sciendo

PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B,
Vol. 73 (2019), No. 2 (719), pp. 67–77.

DOI: 10.2478/prolas-2019-0012

Review

IMMUNOLOGICAL MECHANISMS OF AUTOIMMUNE THYROID DISEASES: A SHIFT IN THE TRADITIONAL TH1/TH2 PARADIGM

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Communicated by Aivars Lejnieks

Autoimmune thyroid diseases (AITD) mainly include Hashimoto's thyroiditis (HT) and Graves' disease (GD), which are characterised by the presence of circulating antibodies against various thyroid autoantigens and infiltration of the thyroid gland by autoreactive lymphocytes. Despite the significant advancement in the knowledge of AITD pathogenesis in the last decade, the specific immunological mechanisms responsible for development of the disease are not thoroughly understood. Classically, HT has long been considered as a T helper (Th)1-mediated disease, while a Th2-driven autoimmune response is dominant for GD development. However, this classification has changed due to the description of Th17 lymphocytes, which suggested participation of these cells in AITD, particularly HT pathogenesis. Moreover, a shift in the balance between Th17 and T regulatory (Treg) cells has been observed in thyroid autoimmunity. We have observed overexpression of IL-17, the prominent effector cytokine of Th17, within thyroid tissues from HT and GD patients in our studies. The present review will focus on recent data regarding the role of Treg and Th17 lymphocytes in AITD pathogenesis. In addition, the impact and proposed mechanisms of the predominant environmental factors triggering the autoimmune response to the thyroid will be discussed.

Key words: *Hashimoto's thyroiditis, Graves disease, T helper 17 cell, T regulatory cell, environmental factors.*

INTRODUCTION

Autoimmune thyroid diseases (AITD) present with two pathogenetically different diseases: Hashimoto's thyroiditis (HT) and Graves' disease (GD). These two are clinically diverse and taken together make thyroid condition the commonest autoimmune disease. However, there is significant geographic variation in the worldwide reported incidence and prevalence of HT and GD. AITD prevalence is about 5% in the overall population, whereas the prevalence of thyroid antibodies is estimated to be 10–20% of all women (Hollowell *et al*., 2002; Pyzik *et al*., 2015). The worldwide incidence of HT is reported to be 0.3–1.5 cases per 1000 persons per year (Latina *et al*., 2013). Furthermore, HT is the most common cause of primary hypothyroidism in iodine-sufficient regions. Like most autoimmune disorders AITD exhibits a strong female bias in prevalence: HT affects women five to ten times more (Pyzik *et al*., 2015), and GD four to five times more often than men (Carlé *et al*., 2011). It is also known that the prevalence of thyroid autoimmunity increases with age reaching the highest number of cases between 45–65 years in HT and between 33–50 years in GD (Cooper and Stroehla, 2003).

The prevalence and incidence of autoimmune diseases, including AITD, has increased significantly over the last decades. AITD has become a public health problem worldwide, including in Latvia. In our previous study of iodine deficiency during pregnancy, it was revealed that 10.7% of the 739 pregnant women participating nationwide had elevated

thyroperoxidase antibody (TPOAb) levels suggesting preexisting thyroid autoimmunity (Konrade *et al*., 2015). Furthermore, data on thyroid medicinal product use trends from the Latvian National Health Service and State Agency of Medicines showed a steady increase in the number of people using thyroxine and thiamazole: thyroid therapy defined daily dose (DDD) per 1000 inhabitants increased from 10.23 in 2009 to 17.40 in 2017, thereby extremely increasing disease burden on health, health costs, education, society and family life (Anonymous, 2018).

AITD are characterised by the presence of circulating antibodies against thyroid autoantigens and infiltration of the thyroid gland by autoreactive lymphocytes (Tomer, 2014). Interestingly, although TPOAb and thyroglobulin antibodies (TgAb) are detected in 90–95% and 70–80% of AITD patients, respectively, the prevalence of both antibodies in patients with non-thyroid immune diseases is 10–15% (Carvalho *et al*., 2013). HT results predominantly from the cellular immune response, which involves T helper (Th)1 and Th17 cells and leads to cell death of the thyrocytes with subsequent hypothyroidism, whereas GD mainly promotes Th2-related humoral autoimmunity causing production of TSH receptor (TSHR) antibodies and growth of the thyrocytes leading to the development of hyperthyroidism (Morshed *et al*., 2012). However, both thyroid disorders may coexist in the same individual causing mixed Th1/Th2/Th17 immune responses.

Various environmental and endogenous factors may act together to trigger thyroid autoimmunity in persons with predisposing genetic variants causing elevated thyroid autoantigen presentation and a loss of immune tolerance. Despite numerous studies undertaken and knowledge accumulated on the aetiology and pathogenesis of AITD in the last decade, the specific immunological mechanisms responsible for development of the disease are not thoroughly understood.

GENETIC SUSCEPTIBILITY

The role of genetic background in the aetiology of AITD is highlighted by numerous epidemiological studies showing that genetic factors contribute in about 70–80% cases the development of thyroid autoimmunity (Tomer and Davies, 2003; Hansen *et al*., 2006). The familial clustering of AITD was confirmed by several studies 50 years ago. It has been shown later that almost 50% of the siblings of GD patients have thyroid autoantibodies and that 33% of those with HT or GD develop AITD themselves (Villanueva *et al*., 2003). Increased familiar clustering of AITD has been reported in German study indicating a 32-fold enhanced risk for developing HT in children and a 21-fold enhanced risk in siblings of patients with HT (Dittmar *et al*., 2011).

During the last decades, a number of twin studies have examined the aetiology of several phenotypes related to AITD and have provided new data on the genetic contribution to AITD. A strong influence of genetic factors on the development of AITD has been demonstrated by twin studies as well — the heritability of GD and thyroid autoantibody (TPOAb and TgAb) formation has been reported to be 79% and 73%, respectively (Brix *et al*., 2001; Hansen *et al*., 2006). A study of Hashimoto's hypothyroidism showed 55% and 0% concordance in Danish monozygotic and dizygotic twins, respectively, indicating an essential role of environmental factors in development of the disease (Brix *et al*., 2000). Thus, twin studies have shown that 21–27% of the total phenotypic variance in AITD can be explained by environmental factors.

Therefore, it is critical to investigate and identify the possible interplay of environmental and genetic factors involved in thyroid autoimmunity to propose individualised AITD management strategies, since most environmental factors may be modified. However, the mechanisms by which the environmental factor trigger thyroid autoimmunity in individuals with known susceptibility loci remain unclear. The main known susceptibility genes for AITD can be classified as either immunoregulatory or thyroid-specific genes (Effraimidis and Wiersinga, 2014). TSHR and Tg were recognised as thyroid-specific genes, whereas the human leukocyte antigen (HLA), PTPN22, CTLA-4, FOXP3, FCRL3, CD25, CD40, and other genes as immune-modulating, playing a critical role in the development of the effective immune response including self-tolerance, and cell-mediated and humoral immunity. However, single nucleotide polymorphisms in these genes, which are not specific for AITD were recognised as risk factors for other autoimmune diseases (Lee *et al*., 2015). Tg is one of the main thyroid autoantigens assumed as a major susceptibility gene for AITD (Tomer *et al*., 2002). Whereas in GD patients, a consistent association with polymorphisms of the TSHR gene was reported (Xiong *et al*., 2016).

The occurrence of both AITD is associated with specific variants of the HLA class II genes. They are vital for regulating immune activity by determining the antigen binding specificity and the initiation of the immune response. HLA controls cytokine production and modulates the immune response by cytokine genes on haplotypes as well. Thus, polymorphisms in the HLA genes may lead to HT or GD via regulating the Th1/Th2 and possibly Th17 pathways. HLA-DQA1 and HLA-DR3 were shown to be associated with GD, while polymorphisms in HLA-DR3, DR4, DR5, DQ7, DQB1, DQA1, DQW7 were correlated with the incidence of HT (Zeitlin *et al*., 2008; Badenhoop *et al*., 1990).

Numerous susceptibility genes and loci for AITD have been detected by genome-wide association studies (GWAS) during the last decade. However, these studies involve mainly single genetic factors, which might have a minor effect on the disease development and only the simultaneous presence of certain genetic and environmental factors altogether may lead to the clinical manifestation of the thyroid autoimmunity. Therefore, GWAS should focus on simultaneous investigation of multiple genetic and environmental factors and interactions between them.

PROTECTION AGAINST THYROID AUTOIMMUNITY

Mechanisms of central and peripheral tolerance provide proper regulation of the immune system thus protecting against thyroid autoimmunity. Maturation of T helper CD4+ lymphocytes occurs in the thymus via processes of positive and negative selection. Central immune tolerance refers to apoptosis of autoreactive T cells in the thymus during the foetal life. T cells that escape negative selection are prevented from triggering autoimmunity by mechanisms of peripheral tolerance where T regulatory cells (Treg) play a crucial role (Weetman, 2010; Shevach, 2006). Their protective role has been also demonstrated in several animal models of autoimmune diseases (Morris et *al*., 2009).

Treg cells derive from the thymus as a subpopulation of fully differentiated T cells (thymus-derived Treg), naive Th0 cells in the peripheral tissues (peripheral differentiated Treg) or develop *in vitro* conditions (iTregs) (Shevach and Thornton, 2014). The first properly characterised Treg cell subset exhibits expression of the transcription factor forkhead box protein 3 (Foxp3) and high constitutive levels of į chain of the IL-2 receptor (CD25). Foxp3 contributes to the maintenance of self-tolerance by promoting development of Treg while inhibiting the differentiation of Th17 cells (González-Amaro and Marazuela, 2016). Foxp3 mutations in humans can cause an allotropic syndrome of multi-organ autoimmunity such as IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome. Several studies evidenced a defective function of Foxp3+ Treg cells in patients with HT and GD (Glick *et al*., 2013).

Treg cells have been shown to suppress target cells by direct cell-to-cell interaction or secretion of inhibitory cytokines such as transforming growth factor β (TGF-β), interleukin (IL)-10, and IL-35. IL-10 induces suppression of pathogenic Th17 cell responses and maintains Treg suppressive activity and expression of Foxp3, TGF-β regulates differentiation, proliferation and survival of lymphocytes, while the exact role of IL-35 requires further investigation (Chaudhry *et al*., 2011; Huber *et al*., 2011).

Another subset of Treg cells recently described demonstrates constitutive expression of CD69 but does not express Foxp3 or CD25. These cells exert their immunosuppressive activity mainly through the production of IL-10 and TGF-β (Han *et al*., 2009). Interestingly, increased levels of CD69+ Treg cells were found in both peripheral blood and thyroid tissue of AITD patients. However, these lymphocytes were dysfunctional and unable to effectively down-modulate the autoimmune process and tissue damage, thus suggesting their role in the pathogenesis of autoimmune diseases (Rodríguez-Muñoz *et al*., 2016). Finally, Foxp3- IL-10 secreting type 1 regulatory (Tr1) cells have been shown to inhibit T cell activity by different mechanisms, such as inhibitory cell-cell interactions via cytotoxic T lymphocyte antigen-4 (CTLA-4) or programmed cell death protein-1 (PD-1) and secretion of granzyme B and perforin (Roncarolo *et al*., 2014).

Several studies have found decreased frequency and/or a defective function of Treg in patients with HT or GD (Li *et al*., 2016) and highlighted the essence of results previously observed in animal models. Although the number of Treg cells reported is variable due to use of different detection markers and estimations related to disease stages, the majority of studies suggest that the reduction or functional defects of Treg is tightly associated with the development of thyroid autoimmunity. Recently, a possible role of regulatory B cells (Breg) in the maintenance of peripheral tolerance and inhibition of immune responses to specific self-antigens via release of IL-10, TGF-β, Fas ligand, and tumour necrosis factor (TNF)-related apoptosis inducing ligand has been established as well (Kristensen *et al*., 2015). Thus, both Treg and Breg cells may act as inhibitors of inflammatory and autoimmune responses to prevent autoimmunity. In certain individuals, however, autoreactive T lymphocytes escape from the control of these immunoregulatory mechanisms and may lead to loss of the peripheral self-tolerance with subsequent development of autoimmune disease via activation, proliferation and differentiation. Reduction of peripheral self-tolerance occurs due to enhanced Th17 cell response as compared with induced regulatory Th10 cell response (Papp *et al*., 2017).

PATHOGENESIS OF AITD

Thyroid autoimmunity appears as a result of the breakdown or reduction of self-tolerance to the three major thyroid proteins — TPO, TG, and TSHR occurring in the central or peripheral organs of the immune system. This causes the infiltration of the thyroid gland by T and B lymphocytes followed by production of AITD specific antibodies, induction of the thyrocyte apoptosis and the gland destruction in HT. Although traditionally the pathogenesis of HT is due to T cell-mediated autoimmunity and GD is a result of humoral autoimmunity, cellular and humoral immune responses are closely connected and cross-linked (Ramos-Leví and Marazuela, 2016). Despite comprehensive research in the last decades, the exact mechanisms of initiation and progression of thyroid autoimmunity have not been completely established.

The genetic background, self-antigens, and various environmental triggers together determine features of the autoimmune response in AITD and cause the enhanced thyroid antigen presentation and reduction of immune tolerance. Antigen-presenting cells (APC), and especially dendritic cells colonising the thyroid gland, present specific thyroid antigens to T lymphocytes via the MHC complex in the lymph nodes. This results in activation and proliferation of autoreactive T and B lymphocytes, and production of different cytokines by immune and thyroid cells. In fact, dendritic cells may be functionally subdivided into two groups — immunogenic or tolerogenic — depending on the activation of autoreactive T-cells or Treg, respectively (Maldonado and von Andrian, 2010). Moreover, several studies have revealed increased levels of dendritic cells within inflammatory infiltrates of the thyroid in both GD and HT patients

(Roura-Mir *et al*., 2005; Mao *et al*., 2011). Once activated, T helper (CD4+) cells can be differentiated into at least four main functional subsets according to the production of specific cytokines — Th1, Th12, Th17, and Treg. The development of the Th1 population is stimulated in the presence of either IL-12 or interferon (IFN)-γ through transcription of T-bet, whereas differentiation of Th2 cells is driven by IL-4 via the master transcription factor GATA3 (Peck and Mellins, 2010).

Classically, HT has long been considered as a Th1-mediated disease, while a Th2-driven autoimmune response is dominant for GD development. However, this classification has changed due to the description of Th17 cell, which suggested an evident participation of these cells in AITD, and particularly HT pathogenesis. In HT, increased Th1 activity caused by upregulation of pro-inflammatory cytokines such as IL-2, IL-1b, IFN-γ, TNF-α leads to cell-mediated immunity and thyrocyte death in apoptotic pathways. Thus, autoreactive Th1 cells recruit CD8+ cytotoxic T cells, which cause thyrocyte apoptosis by action of granzyme and perforin. In addition, autoreactive T lymphocytes induce antibody production by B cells leading to necrosis of thyroid cells by complement system activation. Finally, thyrocytes can undergo caspase-mediated apoptotic death in a paracrine way by expression of the CD95/Fas death receptor (Fröhlich and Wahl, 2017). Although the contribution of anti-TPO antibodies to destruction of the thyroid gland compared to cytotoxicity is minor, autoantibodies have shown pathogenic effects including complement activation and induction of oxidative stress, indicating that HT is also a Th2-mediated disease. Moreover, it has been revealed that anti-TPO antibodies can cause damage of cultured thyroid cells performed upon binding to TPO located on the apical cell membrane via both antibody-dependent cytotoxicity and complement-dependent cytotoxicity (Rebuffat *et al*., 2008).

In GD, there are increased levels of Th2 released cytokines IL-4, IL-5, IL-6, IL-10, IL-13, which mainly mediate humoral response by stimulating production of TSH receptor antibodies, growth of the thyrocytes and apoptosis of the thyroid gland infiltrating lymphocytes via downregulation of Fas/Fas ligand and upregulation of the anti-apoptotic molecule Bcl-2 (Berger, 2000; Salmaso *et al.*, 2002). Also, antibodies to TPO and, less frequently, to Tg have been identified in most GD patients. Furthermore, TPO and Tg autoantibodies may comprise immunoglobulin (Ig) G4 as well as IgG1 subclasses, suggesting the participation of both Th2 and Th1 cytokines in GD.

During the last decade, a role of a new subset of Th cells, designated Th17, has been studied in the pathogenesis of thyroid autoimmunity, thus changing the traditional paradigm of Th1/Th2 dichotomy. Several research groups have shown that IL-17A, the prominent effector cytokine of Th17, can induce the release of different pro-inflammatory cytokines responsible for induction and development of chronic inflammatory responses in many autoimmune diseases including AITD.

TH17 CELLS AND THYROID AUTOIMMUNITY

The discovery of a third Th subset has introduced a new understanding of the classical Th1 and Th2 dichotomy. Th17 cells and their hallmark cytokine IL-17 were found to play an important role in the pathogenesis of different inflammatory and autoimmune diseases, which were previously classified as Th1-dependent pathologies. An altered balance between Th17 and Treg cells as well as Treg cell dysfunction has been found in autoimmune diseases (Papp *et al*., 2017). Previous studies have shown a significant increase of Th17 cells and IL-17, revealed in the peripheral blood and thyroid tissues of AITD patients when compared to control subjects, suggesting their contribution to thyroid autoimmunity. Li and colleagues revealed an increased number of thyroid tissue infiltrating Th17 cells and serum levels of IL-17 in patients with HT compared to the thyroid cancers, nodular goiters or healthy controls. Additionally, a strong association between IL-17 expression and stromal fibrosis was observed in HT patients (Li *et al*., 2017). Furthermore, Figueroa-Vega *et al.* observed enhanced levels of Th17 cells and IL-17 mRNA in peripheral blood and thyroid tissue infiltrating inflammatory cells in patients with HT, along with higher levels of IL-6, IL-15, and IL-23, which are involved in the Th17 cell differentiation (Figueroa-Vega *et al*., 2010). Later, Konca Degertekin and colleagues found that hypothyroid patients had lower levels of IL-17 and IL-23 than in euthyroid HT patients, suggesting that hypothyroidism itself has an inhibitory effect on Th17 cytokine responses (Konca Degertekin *et al*., 2016). Less is known about participation of Th17 cells and their cytokines in the pathogenesis of GD. Previous studies showed an enhanced number of CD4+IL-17+ cells in the peripheral blood of children with untreated HT, but not in GD patients (Bossowski *et al*. 2012). Similarly, IL-17 levels in the peripheral blood and thyroid tissues did not differ significantly between adult patients with GD and controls (Qin Q *et al*., 2012). An increased expression of IL-17 within thyroid tissues from HT and GD patients was found also in our study (Zake *et al*., 2018). We observed stronger immunoexpression level of IL-17A in thyroid follicular cells in HT and GD patients when compared to patients with colloid goiter, thus suggesting that Th17 cells had an essential role in AITD pathogenesis ($p < 0.001$ and $p = 0.007$, respectively) (Fig. 1).

Graves' orbitopathy (GO), a serious and most frequent extrathyroidal complication of GD, manifests as orbital inflammation and expansion of adipose tissue and extraocular muscles. Several studies have investigated the involvement of Th17 cells in the pathogenesis and disease activity of GO. Serum IL-17 levels were found to be significantly higher in GO patients than in controls. Patients with active GO had higher serum concentrations of IL-17 compared to inactive GO patients. Furthermore, IL-17 levels were correlated with clinical activity score of GO, thus supporting the role of IL-17 in the pathogenesis and progression of GO (Kim *et al*., 2012). Fibrosis and adipogenesis are the two dominant pathophysiologic orbital processes involved in the

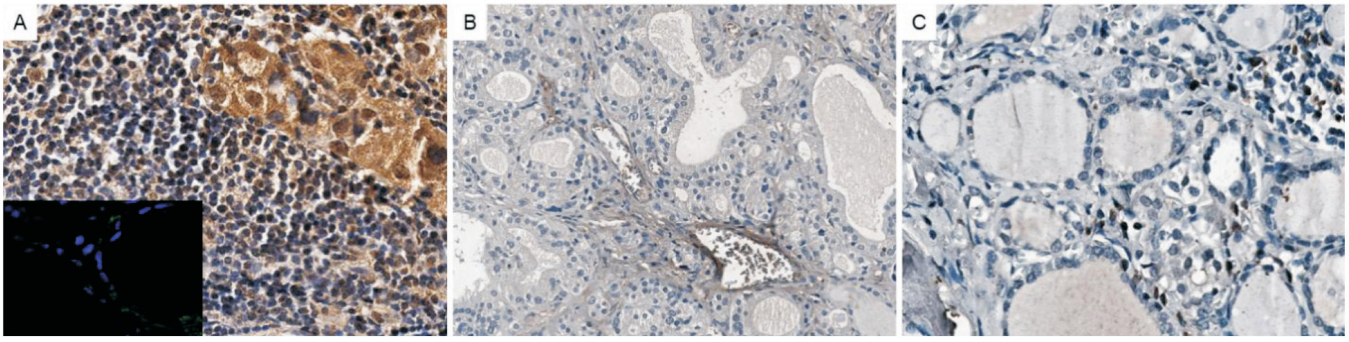

Fig. 1. (A) IL-17 positivity demonstrated in the follicular epithelial cells in HT patient (x400). Confocal microscopy, representative image of IL-17 positive thyrocytes: green staining shows IL-17-specific staining, blue staining shows nuclei, insert (x1000). (B) Weak IL-17 immunoreactivity in GD patient (x250). (C) Colloid goiter with almost nil IL-17 expression (x400).

pathogenesis of GO. Recently, Fang and colleagues reported enhanced levels of pathogenic IFN-γ and IL-22–producing Th17 cells in active GO patients, compared to inactive GO patients and controls (Fang *et al.*, 2017). Additionally, a positive correlation between pathogenic Th17 cells and clinical activity score of GO was observed, indicating that the number of these cells might serve as an indicator of GO severity and activity. The authors also demonstrated that Th17 lymphocytes can promote proinflammatory cytokine production in both CD90+ (favour fibrosis) and CD90– (favour adipose hyperplasia) orbital fibroblasts and stimulate costimulatory molecule expression on orbital fibroblasts that are CD34+. Moreover, both orbital fibroblast subsets can directly induce naive T cell differentiation toward the Th17 phenotype via prostaglandin E2 production (Fang *et al.*, 2017).

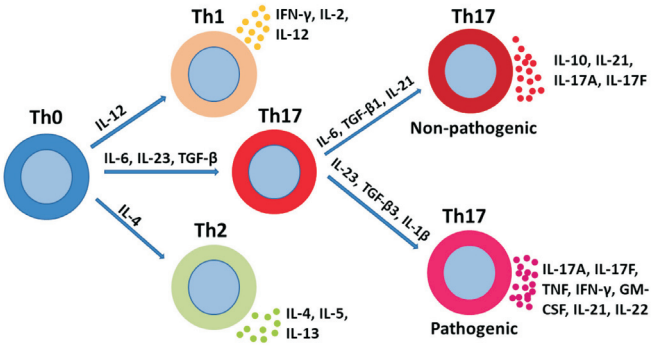

Fig. 2. Th17 subsets and their cytokines. Adapted from "A cellular and molecular view of T helper 17 cell plasticity in autoimmunity" by R. Stadhoudersab, E. Lubberts, R.W. Hendriks, *J. Autoimmun.,* 2018, **87**, 1–15.

Th17 cells are mainly characterised by the production of IL-17A and IL-17F responsible for the development of inflammation, particularly in autoimmune diseases. They can act on epithelial cells, fibroblasts, and macrophages, inducing the release of pro-inflammatory mediators such as cytokines (IL-6, IL-8, TNF-α, IL-1β, GM-CSF, G-CSF), chemokines (CXCL1, CXCL8, CCL2, CCL7, CCL20), and metalloproteinases (Song *et al.*, 2014). IL-17 regulates differentiation of immune cells within the germinal centre of the lymphoid follicle and autoantibody production. It has been found that IL-17 stimulates neutrophil recruitment by inducing CXCL8 by both immune and non-immune cells.

As mentioned above, different cytokines and transcription factors are required for regulating naïve Th lymphocyte differentiation into a Th1, Th2, Th17 or Treg cell subset (Fig. 2). In contrast to convincing experimental data highlighting Th17 cell development, only a few human studies performed in the past have established the cytokine pattern involved in the generation of Th17 cells (Peck and Mellins, 2010; Stritesky *et al.*, 2008). In fact, the cytokine profile necessary for driving the differentiation of Th17 lymphocytes is similar in both humans and mice. TGF-β, along with the proinflammatory cytokines such as IL-1β, IL-6, IL-21, and IL-23, have been found to have an essential role in the development of Th17 cells. It has been found that Th17 lineage is directed by their master transcription factor retinoic acid receptor-related orphan nuclear receptor gamma (RORγ), which is induced by IL-6 and IL-23 via signal transducer and activator of transcription 3 (STAT3). Interestingly, TGF-β is important for the differentiation of both Th17 and induced Treg cells. It has been shown that high doses of TGF-β induce expression of Foxp3, thus promoting Treg differentiation, while low doses of TGF-β in combination with IL-6 promote Th17 polarisation (Stadhouders *et al.*, 2018). In mice, the combination of IL-6, IL-1β, and IL-23 has been found to be sufficient for the differentiation of Th17 cells, indicating TGF-β independent signalling of Th17 development. Th17 cells were also found colonising the gut of TGF-β signalling-deficient mice (Qin *et al.*, 2009). In contrast to mice observations, TGF-β seems to be indispensable for the differentiation of Th17 cells in man. Thus, TGF-β in the presence of IL-6 and IL-21 induces the initial differentiation of Th17 from naïve Th cells, while IL-23 and IL-1β are essential for both complete maturation and stabilisation of the Th17 population (naïve Th cells do not express IL-1 and IL-23 receptor) (Stritesky *et al.*, 2008). Although IL-23 is not required for the induction of Th17 development, it is a crucial factor for the stabilisation and generation of the pathogenic phenotype of Th17 cells via STAT4 (Croxford *et al.*, 2012). IL-23, produced by dendritic cells and macrophages, can maintain Th17 cell differentiation by suppressing IL-10 secretion and promoting IL-22 and GM-CSF production.

Although the Th17 subset was identified more than a decade ago, it has become clear only recently that Th17 cells are heterogeneous and not uniform in function, exhibiting under certain cytokine exposure two different cellular phenotypes: pathogenic and non-pathogenic (Stadhouders *et al*., 2018). Th17 cells differentiated in the presence of TGF-β1 and IL-6 co-produce IL-17 and IL-10. These cells are assigned to the non-pathogenic subset of the Th17-lineage, as they do not induce tissue inflammation and may inhibit an autoimmune inflammation. By contrast, Th cells upon exposure to IL-23, IL-1β, and IL-6 can generate highly pathogenic Th17 lymphocytes, which drive the autoimmune inflammation (Ghoreschi *et al*., 2010). These pathogenic lymphocytes can secrete both common and pathogenic sets of molecules, such as IL-17A/F, IL-21, IL-22, IL-26, IFN-γ, TNF, and GM-CSF (Stadhouders *et al*., 2018). Enhanced levels of IL-23 were observed in the peripheral blood and within thyroid tissues of HT patients but it still remains unclear whether IL-23 is involved in the pathogenesis of GD. Recently, when studying the immunoexpression of IL-23 and IL-1β within thyroid tissue of AITD subjects, we found that expression of both interleukins was significantly increased in HT patients compared to GD and colloid goiter patients, but no difference was found between the expression level of interleukins in patients with GD and colloid goiter (unpublished data).

Cytokines play a crucial role in modulating immune response in both AITD. Cytokines produced by activated T cells may drive the autoimmune response skewing toward the Th17 phenotype and away from Th1 or Th2 phenotypes. Therefore, evaluation of T cell subsets linked to certain cytokine production in AITD could help to identify the main immunological mechanisms involved in thyroid autoimmunity thus deepening our knowledge about disease outcome and treatment strategies. Th17 cells exhibit various therapeutic targets, and treatment strategies include blockade of the differentiation of Th17 cells, inhibition of Th17 neutralising cytokines, and Th17-specific transcription factors (Maddur *et al*., 2012). Furthermore, several IL-17 neutralising monoclonal antibodies, such as secukinumab, ixekizumab and brodalumab, have been developed in recent years, which have demonstrated impressive therapeutic effects in patients suffering from psoriasis (McInnes *et al*., 2015). Further experimental and clinical studies are needed to better clarify the role of different Th subsets in AITD.

ENVIRONMENTAL FACTORS

Increased iodine intake appears as the most important among environmental factors studied and is suggested as influencing the development of AITD. Other suggested risk factors include selenium deficiency, smoking, alcohol, stressful life events, infections, several drugs, and exposure to chemical compounds. Prevention of iodine deficiency disorders by food iodine fortification has been successfully implemented in many countries in the past century. However, other preventive interventions for AITD may be complicated or even impracticable. It would be extremely important to recognise which preventive interventions can be taken by subjects with a risk to develop AITD. Excess iodine intake and a relative selenium deficiency appear to be the predominant environmental factors triggering the autoimmune response to the thyroid.

Iodine intake. Iodine intake contributes to thyroid function and the development of thyroid gland disorders. The recommended daily allowance of iodine for adults is 150 μg, increasing to 250 μg in pregnancy and lactation. It is well known that iodine-sufficient populations compared to those that are iodine-deficient appear to have higher incidences of thyroid-specific antibodies and autoimmune hypothyroidism. Data from epidemiological studies show that, due to reduced synthesis of thyroid hormone, severe iodine deficiency may develop revealing the increased prevalence of goiter and hypothyroidism, whereas chronic mild-to-moderate iodine deficiency may cause toxic nodular goiter and hyperthyroidism (Zimmermann and Boelaert, 2015). By contrast, chronic excessive iodine intake or a rise in usual intake, especially after the implementation of mandatory food iodine fortification (e.g. universal salt iodisation), may lead to the increased prevalence of thyroid autoimmunity and subclinical hypothyroidism in parallel with a decrease in rates of iodine deficiency-related thyroid disorders (Teng *et al*., 2006). Thus, the prevalence of TPOAb in the Danish population before and 4–5 years after a cautious mandatory iodisation of salt aiming to adjust iodine intake to a low recommended level was 14.3% and 23.8%, respectively (Pedersen *et al*., 2011). Furthermore, the rise in the frequency of thyroid antibodies was most pronounced in women aged 18–45. Five to seven years after iodine fortification, the overall incidence rate of overt hypothyroidism increased as well, reaching 47.2/100 000 per year compared to 38.3/100 000 per year at baseline (Pedersen *et al*., 2007). In the Pescopagano survey in Italy, introduction of the salt iodisation programme 15 years later resulted in increased prevalence of TPOAb (12.6% vs 19.5%) and also HT rates (3.5% vs 14.5) (Aghini Lombardi *et al*., 2013). However, it has been also shown that the optimisation of nutritional iodine intake may result in lowered incidence of autoimmune thyroiditis. After implementation of mandatory fortification of salt with iodine in Brazil in 1956, adjustments of the iodine concentration in salt were performed in 2003 and 2013 by decreasing the recommended iodine concentration to 20–60 and 15–45 mg per kg of salt, respectively. A cross-sectional study conducted in 2013 demonstrated a trend toward a decreased prevalence of HT and a decrease in urinary iodine concentration to optimal levels. (Miranda *et al*., 2015). However, it is unclear what will be the impact of a new continuing reduction in salt iodine concentration on thyroid function. The first systematic review and meta-analysis regarding the effect of excess iodine intake on thyroid disease prevalence in different populations, which was published recently, indicated that although universal salt iodisation decreased goiter rates, chronic excess iodine intake from water or poorly monitored salt was a risk factor for hypothyroidism in free-living populations (Katagiri *et al*., 2017). Therefore, accurate monitoring of io-

dine concentration both in salt and water is required for prevention of thyroid disorders.

The mechanisms by which increased chronic intake of dietary iodine contributes to thyroid autoimmunity are not completely understood. In susceptible individuals, iodine excess induces thyroid gland infiltration by lymphocytes liberating cytokines and chemokines, thus leading to generation of thyroid antibodies. Moreover, high iodine intake enhances Th17 and inhibits Treg cell differentiation, while it triggers an abnormal expression of TNF-related apoptosis-inducing ligand in thyrocytes, thereby inducing cell death of thyroid cells (Yu *et al*., 2011). It has been shown recently that excess iodine promotes apoptosis of thyroid follicular epithelial cells seen in HT by inhibiting autophagy activity. This process is mediated through TGF-β1 downregulation and activation of the Akt/mTOR signaling pathway. In addition, excess iodine increases production of reactive oxygen species contributes to oxidative stress and thyrocyte apoptosis (Xu *et al*., 2016). Excessive iodine may also alter the conformation of TG and promote its immunogenicity by increasing the affinity of TG determinants for the T cell receptor (Carayanniotis, 2011). Furthermore, chronic high iodine exposure may induce autoantigen presentation activity of thyrocytes and dendritic cells as well as activate autoreactive T cells. Finally, excess iodine-induced hypothyroidism in HT may be due to a pathologically persistent inhibitory Wolff-Chaikoff effect on thyroid hormone synthesis (Markou *et al*., 2001).

Selenium status. Selenium status is an important parameter of general population health, and it has been hypothesised that nutritional selenium deficiency may trigger the initiation or progression of thyroid autoimmunity. Various effects of selenium are recognised, ranging from antioxidant and anti-inflammatory to the production of active thyroid hormone (Rayman, 2012). The amino acid selenocysteine is a major form of thyroid selenium presented either by enzymes such as glutathione peroxidases (GPx), thioredoxin reductases, iodothyronine deiodinases or proteins without enzymatic function, known as selenoproteins (SELENO) P, M, S (Valea *et al*., 2018). Enzyme proteins have an important role in protecting thyrocytes from oxidative damage and, also, in thyroid hormone metabolism. GPx provide thyroid antioxidant protection against free radicals and oxidative stress, catalysing the detoxification of hydrogen peroxide and organic hydroperoxides. The biomarkers of selenium status and function available for human studies include GPx3 (10–25% of plasma selenium), SELENOP (20–70% of plasma selenium), and GPx1, which can be assayed in erythrocytes, lymphocytes as well as tissue biopsy specimens (Combs, 2015). GPx3 is also secreted at the apical pole of the thyrocyte, where it degrades excess hydrogen peroxide that has not been used by thyroid peroxidase, whereas SELONOP, the major selenoprotein in plasma, is crucial for the specific distribution and transport of selenium to several target tissues. Studies in many countries have shown the effects of geographic variation in the selenium contents in food and plasma selenium concentrations in different populations around the world.

Selenium deficiency has been recognised in several pathological thyroid conditions including nodular goiter, thyroid cancer, and AITD. Serum selenium levels have been shown to be lower in newly diagnosed GD patients compared to healthy subjects (Bülow Pedersen *et al*., 2013). Lower selenium levels were evidenced in GD subjects compared to those without this disease, suggesting that relative selenium deficiency may be an independent risk factor contributing to the development of orbitopathy in GD patients (Khong *et al*., 2014). It is also well known that selenium supplementation is recommended to prevent progression of mild GO. Selenium levels have been shown to be lower in patients with HT as well. A recent cross-sectional study involving more than six thousand participants from two provinces in China that had high genetic, environmental, lifestyle as well as iodine status similarities, except for very different soil-selenium concentrations, revealed an increased prevalence of HT but not GD in the province with lower selenium intake (Wu *et al*., 2015).

Analysis of selenium status in HT and GD patients suggests that supplementation of this trace element may be beneficial in these patients. It has been observed that selenium supplementation decreases TPOAb levels more effectively in individuals with a lower baseline level (Toulis *et al*., 2010). Furthermore, regions with deficient, higher than adequate or high iodine intake may have more need for selenium through its role within selenoproteins, protecting the thyroid gland from oxidative damage as well as increasing immune tolerance (Hu and Rayman, 2017). It has been also demonstrated that selenium supplementation can upregulate Treg cells that have been reduced by excess iodine intake (Xue *et al*., 2015).

Reduction of circulating thyroid autoantibody levels by selenium supplementation in individuals with HT was described almost two decades ago. Over the last years, numerous prospective clinical trials were performed to examine whether selenium supplementation either with sodium selenite or selenomethionine might have beneficial effects for the treatment of HT. A meta-analysis published in 2016 showed that selenium supplementation effectively reduced TPOAb levels at 3, 6, and 12 months in levothyroxine-treated HT patients. Importantly, in untreated patients, there was a decrease in TPOAb levels after 3 months, but not after 6 or 12 months of supplementation (Wichman *et al*., 2016). Another meta-analysis study was published evaluating several types of the outcome, except for TPOAb levels (Winther *et al*., 2017). It demonstrated that TSH and ultrasound finding improvement with selenium had a very low to low level of evidence, while the quality of life improvement had a low to moderate level of evidence. Although a role for selenium supplementation in the treatment of HT is still discrepant, the correction of a selenium deficiency may have other health benefits. It is highly important to assess patients' selenium status before and during selenium administration as well as to identify and correct selenium deficiency in these patients. However, it remains unclear how selenium supplementation may affect HT in patients with

higher baseline selenium intake. Further randomised controlled trials are required before selenium supplementation can be routinely suggested by clinicians in patients with HT.

Stress as a trigger. According to studies and observations, stress does not have any triggering role in HT. However, among the non-genetic factors involved in GD, one is stress. Despite several retrospective case-control studies, which found a higher frequency of stressful life events in the year preceding the primarily diagnosed GD, the role of stress as a trigger still remains controversial. A prospective study by Effraimidis *et al.* with a five-year follow-up period did not detect any causal relationship between stressful life events and GD (Effraimidis *et al*., 2011). In contrast, a role of stress in triggering both the onset and the recurrences of hyperthyroidism in patients with GD was highlighted by continued follow-up for 5 years after antithyroid drug withdrawal (Vita *et al*., 2014). Stress may affect the immune system both directly and indirectly through the activation of nervous and endocrine systems. Activation of the hypothalamic-pituitary-adrenal axis and the sympathoadrenal system occurs under exposure to stress causes enhanced secretion of glucocorticoids and catecholamines, which both have a similar immunomodulatory effect and are consistent with an imbalance in favour of Th2 cells. Hormones suppress the production of IL-2 by antigen-presenting cells and increase the secretion of IL-4 and IL-10 by Th2 cells, directing the immunity toward a Th2 response (Chrousos and Elenkov, 2006). In addition, the decrease in DHEA during stress can also stimulate a Th2-type immunity. Altogether, this may promote the development of GD, which is considered to be a Th2-dependent disease. However, recent studies provide evidence for the presence and role of Th17 cells in the pathogenesis of GD. Interestingly, it has been shown that female C57BL/6 mice under chronic exposure to stress demonstrate a shift toward proinflammatory Th1/Th17 versus Th2 responses (Harpaz *et al*., 2013).

Immune-related thyroiditis. Drugs such as amiodarone, lithium, and biological agents can contribute to the manifestation of AITD via immune mediated effects or direct effects of drugs on the thyroid. Biological agents are widely used in the treatment of cancer, nonmalignant diseases, and several autoimmune disorders. Indeed, the reported incidence of *de novo* development of thyroid autoantibodies in hepatitis C patients treated with IFN varied in studies from 2% to 40% (Mandac *et al*., 2006). IFN-related thyrotoxicosis in more than 50% of these patients was due to destructive thyroiditis, while in the remainder due to GD. Interestingly, a recent review showed that treatment with biological antirheumatic agents (TNF-α inhibitors and rituximab) did not seem to induce or worsen AITD in rheumatoid arthritis patients (Bliddal *et al*., 2017). However, the monitoring of thyroid status is recommended due to the well-established association between rheumatoid arthritis and AITD. Similarly, in patients with inflammatory bowel disease, there was no change regarding thyroid autoantibodies after treatment with anti-TNF (Paschou *et al*., 2018). Immune checkpoint inhibitors (ICPi) (anti-CTLA4 and anti-PD1 therapy), which are widely used in cancer therapy, can also trigger thyroiditis. However, ICPi-related thyroid dysfunction is typically due to destructive thyroiditis, which manifests as thyrotoxicosis followed by the transition to hypothyroidism. The role of antibodies in the pathophysiology of ICPi-related thyroiditis remains unclear (Priyanka *et al*., 2018; Chang *et al*., 2019). The reported prevalence of TPOAb/TgAb positivity is relatively low, and only two cases of ICPi-related GD have been reported. Furthermore, the *de novo* development of thyroid autoantibodies might be due to humoral response to the exposure of antigens caused by a destructive thyroiditis. Therefore, routine monitoring of TPOAb/TgAb has not been demonstrated to be helpful (Chang *et al*., 2019).

CONCLUSIONS

Although AITD present with two pathogenetically and clinically different pathologies, the cellular and humoral immune responses implicated in HT and GD are closely connected and cross-linked. Despite comprehensive research in the last decades, the specific immunological mechanisms of the initiation and progression of thyroid autoimmunity remain unclear. Numerous recent studies have highlighted an essential pro-inflammatory role of a new subset of the Th cells, designated Th17, in the pathogenesis of AITD, thus changing the traditional paradigm of Th1/Th2 dichotomy. It has been found that Th17-lineage is heterogeneous, exhibiting under certain cytokine exposure two different cellular phenotypes: pathogenic and non-pathogenic. On the other hand, Treg cells are responsible for the maintenance of self-tolerance, thus protecting against thyroid autoimmunity. An altered balance between Th17 cells and Treg as well as Treg cell dysfunction has been found in AITD. Future studies highlighting the role of Th17 in autoimmune inflammation are highly required. Evaluation of different T cell subsets linked to certain cytokine production in AITD could help identify the immune mechanisms involved in thyroid autoimmunity, thus deepening our knowledge about disease outcome and treatment strategies. Many environmental factors can influence the development of AITD, including increased iodine intake, selenium deficiency and stress. The mechanisms of the interaction between genetic and environmental factors also deserve further investigation, which will have a significant impact on the prevention of AITD. Therefore, it is critical to investigate the possible interplay of environmental and genetic factors as well as to identify the possible mechanisms and immunomodulating effects of environmental factors involved in thyroid autoimmunity, to propose individualised AITD management strategies, since most environmental factors may be modified.

ACKNOWLEDGMENTS

This work was supported by the Latvian Council of Science project No. lzp-2018/2-0059.

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Received 12 November 2018
Accepted in the final form 5 February 2019

AUTOIMŪNO VAIROGDZIEDZERA SLIMĪBU IMUNOLOĢISKIE MEHĀNISMI: TRADICIONĀLĀS TH1/TH2 PARADIGMAS MAIŅA

Autoimūnās vairogdziedzera slimības ietver Hasimoto tireoidītu (HT) un Greivsa slimību (GS), kuras raksturo asinīs cirkulējošas antivielas pret dažādiem vairogdziedzera autoantigēniem un vairogdziedzera audu infiltrācija ar autoreaktīviem limfocītiem. Lai gan pēdējo desmit gadu laikā sasniegts neizmērojams progress vairogdziedzera autoimūno slimību patoģenēzes izpratnē, tomēr detalizēts slimību attīstības imunoloģiskais mehānisms joprojām pilnībā nav skaidrs. Pieņemts uzskatīt, ka HT attīstību nosaka 1. tipa T līdzētājšūnas (Th1), bet GS attīstās pa Th2 šūnu determinēto autoimūnās reakcijas patoģenēzes ceļu. Šo tradicionālo pieņēmumu mainījuši pierādījumi par Th17 šūnu lomu vairogdziedzera autoimūno slimību attīstībā, galvenokārt HT patoģenēzē. Jāuzsver, ka attīstoties autoimūnajam procesam, izzūd līdzsvars regulatoro T šūnu un Th17 limfocītu starpā. Savos iepriekš veiktajos pētījumos GS un HT pacientu vairogdziedzera audos esam pierādījuši pastiprinātu IL-17 ekspresiju, kas ir Th17 šūnu galvenais efektorais citokīns. Šajā literatūras apskatā galvenokārt analizēta regulatoro T un Th17 šūnu loma autoimūno vairogdziedzera slimību patoģenēzē. Tāpat apskatīta svarīgāko ārvides faktoru nozīme un mehānismi autoimūno slimību izcelsmē, kas ir svarīgi arī Latvijas kontekstā.