993. **133**(2): p. 822-8.

156. Girasole, G., et al., *Oestrogens prevent the increase of human serum soluble interleukin-6 receptor induced by ovariectomy in vivo and decrease its release in human osteoblastic cells in vitro.* Clin Endocrinol (Oxf), 1999. **51**(6): p. 801-7.

157. Srivastava, S., et al., *Estrogen decreases TNF gene expression by blocking JNK activity and the resulting production of c-Jun and JunD.* J Clin Invest, 1999. **104**(4): p. 503-13.

158. Roggia, C., et al., *Up-regulation of TNF-producing T cells in the bone marrow: a key mechanism by which estrogen deficiency induces bone loss in vivo.* Proc Natl Acad Sci U S A, 2001. **98**(24): p. 13960-5.

159. Li, L., et al., *Influence of exercise on bone remodeling-related hormones and cytokines in ovariectomized rats: a model of postmenopausal osteoporosis.* PLoS One, 2014. **9**(11): p. e112845.

160. Gilbert, L., et al., *Expression of the osteoblast differentiation factor RUNX2 (Cbfa1/AML3/Pebp2alpha A) is inhibited by tumor necrosis factor-alpha.* J Biol Chem, 2002. **277**(4): p. 2695-701.

161. Weitzmann, M.N., et al., *Interleukin-7 stimulates osteoclast formation by up-regulating the T-cell production of soluble osteoclastogenic cytokines.* Blood, 2000. **96**(5): p. 1873-8.

162. Siddiqi, A., et al., *Tri-iodothyronine regulates the production of interleukin-6 and interleukin-8 in human bone marrow stromal and osteoblast-like cells.* J Endocrinol, 1998. **157**(3): p. 453-61.

163. Siddiqi, A., et al., *Serum cytokines in thyrotoxicosis.* J Clin Endocrinol Metab, 1999. **84**(2): p. 435-9.

164. Ohta, K., et al., *Antitumor actions of cytokines on new human papillary thyroid carcinoma cell lines.* J Clin Endocrinol Metab, 1996. **81**(7): p. 2607-12.

165. Yip, I., et al., *Antitumor actions of interferon-gamma and interleukin-1 beta on human papillary thyroid carcinoma cell lines.* J Clin Endocrinol Metab, 1995. **80**(5): p. 1664-9.

166. Sun, L., et al., *Genetic confirmation for a central role for TNFalpha in the direct action of thyroid stimulating hormone on the skeleton.* Proc Natl Acad Sci U S A, 2013. **110**(24): p. 9891-6.

167. Baliram, R., et al., *Hyperthyroid-associated osteoporosis is exacerbated by the loss of TSH signaling.* J Clin Invest, 2012. **122**(10): p. 3737-41.

168. Grey, A., et al., *Circulating levels of interleukin-6 and tumor necrosis factor-alpha are elevated in primary hyperparathyroidism and correlate with markers of bone resorption--a clinical research center study.* J Clin Endocrinol Metab, 1996. **81**(10): p. 3450-4.

169. Grey, A., et al., *A role for interleukin-6 in parathyroid hormone-induced bone resorption in vivo.* Endocrinology, 1999. **140**(10): p. 4683-90.

170. Masiukiewicz, U.S., et al., *Estrogen modulates parathyroid hormone-induced interleukin-6 production in vivo and in vitro.* Endocrinology, 2000. **141**(7): p. 2526-31.

171. Mitnick, M.A., et al., *Parathyroid hormone induces hepatic production of bioactive interleukin-6 and its soluble receptor.* Am J Physiol Endocrinol Metab, 2001. **280**(3): p. E405-12.

172. Standal, T., et al., *gp130 in late osteoblasts and osteocytes is required for PTH-induced osteoblast differentiation.* J Endocrinol, 2014. **223**(2): p. 181-90.

173. Dai, J., et al., *Chronic alcohol ingestion induces osteoclastogenesis and bone loss through IL-6 in mice.* J Clin Invest, 2000. **106**(7): p. 887-95.

174. Fujikawa, Y., et al., *The effect of macrophage-colony stimulating factor and other humoral factors (interleukin-1, -3, -6, and -11, tumor necrosis factor-alpha, and granulocyte macrophage-colony stimulating factor) on human osteoclast formation from circulating cells.* Bone, 2001. **28**(3): p. 261-7.

175. Menaa, C., et al., *Enhanced RANK ligand expression and responsivity of bone marrow cells in Paget's disease of bone.* J Clin Invest, 2000. **105**(12): p. 1833-8.

176. Benigni, F., et al., *Six different cytokines that share GP130 as a receptor subunit, induce serum amyloid A and potentiate the induction of interleukin-6 and the activation of the hypothalamus-pituitary-adrenal axis by interleukin-1.* Blood, 1996. **87**(5): p. 1851-4.

177. Taga, T., *The signal transducer gp130 is shared by interleukin-6 family of haematopoietic and neurotrophic cytokines.* Ann Med, 1997. **29**(1): p. 63-72.

178. Leng, S.X. and J.A. Elias, *Interleukin-11.* Int J Biochem Cell Biol, 1997. **29**(8-9): p. 1059-62.

179. Romas, E., et al., *The role of gp130-mediated signals in osteoclast development: regulation of interleukin 11 production by osteoblasts and distribution of its receptor in bone marrow cultures.* J Exp Med, 1996. **183**(6): p. 2581-91.

180. Nakchbandi, I.A., et al., *IL-6 negatively regulates IL-11 production in vitro and in vivo.* Endocrinology, 2001. **142**(9): p. 3850-6.

181. Bellia, A., et al., *Serum 25-hydroxyvitamin D levels are inversely associated with systemic inflammation in severe obese subjects.* Intern Emerg Med, 2013. **8**(1): p. 33-40.

182. Kim, B.J., et al., *Higher serum carcinoembryonic antigen levels associate with more frequent development of incident fractures in Korean women: A longitudinal study using the national health insurance claim data.* Bone, 2015. **73**: p. 190-7.

183. Liu, Y.Z., et al., *Attenuated monocyte apoptosis, a new mechanism for osteoporosis suggested by a transcriptome-wide expression study of monocytes.* PLoS One, 2015. **10**(2): p. e0116792.

184. Hueston, C.M. and T. Deak, *The inflamed axis: the interaction between stress, hormones, and the expression of inflammatory-related genes within key structures comprising the hypothalamic-pituitary-adrenal axis.* Physiol Behav, 2014. **124**: p. 77-91.

185. Vankelecom, H., et al., *Production of interleukin-6 by folliculo-stellate cells of the anterior pituitary gland in a histiotypic cell aggregate culture system.* Neuroendocrinology, 1989. **49**(1): p. 102-6.

186. Rivest, S., *Regulation of innate immune responses in the brain.* Nat Rev Immunol, 2009. **9**(6): p. 429-39.

187. Dantzer, R., et al., *From inflammation to sickness and depression: when the immune system subjugates the brain.* Nat Rev Neurosci, 2008. **9**(1): p. 46-56.

188. Kanczkowski, W., et al., *Hypothalamo-pituitary and immune-dependent adrenal regulation during systemic inflammation.* Proc Natl Acad Sci U S A, 2013. **110**(36): p. 14801-6.

189. Laflamme, N., S. Lacroix, and S. Rivest, *An essential role of interleukin-1beta in mediating NF-kappaB activity and COX-2 transcription in cells of the blood-brain barrier in response to a systemic and localized inflammation but not during endotoxemia.* J Neurosci, 1999. **19**(24): p. 10923-30.

190. Nadeau, S. and S. Rivest, *Regulation of the gene encoding tumor necrosis factor alpha (TNF-alpha) in the rat brain and pituitary in response in different models of systemic immune challenge.* J Neuropathol Exp Neurol, 1999. **58**(1): p. 61-77.

191. Perlstein, R.S., et al., *Synergistic roles of interleukin-6, interleukin-1, and tumor necrosis factor in the adrenocorticotropin response to bacterial lipopolysaccharide in vivo.* Endocrinology, 1993. **132**(3): p. 946-52.

192. Sothern, R.B., et al., *Circadian characteristics of interleukin-6 in blood and urine of clinically healthy men.* In Vivo, 1995. **9**(4): p. 331-9.

193. Papanicolaou, D.A., et al., *Acute glucocorticoid deficiency is associated with plasma elevations of interleukin-6: does the latter participate in the symptomatology of the steroid withdrawal syndrome and adrenal insufficiency?* J Clin Endocrinol Metab, 1996. **81**(6): p. 2303-6.

194. Marin, P., et al., *Cortisol secretion in relation to body fat distribution in obese premenopausal women.* Metabolism, 1992. **41**(8): p. 882-6.

195. Imura, H., J. Fukata, and T. Mori, *Cytokines and endocrine function: an interaction between the immune and neuroendocrine systems.* Clin Endocrinol (Oxf), 1991. **35**(2): p. 107-15.

196. Path, G., et al., *Interleukin-6 and the interleukin-6 receptor in the human adrenal gland: expression and effects on steroidogenesis.* J Clin Endocrinol Metab, 1997. **82**(7): p. 2343-9.

197. Weber, M.M., et al., *Interleukin-3 and interleukin-6 stimulate cortisol secretion from adult human adrenocortical cells.* Endocrinology, 1997. **138**(5): p. 2207-10.

198. Auernhammer, C.J. and S. Melmed, *Leukemia-inhibitory factor-neuroimmune modulator of endocrine function.* Endocr Rev, 2000. **21**(3): p. 313-45.

199. Slota, C., et al., *Norepinephrine preferentially modulates memory CD8 T cell function inducing inflammatory cytokine production and reducing proliferation in response to activation.* Brain Behav Immun, 2015.

200. van Gool, J., et al., *The relation among stress, adrenalin, interleukin 6 and acute phase proteins in the rat.* Clin Immunol Immunopathol, 1990. **57**(2): p. 200-10.

201. Papanicolaou, D.A., et al., *Exercise stimulates interleukin-6 secretion: inhibition by glucocorticoids and correlation with catecholamines.* Am J Physiol, 1996. **271**(3 Pt 1): p. E601-5.

202. Fan, J., et al., *Interleukin-6 increases intracellular Ca2+ concentration and induces catecholamine secretion in rat carotid body glomus cells.* J Neurosci Res, 2009. **87**(12): p. 2757-62.