Endotext

IMMUNE SYSTEM EFFECTS ON THE ENDOCRINE SYSTEM

Maria P. Yavropoulou, MD, Senior Consultant in Endocrinology, First Department of Propaedeutic and Internal Medicine, National and Kapodistrian University of Athens, Laiko University Hospital, Athens, Greece, email: myavropoulou@med.uoa.gr

Petros P. Sfikakis, MD, Professor of Internal Medicine-Rheumatology, First Department of Propaedeutic and Internal Medicine, National and Kapodistrian University of Athens, Laiko University Hospital, Athens, Greece, email: psfikakis@med.uoa.gr

George P. Chrousos, MD, ScD, Professor Emeritus of Pediatrics and Endocrinology, National and Kapodistrian University of Athens, Holder, UNESCO Chair on Adolescent Health Care, Director of the University Research Institute on Maternal and Child Health and Precision Medicine at the National and Kapodistrian University of Athens, Greece, email: chrousos@gmail.com

Updated November 7, 2023

ABSTRACT

Among the most important and complex systems in the human body are the endocrine and immune systems. Emerging research over the last decade has shed light on their remarkable interplay, revealing a multitude of bidirectional communication pathways and reciprocal regulation mechanisms. Endocrine diseases, such as autoimmune thyroiditis, diabetes mellitus type 1 and type 2, osteoporosis, and disorders of the hypothalamic-pituitary-adrenal (HPA) axis, as well as endocrine malignancies, such as thyroid cancer, are highly interconnected with dysregulations of the immune system. Thus, multiple cytokines, chemokines, and evolving inflammatory processes are involved in the pathogenesis of immune-related endocrine disorders, providing potential targets for immune-based therapeutic approaches. In this chapter, we provide a comprehensive overview of the molecular mechanisms underlying these complex endocrine-immune interactions, and discuss the implications of immune system function or dysfunction in endocrine disorders.

INTRODUCTION

The immune system is a host defense system that comprises numerous biological structures and processes to defend the human body against potentially harmful substances and invading pathogens. It functions through a series of coordinated mechanisms, including innate and adaptive immunity. The innate immune response consists of i) phagocytosis by macrophages, neutrophils, monocytes, and dendritic cells, and ii) cytotoxicity by natural killer cells, providing an immediate, nonspecific defense against a wide range of invaders by recognizing common patterns shared by many pathogens (1).

Adaptive immunity, on the other hand, is an acquired, specially designed defense system; it develops over time and utilizes highly specialized immune cells involving antibody-dependent complement or cell-mediated cytotoxicity produced by T cells that recognize injurious agents, such as heat shock proteins or microbial antigens. During adaptive immunity, antigens taken up by antigen-presenting cells (APCs) are presented to T cells through binding with major histocompatibility complex (MHC) molecules on the surface of these cells. Activated CD4 helper T cells stimulate the release of cytokines, such

as interleukin (IL)-2, which i) induce T cell proliferation and activation, ii) stimulate killer cell activity by CD8 suppressor T cells, and iii) activate B cells to differentiate into plasma cells and produce antibodies. Naïve T cells differentiate mainly into two main subsets that produce a different set of cytokines and regulate distinct immune functions. T-helper 1 (Th1) cells produce mainly interferon-γ (IFN)-γ, tumor necrosis factor-α (TNF)-, and IL-12 to regulate cell-mediated responses, while T-helper 2 (Th2) cells secrete IL-4, IL-5, and IL-13, to stimulate antibody production. In addition, three other subsets of T helper cells have been identified: Th22, which secrete IL-22, Th17, which secrete IL-17, and Treg, which secrete transforming growth factor (TGF)- b, all of which also play a role in the pathogenesis of autoimmune diseases (2).

Multiple regulatory mechanisms are involved in maintaining central and peripheral T and B cell tolerance (1). Defects in the processes that ensure immune cell tolerance may induce a maladaptive immune response to a self-antigen and lead to the development of autoimmune diseases.

Emerging research of the last few decades has shed light on the remarkable interplay between endocrine and immune systems, revealing a multitude of bidirectional communication pathways and reciprocal regulation.

Autoimmune endocrine diseases, such as Hashimoto thyroiditis, diabetes mellitus type 1 (DM1), and Addison disease, as well as endocrine malignancies, such as differentiated, anaplastic, and medullary thyroid cancer (3), and other endocrine disorders, including diabetes mellitus type 2 (DM2), osteoporosis, as well as a dysfunctional hypothalamic-pituitary-adrenal (HPA) axis response to stress and inflammation, are highly interconnected with dysregulations of the immune system.

This chapter seeks to elucidate the interplay between the endocrine and immune systems, exploring their interconnections and highlighting the impact of their crosstalk on health and disease. We present a comprehensive overview of the molecular mechanisms underlying this interaction and discuss the potential therapeutic implications of targeting the immune system for the management of endocrine diseases.

IMMUNE SYSTEM AND THYROID DISEASE

Autoimmune Thyroid Disease

Autoimmune thyroid disease (AITD) results from a dysregulation of the immune system that leads to loss of tolerance to thyroid antigens and to an autoimmune attack on the thyroid gland. The most common clinical manifestations of AITD are Hashimoto's thyroiditis and Graves' disease, while less prevalent manifestations are drug-induced thyroiditis, postpartum thyroiditis, or thyroiditis associated with polyglandular syndromes (i.e., autoimmune polyglandular syndromes type 1 and type 2). The underlying molecular mechanisms of AITD involve both circulating autoantibodies and T cell immune mechanisms, while genetic background, as well as cross-reactivity to external antigens (4-6), are also implicated.

There are three major thyroid autoantigens that are targeted during autoimmune thyroid attack and are critical for thyroid homeostasis, namely, thyroglobulin (Tg), thyroid peroxidase (TPO), and the thyrotropin receptor (TSHR) (Figure 1).

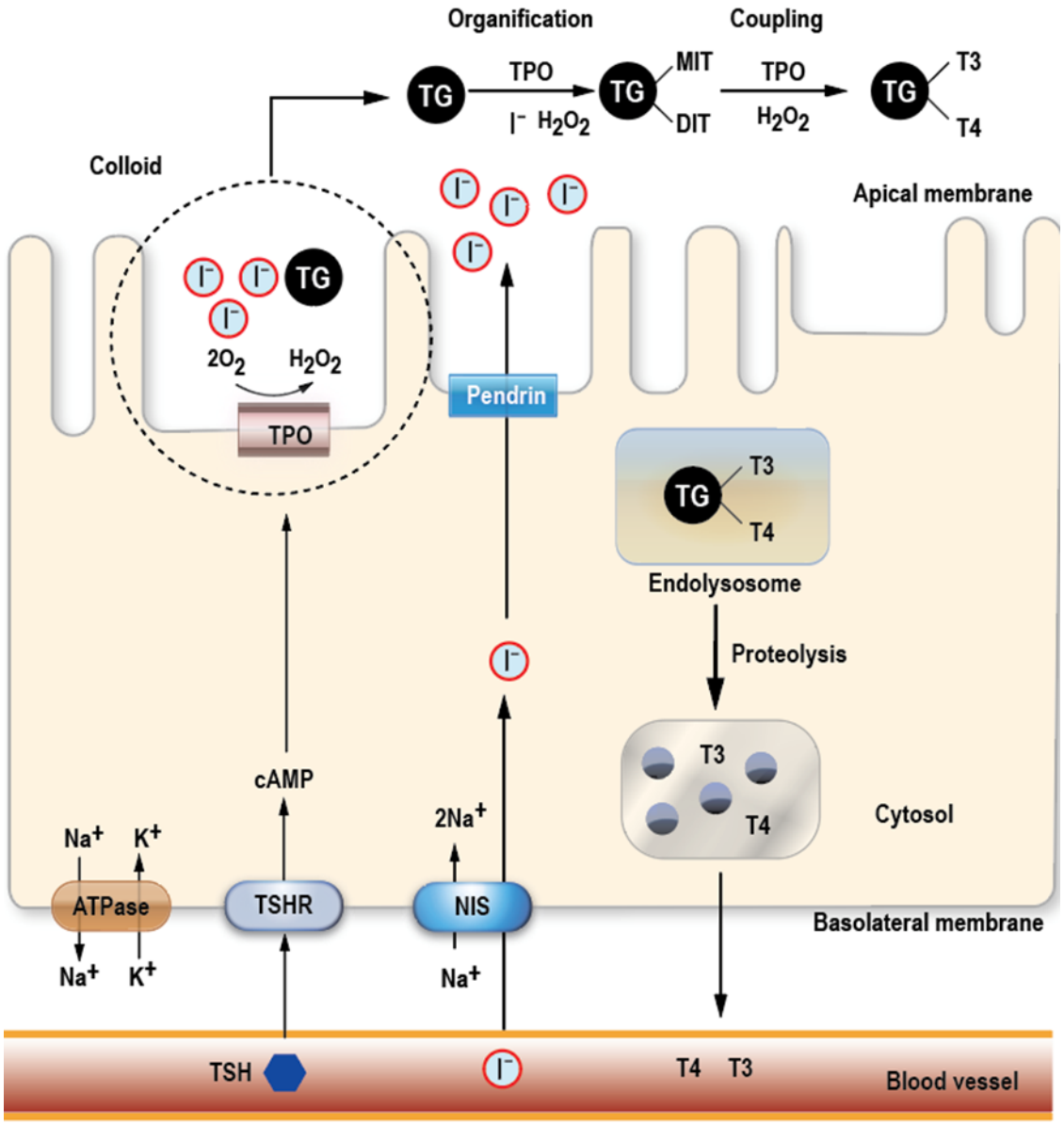

Figure 1. Thyroid proteins that serve as autoantigens. Thyroglobulin (Tg) function as storage protein in thyroid cells, playing a critical role in the synthesis and release of thyroid hormones. Thyroid peroxidase (TPO) catalyzes iodination of tyrosines in thyroglobulin, which attaches one or two iodine molecules to form monoiodotyrosine (MIT) or diiodotyrosine (DIT), respectively. In addition, thyroid peroxidase catalyzes the coupling of iodotyrosine residues to form triiodothyronine (T3) and thyroxine (T4) attached to thyroglobulin. Thyrotropin receptor (TSHR) is a transmembrane G-protein coupled receptor that upon stimulation by circulating TSH activates the expression of downstream effector genes to regulate thyroid growth, thyrocyte differentiation, and thyroid hormone synthesis. Sodium/iodide symporter (NIS) is a membrane glycoprotein, which actively cotransports two sodium cations per each iodide anion, using the electrochemical sodium gradient generated by the Na+/K+-ATPase. Pendrin is involved in the apical

iodide efflux in thyroid cells. It can also exchange chloride and bicarbonate. [Modified by Boguslawska et al (7)].

Thyroglobulin is a soluble glycoprotein homodimer composed of two subunits of ~330 kDa in size and is the most abundant glycoprotein in the thyroid gland. It is the scaffold for the synthesis of thyroid hormones and the storage-form of thyroid hormones inside the gland. Recently, researchers described the first atomic structure of full-length Tg and identified its hormone-forming tyrosine residues (8). Anti-Tg antibodies (TgAb) act mainly through antibody-dependent cytotoxicity cells rather than through complement fixation (7). In AITD, the prevalent TgAb species recognize native rather than denatured antigens and bind to a number of overlapping epitopic domains located mainly in the central region and C-terminal end of Tg. Of note, TgAb in the serum of healthy subjects have a different epitopic pattern (9).

Another major thyroid antigen is TPO, a glycosylated heme-containing homodimer of two 107-kDa transmembrane subunits located in the apical membrane of thyrocytes (Figure 1). It catalyzes the iodination of tyrosyl residues in Tg and the coupling of iodotyrosine residues to form iodothyronines attached to Tg (10). Both humoral and cellular immune responses are directed against TPO. TPO autoantibodies (TPOAb) occur in almost all patients with Hashimoto thyroiditis and approximately 75% of individuals with Graves' disease (11). In addition, TPOAb may be involved in autoimmune thyroid cell death via antibody-dependent cytotoxic cells and C3 complement-mediated cytotoxicity (7). Specific patterns of TPOAb recognition remain stable in an individual over time and are genetically transmitted through family lineages (12).

Thyrotropin receptor is primarily expressed on the basolateral membrane of thyrocytes (Figure 1) and belongs to the transmembrane G protein-coupled receptor family. The intracellular signaling pathway that is activated by the interaction of TSH with TSHR is indispensable for the synthesis of thyroid hormones and the proliferation of follicular epithelial cells. TSHR-stimulating antibodies (TSAb) act as TSHR agonists and stimulate thyroid growth and production of thyroid hormone in an autonomous and unregulated manner. On the other hand, TSHR-blocking antibodies (TBAb) act as antagonists that block the intracellular signaling of TSH, leading to decrease of thyroid hormone synthesis and subsequently hypothyroidism. Neutral antibodies to TSHR, which may also be detected in the serum of patients with Graves' disease, bind to the receptor but do not alter its activity (13). The exact antigenic sites of TSHR-specific TBAb and TSAb overlap and are mostly directed to the extracellular A subunit of the receptor (Figure 1) (14,15).

Other thyroid antigens include the iodide transporters, sodium iodide symporter (NIS), and pendrin (Figure 1). The presence of NIS antibodies is increased in AITDs, especially in patients with Graves' disease, whereas their expression in euthyroid individuals is rare (16). Pendrin is an apical membrane-bound iodide transporter, but the diagnostic value of antibodies against pendrin is rather low (16).

Although the above-described circulating autoantibodies are useful markers of thyroid autoimmunity, it is the T cell immune mechanism, i.e., the loss of immune self-tolerance, that is the core of AITD pathophysiology. Loss of immune self-tolerance may result from either: i) the loss of central tolerance (i.e., disturbed deletion of autoreactive T cells in the thymus), ii) dysfunction of peripheral tolerance (i.e., impaired apoptosis of self-reactive T cells and inhibition of the activity of T-regulatory cells), or iii) disturbed energy (i.e., disturbance of the functional inactivation that prevents the lymphocytes from activating an immune reaction against the antigen).

Patients with AITD express IFN-γ-induced MHC class II molecules, which promotes the presentation of thyroid autoantigens and activates T cells (4). The subsequent infiltration of the thyroid gland by APCs (dendritic cells and macrophages) may be triggered by inflammation resulting from either viral or bacterial infection or exposure to toxins. The common mechanism involved in the initiation and perturbation of the inflammatory processes in AITDs and in other autoimmune endocrine diseases (e.g., type 1 diabetes and Addison disease) is the Th1-cytokine/chemokine axis (17). Upon activation, Th1 lymphocytes produce IFN-γ -and TNF-α, which stimulate thyrocytes and retroorbital cells (in Graves ophthalmopathy) to secrete chemokines (CXCL10, CXCL9, and CXCL11). Chemokines, in turn, bind and activate the CXCR3 receptor on Th1 cells and further enhance IFN-γ and TNF-α secretion in a positive feedback loop which aggravates recruitment and activation of inflammatory cells in the affected organs (Figure 2). In advanced thyroiditis, the thyroid gland is infiltrated by B cells (representing up to 50% of the infiltrating immune cells), as well as cytotoxic T lymphocytes and CD4+ cells (7).

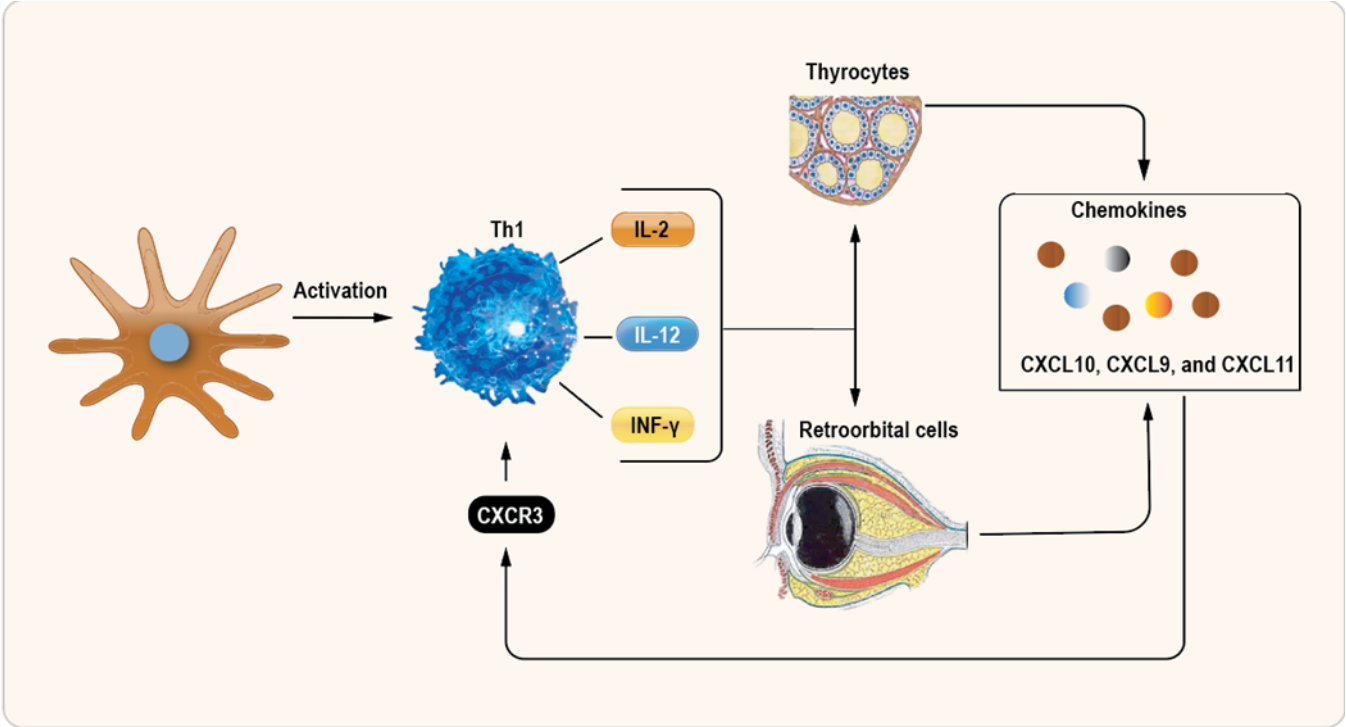

Figure 2. Depiction of the molecular mechanism involved in the inflammatory processes in autoimmune thyroid diseases. Activation of Th1 lymphocytes by antigen presenting cells produce INF-γ -and IL-2 and 12, which stimulate thyrocytes and retroorbital cells to secrete chemokines (CXCL10, CXCL9, and CXCL11). Chemokines bind and activate the CXCR3 receptor on Th1 cells, further enhancing IFN-γ and ILs secretion. APC, antigen presenting cells; IFN-γ, interferon gamma; IL-2, interleukin 2; IL-12, interleukin-12; CXCR3, C-X-C Motif Chemokine Receptor 3.

In Hashimoto thyroiditis, the humoral immune response is characterized by the presence of autoantibodies to TPO or Tg and is related to thyroid lymphocytic infiltration. These autoantibodies are themselves cytotoxic or may affect antigen processing or presentation to T cells. Th1 cells are the predominant T cell clones found in patients with Hashimoto thyroiditis: they promote apoptosis of thyrocytes through secretion of IL-12, TNF-α, and INF-γ, which activate cytotoxic T lymphocytes and macrophages (18). In addition, the Toll-like receptor-3 protein is overexpressed in human thyrocytes surrounded by immune cells in all patients with Hashimoto thyroiditis, but not in Graves' disease or in euthyroid individuals (17).

In patients with Graves' disease, the predominant antibodies are directed against the TSHR. T cells are activated through the presentation of TSHR peptides and, in turn, trigger B-cells and plasma cells that infiltrate the thyroid to produce autoantibodies directed against the TSHR. Activity of B-cells and plasma cells is also regulated by liver-produced insulin growth factor 1 (IGF1). In contrast to TPO and Tg, TSHR is widely expressed in extrathyroidal tissues and cells, including lymphocytes, adipose tissue, and fibroblasts. In consequence, the presence of TSHR antibodies contributes to the extrathyroidal manifestations of Graves' disease, such as Graves ophthalmopathy, Graves dermopathy, and Graves-associated thymus hyperplasia (19).

Particularly in Graves ophthalmopathy, the TSHR autoantigen is presented by macrophages and B cells recruited to the orbit (20). Activated T cells, in turn, initiate an immunological attack on the orbital fibroblasts expressing TSHR. In response to the cytokines released by Th cells, orbital fibroblasts and adipocytes —both expressing TSHR— produce and deposit large amounts of glycosaminoglycans (e.g., hyaluronan), leading to increased osmotic pressure and water uptake, swelling of the extraorbital muscles, and increased accumulation of orbital adipose tissue. The process is enhanced by the IGF1/IGF1R signaling pathway in fibroblasts and adipocytes, as well as the crosstalk between TSHR and IGF1R intracellular signaling (21). A similar molecular pathophysiology may underlie Graves dermopathy (19).

NON-CODING RNAs

In recent years, non-coding RNAs, which are known to modulate gene transcription at the post-transcriptional level, have attracted a great deal of attention as potential biomarkers in various endocrine diseases. Although the study of microRNAs and circular RNAs is still in its infancy, these newly discovered non-coding, single-stranded RNA molecules have been implicated in the development and progression of AITDs.

A cluster of biomarkers consisting of miR-205/miR-20a-3p/miR-375/miR-296/miR-451/miR-500a/miR-326 has been reported to be differentially expressed in patients with Hashimoto thyroiditis (22,23). Similarly, multi-miRNA-based biomarkers, such as miR-762/miR-144-3p or miR-210/miR-155/miR-146, were differentially expressed in the serum of patients with Graves' disease compared to healthy individuals. These dysregulated miRNAs can target key genes involved in the immune response and thyroid function. Regarding their prognostic role, higher miR-21-5p expression is associated with a worse prognosis for patients with Graves' disease, whereas impaired expression of miR-155 correlates with the size of the goiter (22,24). Further understanding of the role of miRNAs in AITDs could provide valuable insights into disease mechanisms and potentially identify novel therapeutic targets. Data on other non-coding RNAs (such as long-noncoding RNAs and circular RNAs) are scarcer. Impaired expression of n335641, TCONS-00022357-xloc-010919, and n337845 was found in B cells of patients with Graves' disease (25), while

altered expression of 627 circRNAs in PBMCs of patients with Hashimoto thyroiditis has been tested for their potential prognostic value (26).

GUT MICROBIOME

Emerging evidence suggests that the composition and function of the gut microbiome may be involved in AITDs. The gut microbiome refers to the complex community of microorganisms residing in the gastrointestinal tract, which plays a vital role in various aspects of human health, such as prevention of intestinal colonization by pathogenic bacteria, fermentation/degradation of food debris, and production of nutrients. Studies have indicated that alterations in the gut microbiome can influence immune responses and contribute to the development of autoimmune diseases (7). In this context, dysbiosis, or an imbalance in the gut microbiota, has been observed in patients with Hashimoto thyroiditis and Graves' disease, thus distinguishing them from healthy controls, while it was associated with the stage of disease, the level of thyroid autoantibodies, and the response to therapy.

Targeting the microbiome through dietary interventions or probiotics may represent a promising potential therapeutic avenue. It is therefore of interest to note that in hypothyroid patients treated with LT4, symbiotic supplementation for 8 weeks resulted in decrease of TSH concentration and LT4 dose (27). Moreover, the results of a large clinical study, INDIGO, reported a significant effect of LAB4 probiotics on the gut microbiota composition of patients with Graves' disease and a temporary reduction in the serum level of IgG and IgA antibodies (28). Further research involving patients from different populations is required to fully understand the relationship between the gut microbiome and AITDs and to explore potential strategies for intervention.

Postpartum Thyroiditis

Postpartum thyroiditis may occur up to 12 months after delivery. Usually it presents as transient hyperthyroidism (median time of onset, 13 weeks post-delivery), followed by transient hypothyroidism (median time of onset, 19 weeks post-delivery). In the majority of patients, restoration of normal thyroid function occurs. Pregnancy triggers hormonal changes and immune system alterations, such as a shift from Th1 to Th2 cytokine production followed by a "rebound" shift back to Th1 after delivery, and fluctuations in transforming growth factor-beta1 TGF-β1) serum levels (29,30).

Anti-TPO and anti-Tg antibodies are found in almost all patients with postpartum thyroiditis. Notably, up to 50% of women who had anti-TPO antibodies at the end of the first trimester of gestation (i.e., before thyroid antibody titers start to decline during pregnancy) developed postpartum thyroiditis. Furthermore, there is evidence that the anti-TPO antibody titer at 16 weeks of gestation is related to the severity of postpartum thyroiditis (31), while activation of the complement is also involved in the pathogenesis (23).

Euthyroid Sick Syndrome

Euthyroid sick syndrome (ESS) is a condition characterized by alterations in thyroid hormone levels despite normal thyroid gland function. The characteristic laboratory abnormalities of the ESS include low T3 and/or fT3, elevated reverse T3 (rT3), normal or low TSH, and normal or low serum T4 or fT4 concentrations. Clinical conditions that trigger the development of ESS include systemic inflammation, myocardial infarction, starvation, sepsis, surgery, trauma, chronic degenerative diseases, malignancy, and every other condition associated with severe illness.

During illness or periods of severe physiological stress, the immune system releases various proinflammatory cytokines, such as in IL-6, TNF-α, IL-1β, IFN-γ, and TGF-β2. These cytokines disrupt the hypothalamic-pituitary-thyroid axis and interfere with the normal synthesis, secretion, and metabolism of thyroid hormones (Figure 3), while the more severe the illness, the more extensive the hormonal alterations.

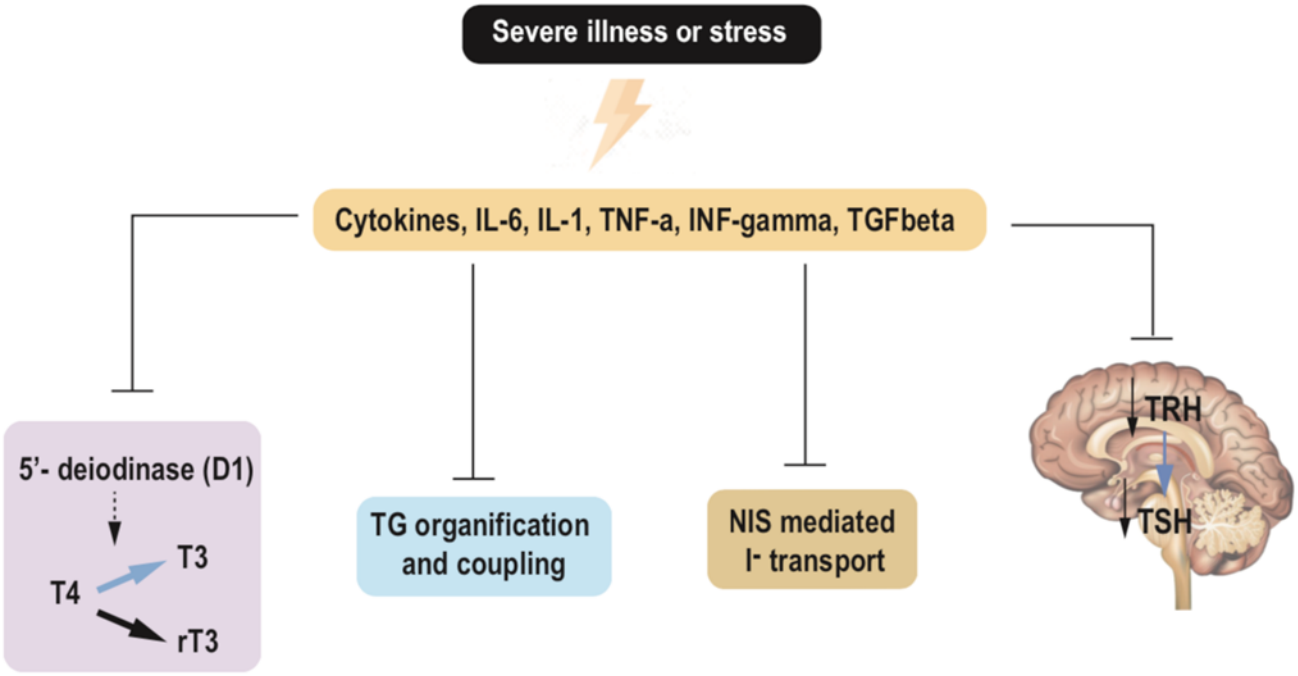

Figure 3. Secretion of proinflammatory cytokines during severe illness or stress inhibits the activity of hepatic deiodinase type 1- suppressing the peripheral conversion of T4 to T3. They also suppress intrathyroidal hormone synthesis, TRH release and TSH secretion from the pituitary. IL-6, interleukin-6; IL-1, interleukin-1; TNF-α, tumor necrosis factor alpha; INF-γ, interferon gamma; TGF-β, tumor growth factor beta; TG, thyroglobulin; NIS, sodium/iodide symporter; TSH, thyroid stimulating hormone; TRH, Thyrotropin-releasing hormone.

Proinflammatory cytokines suppress the peripheral conversion of T4 to T3, resulting in low T3 levels and increase rT3 levels, by inhibiting the activity of hepatic deiodinase type 1, which promotes conversion of T4 to T3 and of rT3 to diiodothyronine (32). They also suppress TRH release and inhibit TSH response to TRH stimulation, leading to a decrease in TSH levels. 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 impaired degradation. Prolonged and severe illness is marked by a decrease in circulating total T4 along with low T3 and high rT3, with very low T4 levels displaying a poor prognosis and having been associated with an increased mortality rate (32). In addition, cytokines reduce iodine uptake by inhibiting sodium-iodine symporter protein expression (25-27), and decrease thyrocyte growth (33), iodide organification (34,35), and thyroglobulin synthesis (36,37).

The central role of cytokines in the pathophysiology of ESS has been further elucidated in studies involving

cytokine administration to humans. TNF-α administration in healthy volunteers caused a decrease in serum T3 and an increase in serum rT3 concentration (38). 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 seen in ESS (39,40), suggesting that the changes of thyroid hormone profile following TNF-α administration might be indirect (i.e., through TNF-α increase in circulating IL-6 levels). Furthermore, both IL-6 and TNF-α can upregulate type 2 deiodinase in the anterior pituitary, affecting TSH release and contributing to the development of the non-thyroidal illness syndrome (41,42).

Leptin, a hormone primarily known for its role in regulating appetite and energy balance, has also been implicated in the development of EES. During acute illness or chronic inflammation, leptin levels are usually elevated. A link between leptin and the proinflammatory cytokines TNF-α and IL-6 in chronic inflammatory diseases, such as chronic obstructive pulmonary disease (43) and ankylosing spondylitis (44), respectively, has also been proposed previously.

The primary effect exerted by leptin on the hypothalamic-pituitary-thyroid axis is alteration of the setpoint for feedback sensitivity of hypophysiotropic TRH-producing neurons in the paraventricular nucleus of the hypothalamus to thyroid hormones (mainly T3) by lowering of the setpoint when leptin levels are suppressed during fasting (45). 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 effects of leptin on hypophysiotropic TRH. It has also been proposed that leptin directly affects hypophysiotropic TRH neurons (46). Leptin has been found to inhibit the conversion of T4 to T3 in peripheral tissues and increase the activity of the enzyme type 3 deiodinase, which converts T4 to rT3. These data suggest that leptin can disturb thyroid function in seriously ill patients via two different independent mechanisms (cytokine-dependent and directly).

Amiodarone-Induced Thyroid Disease

Amiodarone, a benzofuran derivative with a similar structure to that of 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 (47).

Treatment with amiodarone may be related to an increase in lymphocyte subsets leading to an exacerbation of pre-existing autoimmunity (48,49). 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 (50).

Amiodarone-induced hypothyroidism is attributed to an increased susceptibility to the inhibitory effect of iodide on thyroid hormone synthesis and/or to a failure to escape the Wolff-Chaikoff effect (49). Hashimoto thyroiditis is the most common risk factor for amiodarone-induced hypothyroidism and it is considered the most likely reason for the female preponderance of this clinical entity (51). Female patients with positive anti-TPO and anti-Tg autoantibodies have a relative risk of 13.5% for developing amiodarone-induced hypothyroidism compared to men without thyroid autoantibodies (20).

The pathogenesis of amiodarone-induced thyrotoxicosis 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 (47,50,52,53).

Differentiating between the two types of amiodarone-induced thyrotoxicosis is an essential step in their management, as treatment of each type is different (50). Type 1 usually responds to thionamide therapy, which blocks hormone synthesis, and perchlorate, which blocks active transport of iodine into the thyroid, whereas type 2 responds to high-dose glucocorticoids (50,53-55). Nevertheless, several studies now suggest that these two types should be treated concomitantly; thus, currently, patients with amiodarone-induced thyrotoxicosis receive both antithyroid drugs and prednisolone. In cases resistant to medical treatment and/or in patients with severe cardiac diseases who cannot interrupt amiodarone or require quick amiodarone reintroduction, total thyroidectomy may be offered after rapid correction of thyrotoxicosis following combination treatment with thionamides, $KClO_4$, glucocorticoids, and a short course of iopanoic acid (56).

Thyroid Cancer

Thyroid cancer is the most common endocrine cancer, the incidence of which has steadily increased over the past few decades (57).

The association of chronic inflammation induced by Hashimoto thyroiditis and thyroid cancer has been long recognized (58). However, the immune response triggered against thyroid cancer and AITDs differs significantly. In thyroid cancer, the immune response is more tolerant and allows tumor growth, whereas in AITDs, the response is more aggressive, triggering cell destruction and reduction of the function of the gland (59). Hashimoto thyroiditis is considered both a risk factor for the development of thyroid cancer (60) and a favorable prognostic factor due to chronic lymphocytic infiltration, which can downregulate tumor aggressiveness (60,61). In Graves' disease, the presence of a strong humoral immune response appears to be protective against thyroid cancer. Patients with increased anti-TPO and anti-Tg levels show lower distant metastasis rates than patients without thyroid autoantibodies (62,63), suggesting their potentially protective role (59).

Immune infiltrates in the tumor microenvironment differ between the different thyroid neoplasm subtypes (Figure 4). In general, differentiated thyroid cancer (DTC) has a higher number of tumor-associated lymphocytes and regulatory T cells (Tregs), while anaplastic thyroid cancer (ATC) and medullary thyroid cancer (MTC) display a high density of tumor-associated macrophages (64). The number of tumor-associated macrophages has been associated with dedifferentiation, lymph node metastases, and reduced survival (65). It is important to note, however, that most of the studies analyzing the immune milieu of DTC have used papillary thyroid cancer (PTC) tumor samples (66-69). Myeloid-derived suppressor cells are associated with aggressive characteristics of differentiated thyroid cancer and are related to poor prognosis (65).

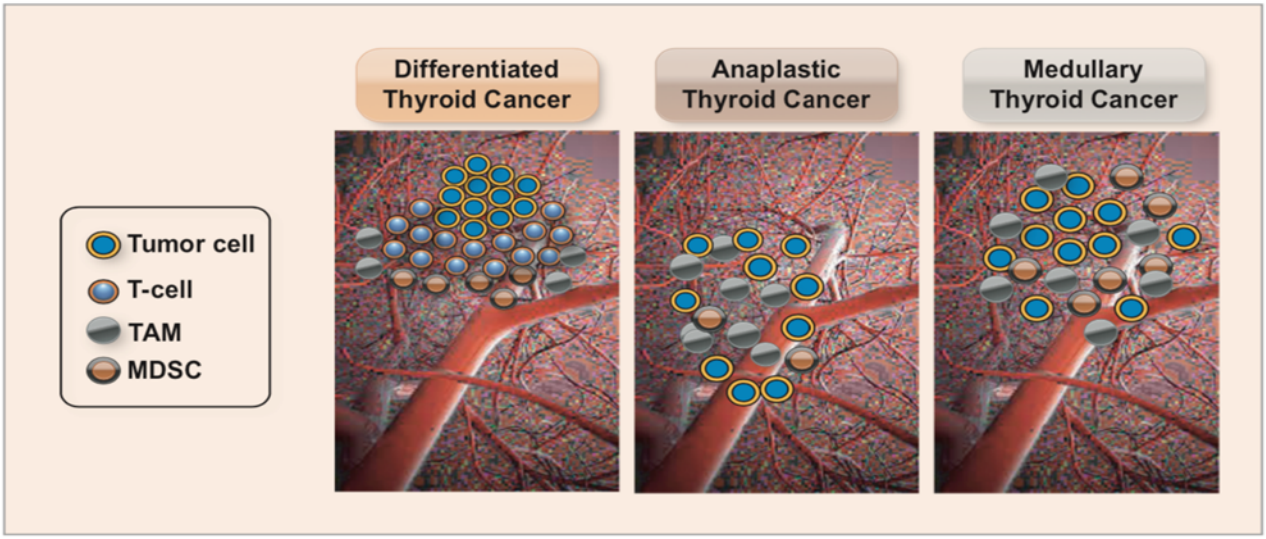

Figure 4. Immune infiltrates differ in different types of thyroid cancer [Modified by Garcia-Alvarez et al, (70)]. TAM, tumor-associated macrophages; MDSC, myeloid-derived suppressor cell.

The dendritic cells, which play a critical role in antigen presentation, are increased in PTC, while neutrophils are found in more aggressive thyroid cancers (such as poorly differentiated or anaplastic). In addition, natural killer cells that play an important role in immunosurveillance are also increased in PTC and are negatively correlated with tumor stage, while lymphocytic infiltration is associated with better overall survival and low recurrence rate (71,72).

Cytokines, which may be produced by thyroid follicular cells and by immune cells infiltrating thyroid tumors, are also related to tumor development. IL-1 and IL-6 stimulate thyroid cell proliferation and tumor growth, while TGF-β, which is a suppressive cytokine, is overexpressed in aggressive cancers (73). In addition, multiple chemokines may be secreted by thyroid cancer or immune cells and affect chemiotaxis, angiogenesis, and lymphangiogenesis (73).

Immunomodulatory proteins, such as programmed death-ligand 1 (PDL1), cytotoxic T-lymphocyte antigen 4 (CTLA-4), T cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte activation gene-3 (LAG-3), and T cell immunoglobulin and ITIM domain (TIGIT), which are considered major immune coinhibitory receptors and promising immunotherapeutic targets in cancer treatment, are also expressed in thyroid cancer, being associated with more aggressive tumor characteristics and a poor prognosis (64). Programmed death-ligand 1 staining by immunohistochemistry has shown higher expression in ATC than in other subtypes (70). Six cohort studies have been published to-date reporting positive PD-L1 expression, varying between 22% and 65%, this being higher compared to that detected in DTC and poorly differentiated thyroid cancer (74-79). TIM-3 expression was observed in 48% of patients with MTC, and in the majority of cases (84.4%) its expression was restricted to tumor cells (80). Other coinhibitory receptors, such as LAG-3 and T cell TIGIT, were observed in a lesser percentage of cases (approximately 3%) (80). Nevertheless, results from clinical trials with immunotherapy as monotherapy or combinations have shown limited efficacy (70). In one phase Ib KEYNOTE-028 trial assessing the efficacy of pembrolizumab in patients with PD-L1+ (membranous staining on ≥1%) locally advanced or metastatic follicular or papillary thyroid cancer, pembrolizumab achieved an objective response rate of 9% and a

median progression-free survival of 7 months (81). Several clinical trials further investigating the efficacy of combination therapy of immune checkpoint inhibitors are currently ongoing.

IMMUNE SYSTEM AND DIABETES MELLITUS

The immune system plays a crucial role in the pathogenesis of both type 1 and type 2 diabetes.
Diabetes type 1, which is immune-mediated in more than 95% of cases, is an organ-specific autoimmune disease characterized by lymphocytic infiltration and inflammation that leads to pancreatic β-cell destruction and absolute insulin deficiency (82). The immune system's attack on pancreatic β-cells is usually triggered by a number of factors, including genetic predisposition and environmental triggers such as viral infections (e.g., Coxsackie B4, mumps, and rubella) or dietary compounds (e.g., cow's milk) (82). The process involves the activation of immune cells, particularly T cells, which recognize self-autoantigens in pancreatic β-cells and initiate an immune response.

On the other hand, in type 2 diabetes, the immune system also plays a different role from that in DM1. Chronic low-grade inflammation, often associated with obesity, leads to immune cell activation and the release of proinflammatory cytokines. These cytokines interfere with the normal functioning of insulin and promote insulin resistance. Macrophages infiltrate adipose tissue and release inflammatory molecules, further exacerbating insulin resistance with increasing adiposity. The immune system, thus, contributes to the development and progression of insulin resistance and eventually promotes the onset of DM2.

Understanding the intricate relations between the immune system and diabetes pathogenesis is essential for the development of effective treatments and interventions for the management of both types of diabetes.

Diabetes Type 1

The susceptibility to develop DM1 is associated with multiple alleles of the major histocompatibility complex MHC I and II locus. More than 90% of patients with DM1 express either HLA DR3, DQ2 or DR4, or DQ8 (83), whereas HLA haplotype DR2, DQ6 is protective against DM1 development.

The primary pathological presentation of DM1 is inflammation of the pancreatic islets, also known as insulitis, caused by infiltration of immune cells, including CD4 and CD8 T cells along with B cells (84-86). Although the initial events triggering autoreactive responses remain unclear, presentation of pancreatic islet autoantigens by the associated MHC class II molecules contribute to priming and expansion of pathogenic T cells.

CD4 T helper cells are required for the development of the autoimmune process in the pancreatic islets, while CD8 cytotoxic T cells are the cells responsible for β-cell destruction (Figure 5). T cell receptors recognize peptides bound to MHC molecules on the surface of antigen-presenting cells (B-cells, dendritic cells, and macrophages). Each T cell then generates a unique receptor for the recognition of an autoantigen presented in the MHC molecule. The interaction between T cell receptor/autoantigen/MHC leads to activation of the T cells.

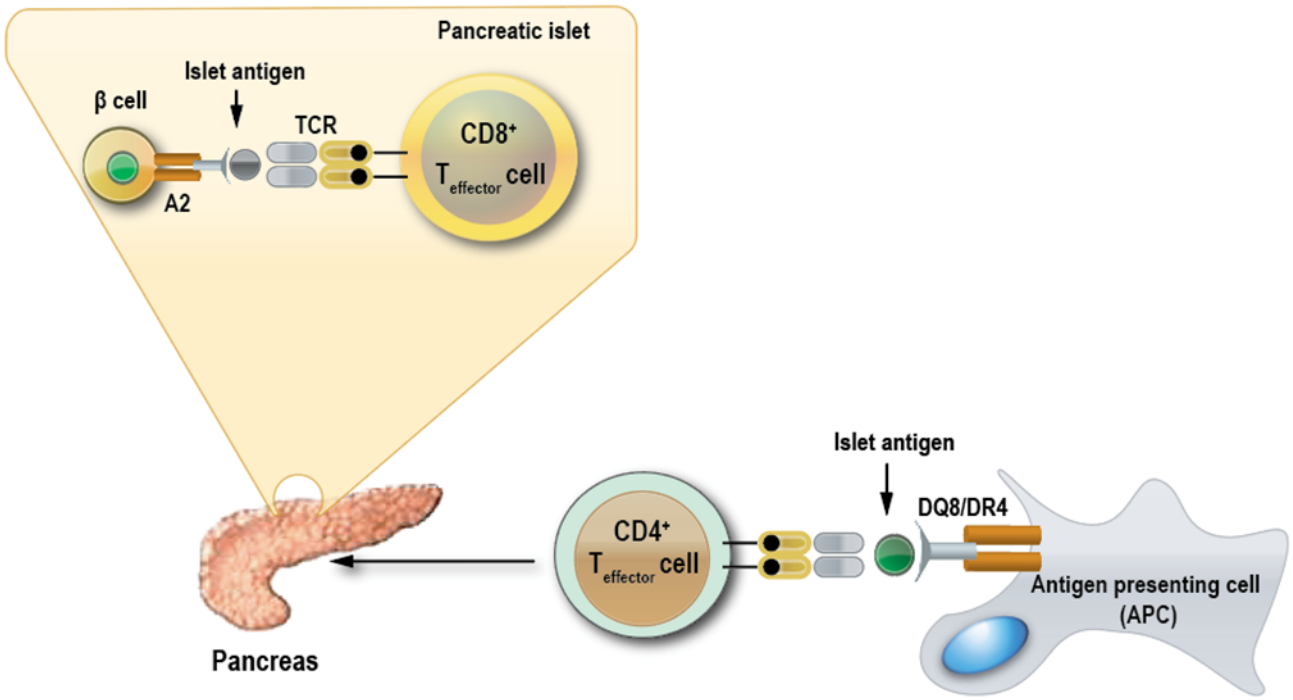

Figure 5. T cell mediated destruction of β- cells in diabetes type 1. CD4+ effector T cells recognize an insulin or islet peptide presented by diabetes-risk conferring HLA-DQ8 or DR4 on APCs, migrate to the pancreas and promote pancreatic β-cell destruction. Inside the pancreatic islets CD8+ effector T cells recognize islet antigens presented by HLA-A2 leading to the destruction of the β-cells. [Modified by Mitchel et al (87)]. TCR, T cell receptor; APC, antigen presenting cell; HLA-A2, human leukocyte antigen-A2.

Three different mechanisms have been proposed to explain T cell activation in DM1. One mechanism is thought to involve molecular mimicry-activated T cell proliferation. The hypothesis for 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 (88). A second mechanism that may trigger molecular mimicry-activated T cell proliferation is “bystander” 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 IFN-α and IFN-β (89). The 3rd mechanism might involve a superantigen-mediated T cell proliferation mechanism: this theory proposes that autoreactive T cells can be inappropriately primed to react against self-structures through an encounter with a superantigen (90).

Multiple autoantigens in the pancreatic islets have been identified, including non-specific islet cell autoantigens (ICA), insulin, glutamic acid decarboxylase 65 (GAD65), insulinoma antigen-2 (IA-2), heat shock protein (HSP), islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP), imogen-38, zinc transporter-8 (ZnT8), and the most recently identified pancreatic duodenal homeobox factor 1 (PDX1), chromogranin A (CHGA), and islet amyloid polypeptide (IAPP) (91). Autoantibodies against these autoantigens may be detected long

before the onset of hyperglycemia and usually decline during the course of the disease (92).

Most patients diagnosed with DM1 have circulating islet cell autoantibodies directed against pancreatic islet autoantigens. However, although the detection of autoantibodies may be useful for DM1 diagnosis and prediction, it is the cellular immune system that eventually infiltrates the pancreatic islets and causes β-cell destruction. In turn, further β-cell destruction leads to more self-antigen presentation and ensuing amplification of the immune response (82,93,94).

Among several proinflammatory cytokines, IL-21, produced by CD8 T cells, is required for the development of DM1, while TNF-α may also be involved (95,96). IL-6 plays an important role in the pathogenesis of vitiligo-associated DM1 (97). In contrast, in vivo experiments with non-obese diabetic mice have shown that IL-4, produced by Th2 cells, may be protective against developing diabetes (95,96,98,99).

Understanding both the pathophysiology and the regulatory mechanisms involved in DM1 is a critical step towards the development of antigen-specific, β-cell-directed, immunomodulatory or cellular treatment modalities (100).

Investigations into the efficacy and safety of various immunotherapeutic strategies against the development of DM1 have been carried out in recent clinical trials and are still ongoing in current trials (101). Among them, T cell-directed therapies that aim at a favorable balance between effector T cell depletion and regulatory T cell preservation have shown the most promising results. Teplizumab, an anti-CD3-directed monoclonal antibody, was the first immunomodulatory agent to demonstrate a significant delay in disease progression in high-risk individuals before clinical onset (102) and has recently (November 17, 2022) been approved by the FDA as the first disease-modifying therapy for DM1 in adults and in children aged 8 years and older.

The Enigma of Pancreatic α-Cell Resistance in Diabetes Mellitus Type 1

Although both insulin-producing β-cells and glucagon-producing α-cells of the pancreatic islets share a similar embryonic origin and are directly exposed to the deleterious immune signals in DM1, it appears that the immune system selectively destroys β-cells, while α-cells survive even in long-term DM1 (103). α-Cells are located in close proximity to β-cells in human pancreatic islets (104), creating a closed communication loop that regulates their function and secretory capacity (105). Dysfunction of α-cells plays a significant role in the pathogenesis of both types of diabetes (106). It has long been proposed that the reduced functional β-cell mass in DM1 and the consequent hypoglycemia were the key mechanisms indirectly inducing dysfunction of α-cells in diabetes (107). Advanced molecular technology of the last decade has, however, challenged this notion, showing that dysfunction of α-cells in diabetes is not secondary to β-cell pathology but is instead directly immune-induced (108-110). Despite this dysfunction, α-cells exhibit a remarkable autoimmune resistance that enables them to survive over β-cells in long-standing diabetes (103,111). Recent studies using single-cell RNA sequencing (109,112) have demonstrated important differences between these two cell types in terms of expression of: i) anti-apoptotic genes, ii) endoplasmic reticulum (ER) stress-related genes, III) innate immune response genes, and iv) antiviral response genes, all of which render α-cells less immunogenic and more resistant to viral infections and ER stress (113). In addition, CD8+ T cells invading the islets in DM1 are reactive to preproinsulin but not to glucagon. Furthermore, although β-cells are essential to life (neither humans nor animal models can survive without them), mice with 98% α-cell ablation retain near-normal glucose homeostasis (114): this points to

the knowledge gap we have, from an evolutionary point of view, regarding the question of why β-cells are more fragile than α-cells. Certainly, greater understanding of the underlying mechanisms responsible for the autoimmune resistance of α-cells is critical since it is likely to reveal intracellular pathways amenable to therapeutic interventions that would increase the resistance of the β-cells themselves to the immune attack of the host's immune system.

Diabetes Type 2

DM2 accounts for 90% of cases of diabetes worldwide (115). The increasing prevalence of DM2 around the world has been largely attributed to an unhealthy lifestyle and resultant development of obesity and overweight (116). Obesity is strongly related to DM2 mainly through inducing insulin resistance in the insulin sensitive tissues in the periphery.

The concept that a smoldering inflammatory process plays an important part in the pathogenesis of DM2 (117) has attracted much attention and is supported by evidence of inflammation in islets, adipose tissue, liver, and muscle that can provoke insulin resistance and β-cell dysfunction (118-120). Adipose tissue is characterized by infiltration by macrophages and other immune cells that produce cytokines and chemokines and contribute to the development of local and systemic chronic low-grade inflammation, this inflammatory milieu being the link between obesity, insulin resistance, and diabetes mellitus (121,122).

Earlier in vivo studies demonstrated that levels of TNF-α (123-125), IL-6, C-reactive protein, plasminogen activator inhibitor, and other inflammation mediators were elevated in adipose tissue and plasma of obese mice (126,127). It was also observed that these inflammatory mediators, together with saturated free fatty acids and reactive oxygen species (ROS), inhibited serine phosphorylation of the insulin receptor substrates (IRS-1 and 2) (128-130) in insulin sensitive tissues, such as adipose tissue and the liver (131), promoting insulin resistance (Figure 6). TNF-α is associated with increased release of free fatty acids by adipose tissue and leads to impaired insulin secretion and signaling (123,132).

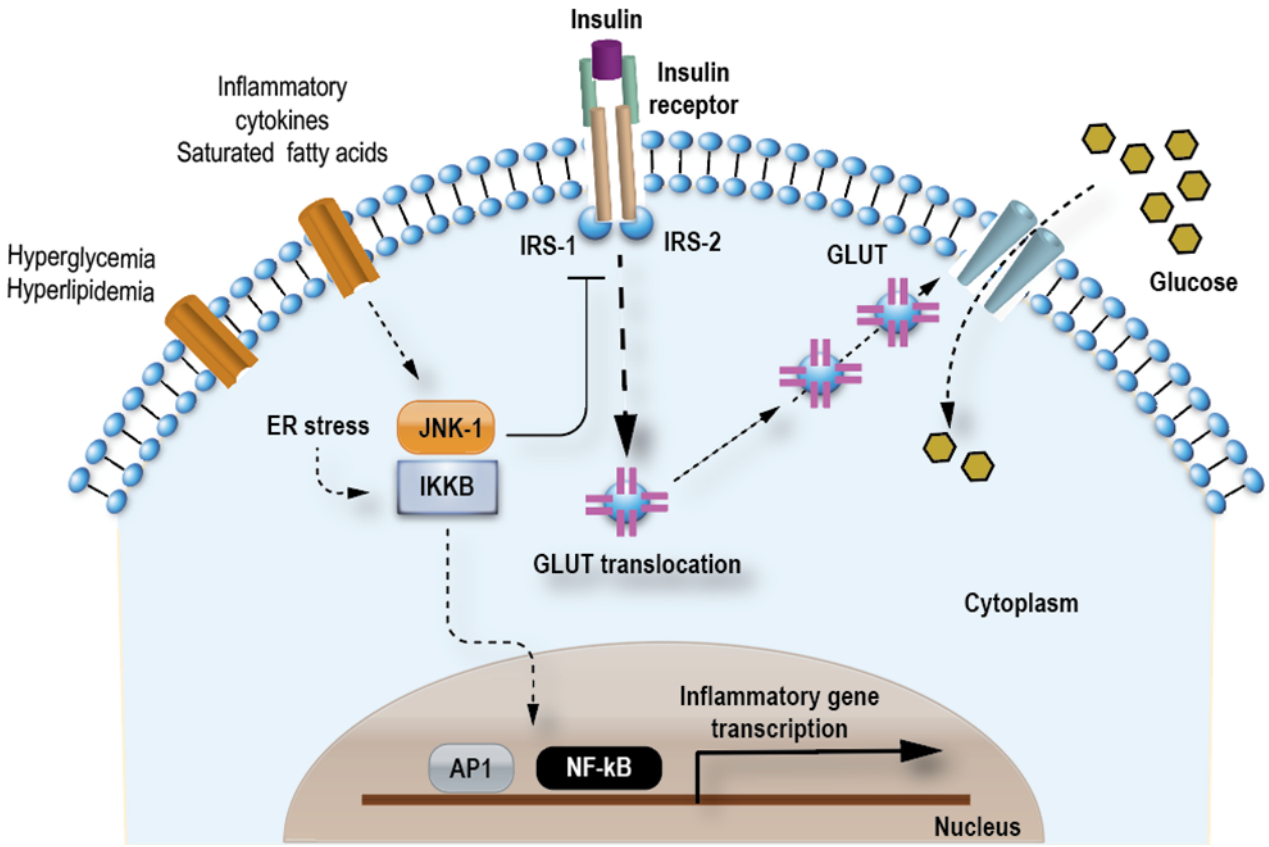

Figure 6. Insulin resistance and inflammation in diabetes type 2. Insulin binds to insulin receptor (IR) in insulin sensitive tissues, and autophosphorylates tyrosine molecules of IRS-1 and -2 substrates. In the presence of obesity, and hyperlipidemia, the influx of free fatty acids, inflammatory cytokines and glucose activates IKKβ and JNK, which are the mediators for stress and inflammatory. In turn IKKβ and JNK inhibit tyrosine phosphorylation of IRS1 and 2 and promote transcriptional activation of genes related to inflammatory and stress responses resulting in insulin resistance. [Modified by Berbudi et al (133)]. IRS 1 -2, insulin receptor substrates; ER, Endoplasmic reticulum; IKKβ, inhibitory kappa B kinase β; JNK1 and c-Jun N-terminal kinase I.

In line with these early in vivo studies, studies in humans have shown that elevated levels of i) nonspecific indicators of inflammation, such as white cell count, fibrinogen, and CRP levels (134-136), ii) markers of reduced fibrinolysis, such as plasminogen activator inhibitor-1 (PAI-1), and tissue plasminogen activator (tPA), iii) von Willebrand factor (vWf), which is a marker of endothelial injury, and iv) early markers of inflammation, such as monocyte chemotactic protein-1 (MCP-1), IL-8, and interferon-γ-inducible protein-10 (137), were predictive of DM2 development.

Furthermore, CRP and/or IL-6 were associated with the incidence of DM2 independently of adiposity or insulin resistance (136,138,139). Visceral adipose tissue appears to be a major source of circulating IL-6 in humans, and obese people with insulin resistance display high levels of plasma IL-6 concentration, also predictive of DM2 development (113). TNF-α is also increased in obese individuals with insulin resistance

(124,140) and it plays a major role in the pathogenesis of obesity-linked DM2 (141).

At the cellular level, chronic exposure of adipocytes to low doses of TNF-α led to a dramatic decrease in insulin-stimulated auto-phosphorylation of the IRS 1-2 (142). Treatment of cultured murine adipocytes with TNF-α induced serine phosphorylation of IRS-1 and convert IRS-1 into an inhibitor of IR tyrosine kinase activity in vitro. TNF-α has also been shown to downregulate glucose transporter GLUT4 mRNA levels in adipocyte and myocyte cultures as well (125,143,144).

Oxidative stress, as a result of increased cytokine levels in DM2, is also thought to play an important role in activating inflammatory genes (145,146) (Figure 6). It is possible that oxidative stress markers do not adequately reflect the impact of increased ROS on β-cells or insulin signaling, while inflammatory, procoagulant or endothelial dysfunction markers are more specific to the pathophysiology of hyperglycemia (145,146). Hasnain et al. showed that islet-endogenous and exogenous IL-22 suppressed oxidative and ER stress caused by cytokines or glucolipotoxicity in mouse and human β-cells by regulating oxidative stress pathways. 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 reinstitution of insulin sensitivity (147).

The chemokine system is also associated with obesity and insulin resistance. MCP-1, which acts on monocytes, macrophages, T cells and NK cells, is increased in obese compared to lean subjects and is related to non-alcoholic fatty liver disease and other lipid overload states (148-153). A short-term program of 4-month lifestyle modification significantly decreases MCP-1 levels, with favorable effects on the glycemic and lipid profile (151).

Collectively, these findings supported the investigation of new therapeutic approaches that target inflammation to ameliorate diabetes and its complications. Regarding the latter, it is important to note that multiple sources of evidence support a pathogenic connection between rheumatoid arthritis (RA) and the mechanisms of DM2, via formation of a vicious circle that is perpetuated by impaired glucose metabolism and inflammation. In this context, ongoing clinical studies have shown that the inhibition of interleukin IL-1 and IL-6 may allow the treatment of RA and concomitant T2D at the same time (154).

Treatment with anakinra, a recombinant form of human IL-1 receptor antagonist that works as a competitive inhibitor of IL-1β, achieved significant improvements of glycemia and secretory function of β-cells (155,156), which was maintained after anakinra withdrawal during a 39-week follow-up (157). Canakinumab, a monoclonal antibody against IL-1β, significantly reduced inflammatory proteins, such as CRP, IL-6, and fibrinogen, in patients with DM2 and high cardiovascular risk (158,159), while regarding glycemic control, it reduced values of HbA1c during the first 6–9 months of treatment, without, however, consistent long-term benefits (159). Antagonists of IL-6 receptor tocilizumab and sarilumab have also been investigated in patients with RA with or without concomitant DM2. Tocilizumab showed a positive effect on insulin resistance in some studies (160-162), while other studies failed to report any beneficial effect on glycemic control (163,164). The efficacy of sarilumab was assessed in a post hoc analysis (165) of three randomized clinical trials in patients with RA with or without DM2 (166-168). Sarilumab, as monotherapy or in combination, significantly reduced HbA1c compared to adalimumab monotherapy or

placebo plus methotrexate/convectional DMARDs in patients with RA and DM2 (165).

Several studies have analyzed the effects of TNF inhibitors (i.e., adalimumab, etanercept, and infliximab) on glucose metabolism, demonstrating a potential favorable effect on insulin resistance and insulin sensitivity (169,170). In a meta-analysis combining data from 22 randomized controlled trials and three cohort studies (171), new-onset DM2 was delayed in RA patients treated with TNF inhibitors.

The Effect of Diabetes on the Immune System

Like a mirror image, chronic hyperglycemia in diabetic patients impairs the host's immune response, which in turn fails to control the spread of invading pathogens, rendering diabetic patients more susceptible to infections (133,172). Both innate immune response defects and defective adaptive immune response are implicated in this incapacity of the immune system to defend against invading pathogens in patients with diabetes. Several mechanisms have been proposed by experimental and human studies including: i) leukocyte recruitment inhibition (173,174), ii) defective pathogen recognition (175), iii) dysfunction of neutrophils (176-178), macrophages resulting in impairment of phagocytosis (179), iv) functional defects in natural killer cells (180), and v) dysfunction of complement activation (181).

OSTEOPOROSIS AND THE IMMUNE SYSTEM

Osteoporosis is a clinical condition characterized by low bone mass and impaired bone microarchitecture associated with an increased risk of fragility fractures. Growing evidence of the last few decades has demonstrated the effect of the immune system on bone metabolism, leading to the emergence of the new field of osteoimmunology (182-185) and immunology of osteoporosis (named as immunoporosis) (184-188).

States of immune dysfunction such as immunodeficiency, inflammatory diseases, or immune response to infections are associated with increased osteoclastic bone resorption and, therefore, increased bone loss and increased fracture risk.

Bone Remodeling and Bone Cells

Bone remodeling is a dynamic and continuous process that is responsible for the maintenance of skeletal health throughout life. It involves three consecutive phases: i) osteoclast-mediated bone resorption; ii) the reversal phase, during which mesenchymal derived osteoblasts are recruited to the bone site of bone resorption; and iii) osteoblast-mediated bone formation. The two processes of bone resorption and bone formation are tightly coupled and under control of the matrix-embedded osteocytes, capable of sensing and integrating mechanical and chemical signals from their environment to regulate bone formation and resorption at the bone surfaces.

Osteoclasts originate from the same myeloid precursor that derives macrophage and dendritic cells and are specialized in bone degradation (186). Osteoblasts are the main bone-forming cells and are derived from mesenchymal stem cells. Osteoclast formation and differentiation is regulated by macrophage colony-stimulating factor (M-CSF) and the receptor activator of nuclear factor-kB (RANK) ligand (RANKL) produced by osteoblasts and osteocytes (189,190). Osteocytes are a significant source of RANKL and its decoy receptor, osteoprotegerin (OPG), which binds to RANKL, preventing its interaction with RANK, while they also secrete the Wnt signaling inhibitor sclerostin, which regulates bone formation (189). RANKL is additionally expressed by fibroblasts and immune cells, including antigen-stimulated T cells and dendritic cells (191-193), while OPG is also produced by B lymphocytes and dendritic cells (194).

Inflammatory Diseases

Activated T cells increase the production of TNF-α and RANKL and stimulate osteoclastogenesis during inflammation (182-185,192-195). Multiple cytokines may promote osteoclastogenesis mainly by regulating the RANK/RANKL/OPG axis. TNF-α, IL-1, IL-6, IL-7, IL-11, Il-17, and IL-23 promote osteoclast differentiation, while IFN-α, IFN-γ, IL-3, IL-4, IL-10, IL-27, and IL-33 are considered anti-osteoclastogenic cytokines that protect bone integrity (195). Th17 cells are considered an osteoclastogenic subset of T cells as they enhance osteoclastogenesis by secreting IL-1, IL-6, Il-17, RANKL, TNF-α, and IFN-γ. Activation of Th2 leads to enhanced production of PTH and promotes the anabolic activity of osteoblasts in several inflammatory states. Furthermore, Th2 lymphocytes are associated with a low RANKL/OPG ratio and inhibition of bone loss (196). In addition, β-cells produce RANKL and OPG and may influence bone formation and absorption, while it has been observed that in HIV infected patients, there is an altered β-cell RANKL/OPG ratio that is inversely correlated with BMD (197).

Interleukin 6, produced by both stromal and osteoblastic cells (198) in response to stimulation by systemic hormones such as PTH, PTH-related peptide (PTH-rP), thyroid hormones, and 1,25-dihydroxyvitamin D3 and other cytokines (i.e., TGF-β, IL-1, and TNF-α), plays a major role in osteoclast development and function. Increased IL-6 levels contribute significantly to the abnormal bone resorption observed in patients with multiple myeloma (199), Paget's disease of bone (200), rheumatoid arthritis (201), and Langerhans cell histiocytosis (202). Effects of increased osteoclast-induced bone resorption are not solely attributable to IL-6, but to all IL-6 family cytokines (203).

TNF-α has also been shown to induce bone resorption and plays an important part in inflammatory bone diseases (192). TNF-α promotes RANKL expression in osteoclast precursors and the formation of multinucleated osteoclasts in the presence of M-CSF. Furthermore, TNF-α increases RANKL and M-CSF expression in osteoblasts, stromal cells, and T lymphocytes, while RANKL can also enhance TNF-α mediated osteoclastogenesis (195). IL-1β increases RANKL expression and stimulates osteoclast formation and bone resorption while also promoting TNF-α induced osteoclastogenesis (204,205).

Postmenopausal Osteoporosis

Estrogen deficiency is a state of increased bone remodeling associated with an increased rate of bone resorption relative to bone formation, resulting in net bone loss. It has been shown that estrogen deficiency-induced bone loss has a complex mechanism mainly involving the immune system rather than a direct effect of estrogen on bone cells (206). Estrogen loss during menopause is associated with an expansion of T and B lymphocytes (207,208) leading to increased production of RANKL (209). In addition, an increased level of proinflammatory cytokines, including TNF-a and IL-1b, is observed in postmenopausal women (210,211). In addition, B lymphocytes may partially contribute to trabecular bone loss in postmenopausal osteoporosis (212). In the absence of estrogens, dendritic cells live longer, increasing their expression of IL-7 and IL-15. In turn, IL-7 and IL-15 induce IL-17 and TNF-a production in a subset of memory T cells, independent of antigen activation (213). These proinflammatory cytokines contribute to inflammation-induced bone loss in postmenopausal osteoporosis by activating low-grade inflammation. In contrast, Treg cells have a bone-protective role in postmenopausal osteoporosis (210). However, it has been shown that Th17/Treg balance is disturbed in estrogen deficiency. Treg cells lose their immunosuppressive function and convert to Th17 cells, which explains the imbalance of Th17/Treg in postmenopausal osteoporosis (214).

Senile Osteoporosis

Senile osteoporosis, on the other hand, is a low-bone turnover disease with decreased bone resorption and significantly reduced bone formation (215), which commonly occurs in older people, above 65, and affects both males and females. In recent years, it was demonstrated that aging is usually accompanied by systemic low-grade chronic inflammation and enhanced inflammatory mediators, such as IL-6 and TNF-a (216). A recent study found that senescent immune cells, such as macrophages and neutrophils, accumulate in bone marrow during aging in rats and mice (217). The senescent macrophages and neutrophils repress osteogenesis by promoting bone marrow mesenchymal stromal cell adipogenesis. In addition to directly inhibiting osteogenesis, the senescent immune cells contribute to chronic inflammation, thus leading to inflammatory bone resorption (217). Aging can tilt the balance of Th1/Th2 toward Th2 cells, resulting in an increased inflammatory response (218) and low-level chronic inflammation, ultimately leading to continuous bone loss.

Thyrotoxicosis-Induced Osteoporosis

IL-6 and IL-8 play a major role in thyrotoxicosis-induced osteoporosis and are increased in patients with thyrotoxicosis due to Graves' disease or toxic multinodular goiter (219). In addition, patients with thyroid carcinoma on TSH suppressive therapy have significantly increased circulating levels of IL-6 and IL-8 compared to controls (219), which are tightly associated with serum T3 and fT4 concentrations. 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 (196). TNF-α elevations due to low TSH signaling in human hyperthyroidism also contribute to the bone loss that has traditionally been attributed solely to high thyroid hormone levels (220). Hyperthyroid mice lacking TSHR had greater bone resorption than hyperthyroid wild-type mice, demonstrating that the absence of TSH signaling contributes to low bone mass (221) in the hyperthyroid state.

Primary Hyperparathyroidism-Induced Osteoporosis

Bone resorption in primary hyperparathyroidism (PHP) also appears to be related to immune system effects. Circulating levels of IL-6 and TNF-α, which are significantly increased in patients with PHP, are strongly correlated with biochemical markers of resorption, returning to normal after successful parathyroidectomy (222). The hypothesis that IL-6 mediates the catabolic effects of parathyroid hormone (PTH) on the skeleton has been further strengthened by the finding that neutralizing IL-6 in vivo attenuates PTH-induced bone resorption in mice, while the resorptive response to PTH was also reduced in IL-6 knockout mice (223). Furthermore, it has been observed that transplantation of parathyroid from humans with hyperparathyroidism to mice lacking T cells was not associated with bone loss, suggesting a possible role of T lymphocytes in PTH-related osteoporosis (224). A direct action of PTH on T lymphocytes may also contribute, as deletion of the PTH receptor from T cells failed to induce bone loss (225). It has been proposed that PTH action on T cells results in secretion of TNF-α and, in combination with RANKL increase and OPG suppression, guides their differentiation to Th17 subsets, with subsequent IL-17 secretion and further RANKL amplification (226).

Drug-Induced Osteoporosis

The immune cells are also involved in drug-induced osteoporosis, such as glucocorticoid and chemotherapy-induced osteoporosis. A recent study demonstrated that glucocorticoid-induced osteoporosis could not be induced in T cell-deficient mice, while re-establishment was found to be possible

by transferring splenic T cells from wild-type mice (227).

Cyclophosphamide, is a chemotherapy drug that causes immunosuppression and is associated with increased risk of osteoporosis (228-230). By improving the functional status of immune cells in an immunosuppressive mouse model induced by cyclophosphamide, bone loss was dramatically reduced (231), pointing to the possible contribution of immune cells in cyclophosphamide-induced osteoporosis.

EFFECTS OF THE IMMUNE SYSTEM ON THE STRESS SYSTEM

The Hypothalamic-Pituitary-Adrenal (HPA) Axis

The relations between the immune and the stress systems are complex and bidirectional, denoting that while stress can affect immune function, immune responses can also influence stress levels through various ways and mechanisms.

INFLAMMATION

During acute inflammation, the immune system is activated in response to infection or injury and releases proinflammatory cytokines and other inflammation-related factors into the central nervous system (CNS), plasma, and endocrine glands. Inflammatory cytokines, such as TNF-α, IL-1, and IL-6, produced by a variety of cells, including monocytes, macrophages, astrocytes, endothelial cells, and fibroblasts, activate the HPA axis leading to an increase of corticotropin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH) and, finally, glucocorticoids (38, 184). In turn, increased circulating levels of glucocorticoids exert suppressive effects on the inflammatory reaction, controlling the immune response and helping the organism to reach its prior healthy homeostasis (232). Similarly, in acute stress, the amplitude and synchronization of CRH secretory pulses is increased, and this is reflected in the levels of ACTH and cortisol in the systemic circulation (233).

The proinflammatory cytokine IL-1, especially its β form, is probably the most important molecule capable of modulating cerebral functions during systemic and localized inflammation. Systemic IL-1β 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 (234). Similarly to 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 (235). All three inflammatory cytokines (IL-1, IL-6, and TNF-α) have the capacity to activate the HPA-axis, but it appears that IL-6 is the most critical component of this cascade. Studies in rats have demonstrated that immunoneutralization of IL-6 abolishes the effects of the other two cytokines on the HPA-axis (236). TNF-α and IL-1, on the other hand, stimulate the production of IL-6, which in turn stimulates the HPA-axis. The final end-product of HPA activation, glucocorticoids, inhibit IL-6 secretion at the transcriptional level through interaction of the ligand-activated glucocorticoid receptor with nuclear factor-kappa B, creating a negative feedback loop. In this way, IL-6 stimulates glucocorticoid release to control inflammation, and glucocorticoids subsequently inhibit IL-6 release through a negative feedback loop preventing uncontrolled and potentially harmful sequalae of inflammatory mechanisms, including tissue damage (237,238).

In an older study involving patients with Cushing disease studied before and after transsphenoidal adenectomy, plasma IL-6 concentration was increased when patients were hypocortisolemic, experiencing symptoms of glucocorticoid deficiency, as part of the “steroid withdrawal syndrome” (i.e.,

pyrexia, headache, anorexia, nausea, fatigue, malaise, arthralgias, myalgias, and somnolence of variable degree). Notably, IL-6 levels did not increase in patients who did not become hypocortisolemic after surgery, while following glucocorticoid replacement, a dramatic decrease of IL-6 levels concomitantly with relief of the observed symptoms was reported (239).

While acute stimulation with IL-6 activates the HPA axis mainly through the hypothalamic CRH neurons, chronic exposure to IL-6 may also directly stimulate the pituitary corticotropic cells and the adrenal cells via CRH receptor-independent mechanisms (240).

In vivo experiments have shown a stimulatory effect of IL-6 on cortisol production by the adrenal cortex in the absence of CRH and subsequent activation of the HPA axis (240) in cytomegalovirus-infected mice (241), as well as in murine colitis (242). In addition, experiments in mice deficient in CRH (CRH KO) and deficient in both CRH and IL-6 (CRH KO)/IL-6 KO) have demonstrated that IL-6 during prolonged immunological challenge may surpass CRH in augmentation of adrenal function (240). Protein expression of IL-6 and IL-6 receptor has been detected in primary cultures of human adrenocortical cells depleted of macrophages (CD68-positive cells), predominantly in the zona reticularis but also in the zona fasciculata and in single cells within the zona glomerulosa and the medulla (243). Moreover, IL-6 was able to induce adrenal steroidogenesis in vitro in a time- and dose-dependent manner in the absence of macrophages, suggesting that IL-6 may be a long-term stimulator of steroidogenesis but with no acute effects (243).

In humans, IL-6 may stimulate cortisol release directly at the level of the adrenal gland in long-term stress situations (244), and the same may also apply in chronic inflammatory diseases, although direct evidence is still lacking (245). In a recent clinical study, increased daily, and especially evening, saliva cortisol secretion, in the context of the acute viral infection COVID-19, appeared to be mostly driven by hypersecretion of IL-6, independently of ACTH (246). However, the hypothesis that IL-6 may partially replace ACTH when there is an acute requirement for increased cortisol secretion has yet to be tested.

PROLONGED OR CHRONIC STRESS AND INFLAMMATION

Acute versus chronic stress and inflammation are distinct conditions that exert extremely different effects on the immune system, each altering its function in a distinct manner. Chronic stress is associated with a blunted circadian cortisol rhythm, a suppressed inflammatory response, and a shift from Th1 to Th 2 and a Th reg to Th 17 immunity. It has clearly been shown that in chronic stress, endogenous glucocorticoids fail to terminate the stress response and, in fact, cause body composition changes reminiscent of those in hypercortisolism, such as visceral adiposity, sarcopenia, and osteoporosis (247-249).

On the other hand, following a period of intense stress, there may be glucocorticoid-induced suppression of the HPA axis (238). In this case, long-term “inadequate” cortisol secretion may unleash its inhibitory effect on immune system activation, resulting in immune dysregulation and expression of sickness-syndrome manifestations. In this case, the post-stress sustained HPA axis suppression and hypocortisolism is reminiscent of the clinical picture of the intrinsic hypocortisolemia of primary adrenal insufficiency (Addison’s disease), associated with immune perturbations due to failure of cortisol to appropriately suppress the increased secretion of proinflammatory cytokines (239,250).

The subsequent protracted lack of axis recovery due to a post-illness state of hypocortisolism in probably predisposed individuals may explain the underlying

pathophysiologic mechanisms responsible for some post-viral infection sickness syndromes (232,251), such as long COVID syndrome (252).

AUTOIMMUNE DISORDERS

In some cases, chronic stress can contribute to the development or exacerbation of autoimmune disorders. Without appropriate cortisol regulation in cases of chronic stress and chronic inflammation, the organism fails to downregulate inflammatory processes, contributing to a vicious cycle where stress, inflammation, and compromised HPA axis function may result in the development of chronic immune-mediated inflammatory diseases, such as rheumatoid arthritis. Stress can potentially trigger or worsen these conditions by dysregulating the immune response.

Cortisol diurnal secretion displays a circadian rhythm in healthy individuals, with the highest levels in the morning and a gradual decline throughout the day, reaching the lowest levels around midnight (253). During acute stress (254-256) or infection (237,257), the rhythm is disturbed and the afternoon and/or midnight cortisol levels do not drop. A disturbed circadian cortisol rhythm with abnormally high afternoon and night cortisol levels was found in patients with even mild or moderate COVID-19 compared to healthy controls (246). However, although not systematically studied, the adrenal response to chronic versus acute exposure to proinflammatory cytokines appears to follow a different pattern.

In patients with rheumatoid arthritis, symptoms follow circadian rhythms with impaired function due to pain and joint stiffness being most severe in the early morning (258,259) because of increased proinflammatory cytokines, such as TNF-a and IL-6, that occur during late night hours (260,261). This explains the inverse relation between diurnal variation of circulating IL-6 and glucocorticoid levels (262). Increased endogenous nocturnal secretion of cortisol could alleviate these morning symptoms, but this is not the case in most patients with rheumatoid arthritis (263-270). To clarify this issue, several studies have been carried out reporting that the optimal time for delivery of glucocorticoid treatment would be during the night in order to target the effects of nocturnal proinflammatory stimuli (271-274).

PSYCHOLOGICAL WELL-BEING

The immune system also plays a role in maintaining overall psychological well-being. Chronic stress and its impact on the immune system can increase susceptibility to mental health problems such as anxiety and depression. Conversely, psychological well-being can improve the human body's immune responses, enhance resistance to diseases (including infectious diseases), and improve mental health (275,276). Changes in psychological status of patients with Alzheimer's induced significant differences in their immune response (277).
In addition, long-term practice of meditation was shown to decrease stress reactivity and exert a favorable therapeutic effect in chronic inflammatory conditions characterized by neurogenic inflammation (278), while joyful activities such as singing were able to boost the immune response in cancer patients and family members (279).

ADRENAL MEDULLA

The chromaffin cells of the adrenal medulla play a role in stress response by secreting catecholamines and various biologically active peptides (238). As the stress response starts, rapidly augmented secretion of norepinephrine and epinephrine is initiated, followed by activation of the HPA axis and increased release of CRH and ACTH and secretion of glucocorticoids (280). CRH and norepinephrine stimulate the

secretion of each other through CRH-R1 and α1-noradrenergic receptors, respectively (281).

Cytokines TNF-α, IL-1, and IFN-γ act directly on chromaffin cells (282-285). It has also been demonstrated that cytokines regulate the secretion of various peptides that are co-secreted with catecholamines, such as vasoactive intestinal peptide (VIP), galanin and secretogranin II, enkephalin and neuropeptide Y (283,285). IL-6 directly modulates the secretion of catecholamines and neuropeptides by chromaffin cells and therefore influences the adrenal stress response. It has been hypothesized that medullary peptides may serve as paracrine modulators of glucocorticoid production (286). It has also been shown that IL-6 increases intracellular Ca2+ concentration and induces catecholamine secretion in rat carotid body glomus cells, a finding which has finally confirmed the relations between IL-6 and catecholamine secretion (287). Furthermore, IL-10 is a critical target downstream of epinephrine and norepinephrine which limits inflammation (288). On the other hand, norepinephrine may act directly on macrophages and dendritic cells to suppress inflammatory cytokine secretion through primarily the β2-adrenergic receptors that are expressed by both innate and adaptive immune cells (289,290).

Although scientific advances of the last decade have shed light on the previously unrecognized major role of the catecholamines epinephrine and norepinephrine in controlling the immune system, much remains to be discovered, and further revelations will reveal new therapeutic targets in the management of inflammation.

ACKNOWLEDGEMENTS

This chapter is an update of a previous chapter and the authors would like to thank Professor Gregory Kaltsas, an author of the prior chapter.

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