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Review article

Immunological aspects of autoimmune thyroid disease – Complex interplay between cells and cytokines

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ABSTRACT

Autoimmune thyroid disease (ATD) is a chronic autoimmune thyroiditis with a complex pathogenesis including environmental factors, genetic background and immune system actions. Despite the large-scale research and discovery of new subpopulations of lymphocytes, cytokines, chemokines and their functions in the human body, the ethiology of ATD in many aspects remains a mystery. This article tries to summarize mostly the immunological aspects of this disease, including the roles of different cells types (dendritic cells, B cells, $CD4^+$ and $CD8^+$ T cells, NK cells and regulatory T cells) and of different cytokines (secreted by Th1/Th2/Th17/Th22 lymphocyte subpopulations and other, including the IL-23 and CXCL10). We describe the role of immunological abnormalities in the ATD pathogenesis and show that for some cells and cytokines their respective roles are not clear, and bi-directional action is possible. Finally, we propose a network of interactions between the immune cells and thyrocytes in the course of ATD.

1. Introduction

Autoimmune thyroid disease (ATD), which is basically a chronic autoimmune thyroiditis, was diagnosed for the first time in 1912 by Dr. Hakaru Hashimoto, who at first called the disease a 'lymphadenoid goiter' [1]. The autoimmune aspect of this disease was only demonstrated in 1957 in rabbit studies and a year later in humans and was named Hashimoto's thyroiditis; currently the name is autoimmune thyroid disease [2,3]. ATD is characterized by destruction of thyrocytes, associated with the presence of autoreactive lymphocytes infiltrating the thyroid gland which results in hypothyroidism development. Sometimes at the beginning of the disease mild or moderate hyperthyroidism can be noted, associated with the release of thyroid hormones into the blood from damaged thyroid glands [4]. In ATD the infiltrate of the thyroid is composed of $CD4^+$ and $CD8^+$ T cells, $CD19^+$ B cells, macrophages and plasma cells. Autoreactive B cells are the main source of autoantibodies against thyroglobulin (TG) and thyroid peroxidase (TPO), and can also be a source of cytokines, contributing to the development of inflammation. B lymphocytes may also act as antigen presenting cells (APCs), and can activate naïve autoreactive $CD4^+$ T cells, by presenting thyroid autoantigens to them [5]. The aim of this article is to present current overview of the immunological processes in ATD patients.

2. $CD4^+$Th and $CD8^+$ cells and related cytokines

2.1. Th1/Th2 lymphocytes

$CD4^+$ T helper lymphocytes induce activity of other immune cells by releasing cytokines. These cytokines help suppress or regulate immune responses. Currently T helper cells can be divided into five subpopulations: Th1, Th2, Th17, Th22 and Treg, depending on the profile of cytokines they produce. The differentiation of the activated $CD4^+$ T cells depends upon the expression of specific transcription factors and cytokines. Excessively stimulated $CD4^+$ cells play a major role in the pathogenesis of ATD. T lymphocytes are involved in the course of this disease in two ways. Stimulation of naïve $CD4^+$ T cells by IL-12, IFN-γ, IL-2, T-bet induces their differentiation into T-helper type 1 cells (Th1) [6]. Th1 cells activate macrophages and cytotoxic lymphocytes that directly damage thyroid follicular cells. Type 2 helper T lymphocytes

Abbreviations: **ATD**, autoimmune thyroid disease (Hashimoto's disease); **APC**, antigen presenting cells; **cDC**, conventional dendritic cells; **IDO**, indoleamine 2,3-dioxygenase; **IFN**, interferon; **KIR**, Killer-cell immunoglobulin-like receptor; **MHC**, major histocompatibility complex; **NIS**, sodium iodide symporter; **NK cell**, natural killer cell; **pDC**, plasmacytoid dendritic cells; **Teff**, effector T cells; **Th cells**, T helper cells; **TG**, thyroglobulin; **TNF**, tumor necrosis factor; **TPO**, thyroid peroxidase; **Treg cells**, T regulatory cells

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(Th2) can cause excessive stimulation and production of B cells and plasma cells, Th2 also produce cytokines such as IL-4, IL-5, IL-6, IL-10 that stimulate anti-thyroid antibodies, leading to development of inflammation in the thyroid gland. It has been proven that thyroid cells themselves contribute to the production of cytokines such as IL-1, IL-6, IL-8, TNF-α, TGF-β, which leads to their destruction [7,8]. Th1 lymphocytes produce, *inter alia*, cytokines such as IFN-γ and TNF-α that inhibit the sodium iodide symporter (NIS) and transcription of its gene in the thyrocytes. In addition, these cytokines may inhibit thyrocyte growth and reduce iodine binding to the thyreoglobulin, thus reducing TG synthesis. They also reduce deiodinase activity [8]. Moreover, cytokines are in many cases pleiotropic, which means that can act both immunostimulatory and immunosuppressive - depending on the specific context and the immune microenvironment. For example, cytokines such as IL-2, IFN-γ and TNF-α have been shown to both potentiate and inhibit the progression of autoimmune disease [9]. Complicated nature of these cytokines in context of autoimmune diseases was thoroughly described by O'Shea et al. [10].

2.2. $CD4^+/CD8^+$ cell ratio

Both clinical and experimental studies provide evidences that changed proportions of $CD4^+$ and $CD8^+$ cells play important roles in development of ATD. Nada and Hammouda have shown that the proportion of $CD4^+/CD8^+$ cells in peripheral blood was increased in patients suffering from autoimmune diseases such as ATD and Graves-Basedow compared to healthy subjects. $CD8^+$ lymphocyte deficiency seems to be one of the main factors in chronic thyroid autoimmune diseases. The decline in the number of $CD8^+$ suppressor cells makes it impossible to stop progression of an autoimmune disease [11]. The results of Yamamoto et al. studies show also that $CD8^+$ numbers are significantly lower in patients with severe course of ATD compared to patients with its milder form [12].

2.3. Th17 lymphocytes

In rat model studies, Th1-mediated mechanisms including production of IL-12, IFN-γ and TNF-α, have been shown to play a major role in the destruction of thyrocytes and thereby in ATD pathogenesis [13]. Recent studies have demonstrated the role of newly discovered cells such as Th17 ($CD4^+IL\text{-}17^+$) or Treg lymphocytes ($CD4^+CD25^{high}FOXP3^{high}$) in the pathogenesis of autoimmune thyroid disease [7]. Th17 lymphocytes are proinflammatory in nature, as they are primarily involved in defense against bacteria and fungi. They provide a link between innate and adaptive immunity. Th17 cells play an essential role in the etiopathogenesis of many autoimmune diseases, in which Th1 was originally considered as a dominant factor [14]. IL-17 (also called IL-17A), produced by Th17 cells, can induce secretion of many proinflammatory cytokines and chemokines that are involved in immune response against external antigens, but may also act itself as a pathogenic agent in many chronic inflammatory and autoimmune diseases such as asthma, psoriasis, multiple sclerosis, rheumatoid arthritis, allergies and many others [15–17]. Th17 lymphocytes represent approximately 1% of $CD4^+$ T cells and participate in the immune response against intracellular antigens. They mainly produce cytokines such as IL-17A, IL-17F, IL-21, IL-9, IL-22, TNF-α. Th17 development from T helper cells can be induced by TGF-β, IL-6, IL-21, IL-23 and transcription factors such as STAT3, RORC2, RORγt, RORα. In contrast, IFN-γ, IL-4, IL-27, IL-2 and retinoic acid have been shown to inhibit the development of Th17 from naïve $CD4^+$ T cells. Th17 cells share a differentiation path with FOXP3 Treg. TGF-β is involved in the development of both Th17 and Treg. In the absence of other cytokines, TGF-β induces FOXP3 via Smad3 activation and results in inhibition of Th17 development. On the other hand, TGF-β in the presence of IL-6, IL-23, IL-1β and TNF-α, activates Smad3 and STAT3, which then activate RORγt, which in turn stimulates Th17 differentiation. Moreover, IL-15 can also induce IL-17 synthesis in Th17 lymphocytes. IL-17 has strong proinflammatory properties, including stimulation of chemokine and cytokine synthesis. The role of Th17 cells in the etiology of ATD remains unclear [7,9,14]. Figueroa-Vega et al., have shown that peripheral blood lymphocytes of ATD patients exhibit enhanced RORC2 induction and thus greater potential for differentiation into Th17 cells *in vitro*. Furthermore, increased levels of IL-6 and IL-15 in blood - and increased numbers of Th17 cells in the circulating blood and thyroid gland have been detected in these patients [14]. Shi et al., demonstrated that mRNA expression for factors related to Th1 was lower in ATD patients compared to the controls and Th17-related factors were significantly higher in ATD patients. What is more, the microenvironment prevailing in ATD patients may contribute to T lymphocyte proliferation toward Th17 [18]. Liu et al. and Qin et al., have demonstrated that ATD patients had significantly elevated levels of IL-6 and IL-23 compared to control subjects [19,20]. Kimura and Kishimoto have proven that IL-6 together with TGF-β induces cell differentiation to Th17 [21]. Elevated levels of Th17 were also detected in children with untreated ATD [22]. The presence of Th17 in ATD patients positively correlates with activity and severity of the disease and with the anti-TPO titers [5]. Recent reports indicate that Th17 cells exhibit some kind of plasticity as they produce both IL-17 and IFN-γ. They were called Th17/Th1 cells, which means that Th17 in the presence of IL-12 can differentiate into Th1 and produce IFN-γ [5].

2.4. Th22 lymphocytes

Activated $CD4^+$ T lymphocytes differentiate also into Th22 cells, which provide defense against microorganisms but also contribute to the pathogenesis of autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, idiopathic thrombocytopenia or ankylosing spondylitis [23]. Differentiation and activation of Th22 lymphocytes are stimulated by IL-6, TNF-α and dendritic cells. The transcription factors: T-bet determines cell differentiation to Th1, GATA-3 into Th2, FOXP3 into Treg, while RORγt and aryl hydrocarbon receptor (AHR) are characteristic for Th17 and Th22. IL-22, produced by Th22 lymphocytes, has pleiotropic effects: proinflammatory in concert with IL-17, TNF-α and IFN-γ, but also regenerative and protective over epithelial cells [24–26]. Recent studies indicate that patients with newly diagnosed autoimmune thyroid disease have greater accumulation of Th1, Th17, Th22 cells and statistically significant higher levels of IFN-γ, IL-17A and IL-22 compared to healthy people. Besides, the percentage of Th17 was positively correlated with Th22, suggesting that they require a similar environment for activation. It is possible, that IL-6 - essential for Th17 differentiation - also stimulates Th22 development.

The summary of changes observed in T cell subpopulations and their roles in ATD pathogenesis is shown in Table 1.

3. Natural Killer cells

Disorders affecting the function and number of Natural Killer cells (NK) may lead to instability in the immune system and uncontrolled production of pathologically altered cells, which can contribute to the development of autoimmunity. These cells mature in the bone marrow as well as in the lymph nodes and liver and IL-15 plays the main role in their development and maturation. NK cells are mainly cytotoxic to neoplastic, infected and autoreactive cells. NK secrete various cytokines that exhibit suppressive action against T and B lymphocytes and even destroy them. Cytotoxic effects of NK cells depend on the balance of stimulating and inhibiting signals received by multiple receptors present on the NK surface. Killer-cell immunoglobulin-like receptor (KIR) plays the most important role in NK activation. Inhibition of NK activation depends on the presence of MHC class I molecule. NK cells may also interfere with APC's (eg, dendritic cells) that stimulate the proliferation of autoreactive B and T lymphocytes, which are essential for the onset of autoimmunity. NK cells have been identified in the organs

Table 1
T cells subsets involved in ATD pathogenesis.

	Subpopulation	Factors regulating development	Mode of action	Result of action
$CD3^+CD4^+$	Th1	IL-12, IFN-γ, IL-2; T-bet	Stimulation of macrophages and cytotoxic lymphocytes; Secreting cytokines: IFN-γ and TNF-α	Damage of thyroid follicules; Inhibition of NIS and transcription of its gene in the thyrocytes; Inhibition of thyrocyte growth and reduction of iodine binding to the thyreoglobulin; Reduction of deiodinase activity
	Th2	IL-4	Stimulation and production of B and plasma cells and production of IL-4, IL-5, IL-6, IL-10	Development of inflammation in the thyroid gland, stimulation of anti-thyroid antibodies production
	Th17	TGF-β, IL-6, IL-21, IL-23; STAT3, RORC2, RORγt, RORα	IL-17A, IL-17F, IL-21, IL-9, IL-22, TNF-α	Contribution to the pathogenesis of autoimmune diseases, including ATD
	Th22	IL-6, TNF-α, DC; RORγt, AHR	IL-22, IFN-γ, IL-17A, IL-6	Contribution to the pathogenesis of autoimmune diseases, including ATD
	Treg	TGF-β, IL-10; FOXP3, STAT1, STAT3	Direct; TGF-β, IL-10	Inhibition of T effector cells, NK and DC proliferation and production of proinflammatory cytokines secretion
$CD3^+CD8^+$		IFN-γ, IL-2, TNF-β	Perforin and granzymes	Apoptosis of thyroid cells

affected by the autoimmune disease. NK are recruited as the first line of defense where an autoimmune reaction occurs. They may inhibit autoimmunity associated with infection by rapid neutralization of the pathogen and inhibition of immunologically mediated tissue destruction. On the other hand, too fierce attack against infected cells can result in their destruction and release of autoantigens. Such a situation could lead to the activation of autoreactive lymphocytes in response to released autoantigens. In addition, NK produce cytokines, such as IFN-γ, which in turn activate macrophages and direct the immune response towards Th1. Thus, NK cells may be involved in the development of ATD at various stages of the disease [27].

4. Treg lymphocytes

Autoimmunity is caused by the loss of tolerance to self antigens. T regulatory lymphocytes are produced both in the thymus and in the periphery from inducible naïve T cells. Several subpopulations of Treg lymphocytes have already been described, each with a distinct phenotype, cytokine production profile, and different mechanism responsible for suppression of an excessive immune response. Treg cells represent 5–10% of T helper lymphocytes. Some are $CD8^+$ expressing cells, while others are $CD4^+$ [11]. Treg are $CD4^+$ T cells which express CD25 and transcription factor FOXP3 are responsible for controlling the autoimmune reaction. Three groups of Tregs were isolated within the $CD4^+CD25^+FOXP3^+$ subpopulation. In humans among natural Treg lymphocytes, two main subpopulations were isolated on the basis of different expression of CD45RA: naïve and/or resting Treg which express $CD25^{+++}CD45RA^+FOXP3^{low}$ and effector and/or activated Treg which express $CD25^{+++}CD45RA^-FOXP3^{high}$ [28]. It has been reported that Treg *in vitro* has the ability to inhibit the proliferation and production of cytokines and also to suppress the immune response of T effector lymphocytes to specific antigens and in antigen-nonspecific way by killing them in direct contact, probably utilizing intracellular granzyme B and perforin [29]. This function is associated with, *inter alia*, the ability to maintain immunological tolerance for autoantigens, but also to regulate the immune response to pathogens, counteract organ transplant rejections or prevent the development of allergic diseases. Tregs have been shown not only to be able to inhibit the proliferation and production of cytokines such as IL-2, IL-4, IL-10, and TGF-β but also to inhibit the production of $CD8^+$T, NK cells or dendritic cells *in vitro*. The polymorphisms of FOXP3 transcriptional factor lead to the loss of regulatory functions in Treg cells in both mice and in humans. Treg's activity is mediated by the production of TGF-β and IL-10 [30]. These cells may express CTLA-4, CD25, GITR or FOXP3 factors. *In vitro* and *in vivo* studies conducted in recent years have confirmed the regulatory role of $CD4^+CD25^{high}$ lymphocytes, their specific role in immune response and contribution to the development of thyroid autoimmune diseases.

In thyroid autoimmune diseases high number of $CD4^+$ T cells exhibit low expression of IL-10 and TGF-β, reduced expression of FOXP3, STAT1 or STAT3 transcriptional genes and essential genes for the Treg growth. Lowered levels of Treg in ATD patients, compared to healthy people, have been described, both in thyroid tissue and in the peripheral blood, where normally present Tregs were apoptotic. Untreated subjects had a negative correlation between $CD4^+CD25^+$ Treg levels and anti-TPO concentration, as well as the lower Treg's ability to inhibit the proliferation of other lymphocytes [31]. In patients treated with levothyroxine the level of Treg increased. This may suggest that Treg function depends on the cell metabolism controlled by thyroid hormones. Damaged Treg can impair immune tolerance and trigger immunization [7]. In addition, lower levels of circulating $CD4^+CD25^{high}$ T cells correlate with disease exacerbation and with worse prognosis [32]. FOXP3 expression and Treg production is induced by TGF-β, which is synthesized by Tregs themselves, fibroblasts, macrophages and thyrocytes. TGF-β is a cytokine, that plays a key role in maintaining immune tolerance by stimulating Tregs and inhibiting cell

Table 2
Cytokines which are elevated or reduced in ATD patients.

	References
Elevated concentration	
IL-6	5, 7, 8, 14, 19, 20
IL-23	19, 20
IFN-γ	13
IL-15	14
IL-22	24, 25, 26
Reduced concentration	
IL-10	5, 7
TGF-β	32

differentiation of effector T cells. Lowered TGF-β have been detected in ATD patients compared to healthy people, which has not changed after levothyroxine treatment [33]. Also IL-12 can cause loss of immunological tolerance by its p40 subunit that can down-regulate the FOXP3 expression through synthesis of nitric oxide. IL-1β in the presence of IL-12 exhibits proinflammatory properties. IL-1β alone exhibits pro-inflammatory properties – it is capable of promoting the IL-2- and TGF-β-induced expression of $FOXP3^+$ Treg in mice *in vitro* [9]. Similar as with Th17 cells, there is growing evidence that Treg cells also exhibit some sort of plasticity. It has been proven, that $CD4^+CD25^{hi}$ Treg lymphocytes exhibit expression of both FOXP3 and RORγt transcription factors [34,35]. Presence of proinflammatory cytokines, such as IL-1β and IL-6, can increase production of IL-17 in $FOXP3^+$ Treg cells, resulting in loss of FOXP3 expression. However, the results of the current studies are contradictory as to whether $IL\text{-}17^+$ $FOXP3^+$ Tregs lose their suppressive functions in contact with IL-17. Voo et al., demonstrated that $IL\text{-}17^+$ $FOXP3^+$ Tregs are capable of inhibiting $CD4^+$ T cell proliferation, while Beriou et al., observed downregulation of $IL\text{-}17^+$ $FOXP3^+$ Tregs suppressor activity affecting inhibition of IFN-γ production [36,37].

5. Dendritic cells

Dendritic cells (DCs) are essential for both antigen response and immune tolerance. Stimulation of the immune system depends on dendritic cells maturity. Only mature DCs can stimulate T lymphocytes, whereas immature dendritic cells exhibit tolerogenic function - in contact with naïve T lymphocytes induce their differentiation into regulatory T cells [38]. Dendritic cells are divided into plasmacytoid (pDC) and conventional (cDC) cells, which differ in phenotypes and profiles of produced cytokines. Cytokines synthesized by DC include: IL-6, IL-10, IL-12, IL-23 and interferons that modulate the activation and proliferation of both Treg and effector T cells (Teff). Moreover, DC express indoleamine 2, 3-dioxygenase (IDO) that breaks down tryptophan (Trp) and leads to so-called tryptophan starvation, preventing from Teff activation, while increasing the Treg differentiation. Leskela et al., have shown that ATD patients, especially those with severe form of the disease, have a reduced amount of peripheral blood pDC that are responsible for inhibition the autoimmune response. In addition, these patients exhibit reduced expression of immunoregulatory molecules (including IDO) and decreased production of tryptophan metabolites, which have favorable effect on Tregs [38].

Two cytokines (IL-23 and CXCL10), of which the former had already been mentioned above, are emerging as potentially important factors in ATD pathogenesis and so require some more elaboration.

5.1. IL-23

IL-23 belongs to the IL-12 family, and both cytokines are produced by dendritic cells and macrophages. IL-12 promotes development of Th1 cells, while IL-23 is essential for Th17 proliferation. IL-23 can mediate inflammation through multiple proinflammatory cytokines including IL-17, IL-8, TNF-α and can also enhance Th17 cellular response. T lymphocytes, NK and dendritic cells can all express IL-23 [26,39]. In the aforementioned study, Figueroa-Vega et al., detected elevated levels of cells synthesizing IL-17 and IL-22 in patients with autoimmune thyroid diseases, mainly with ATD. They have also measured the levels of associated cytokines: IL-6, IL-15 and IL-23, which are known to promote Th17 response. Levels of IL-6 and IL-15 were significantly higher, whereas serum levels of IL-23 tended to be higher in these patients [14]. The authors of other studies have also obtained results indicating elevated levels of IL-23 in ATD patients compared to healthy subjects, which may suggest contribution of this cytokine in the pathogenesis of ATD [26,39].

5.2. CXCL10

CXCL10 chemokine and its receptor (CXCR3) are involved in the etiopathogenesis of many autoimmune diseases such as type 1 diabetes, psoriasis, sarcoidosis, Graves' disease and many others. The CXCL10 secretion by T cells and NK cells depends on the presence of IFN-γ. Under the synergistic influence of IFN-γ and TNF-α, CXCL10 is also synthesized by thyrocytes, which contributes to the development of a closed feedback loop that initiates and enhances the autoimmune process. High level of CXCL10 is a marker of Th1 immune response and it has been detected in patients with autoimmune thyroid diseases, and in particular in people with acute lymphatic infiltration and hypothyroidism. Therefore, it is postulated that CXCL10 should be considered as a marker of strong and more aggressive thyroid inflammation leading to the destruction and decreased function of this organ [40,41].

The summary of cytokine changes in ATD patients is presented in Table 2.

6. Pathogenesis – summary

In the early phase of the disease the APCs migrate and present thyroid autoantigens to T helper cells (Th cells) in thyroid lymph nodes. T lymphocytes recognize antigens in the context of major histocompatibility complex (MHC) molecules located on the surface of antigen presenting cells (e.g. dendritic cells or macrophages). T cells activation via APC requires two different signals. The first signal is generated by a T Cell Receptor (TCR), which binds to MHC molecule. The second is provided by other molecules present on the surface of APC, e.g. molecule B7. Thyroid cells may also express MHC class II, which is necessary for presenting antigens to $CD4^+$ T lymphocytes (thyrocytes can act as a APCs). In ATD patients, in contrast to healthy people, MHC class II molecules are present on follicular thyroid cells. Activation of MHC class II may be a result of IFN–γ and IL-12 production by activated T cells. Thyroid cells, which are expressing MHC class II, are capable of presenting both autoantigens and foreign antigens to T cells, thereby activating them. This may indicate, that induction of MHC class II on follicular cells (eg. by IFN-γ) can lead to an autoimmune process [7]. T lymphocytes may be restimulated by MHC class II on thyrocytes which would enhance the autoimmune reaction. In turn, IL-10 produced by regulatory T cells can reduce the expression of MHC class II molecules [5]. In addition, the migration of lymphocytes to the thyroid is stimulated by enhanced expression of cell adhesion molecules in activated endothelium - selectins and integrins (Beta-1 integrin, VCAM-1, ICAM-1, P-selectin) which has been described in ATD [42]. Thyrocytes themselves secrete cytokines and chemokines, which control the migration of lymphocytes via activation of CCR5 and CXCR3 receptors. Infiltrating T lymphocytes are characterized by increased production of IFN–γ and TNF-α, which in turn stimulates the secretion of chemokines in thyrocytes [43]. Uncontrolled proliferation of autoreactive $CD4^+$ T cells, which induces production of cytotoxic T $CD8^+$ cells through IFN-γ, IL-2 i TNF-β, occurs in ATD. These $CD8^+$ T lymphocytes secrete destructive molecules: perforin and granzymes

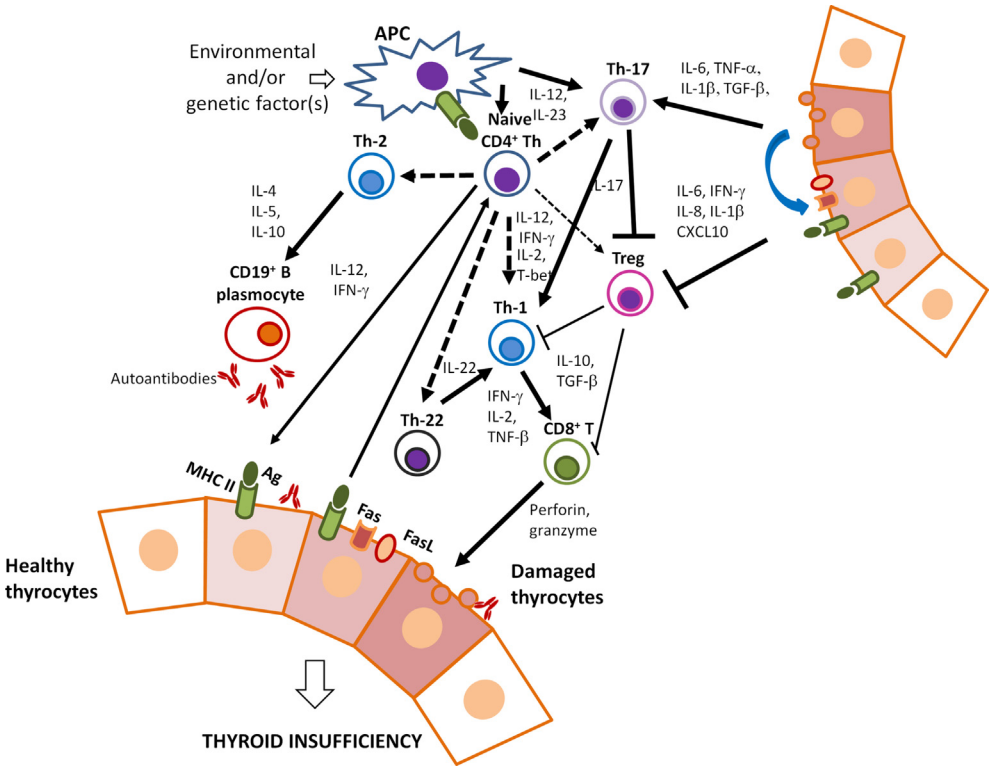

Fig. 1. Network of immune cells - cytokines – thyrocyte interactions in autoimmune thyroid disease. The presence of certain environmental and/ or genetic factors may trigger activation of antigen presenting cells (APC) which in turn present allo- and auto-antigens to naïve helper T cells (Naïve CD4$^+$ Th) resulting in their differentiation. Specific cytokines (eg. IL-12) produced by Th1 cells induce expression of MHC II on thyroid cells and also promote further differentiation of CD4$^+$ T lymphocytes, which in turn influenced by IFN-γ, IL-2 and TGF-β induce activation of cytotoxic CD8 + T cells. The latter destroy thyroid cells what leads to excessive release of proinflammatory cytokines, including IL-1b, IL-6, TGF-b, TNF-a, and cytokines (CXCL10). That situation creates an amplification feedback loop that initiates and perpetuates the autoimmune process, additionally inducing the expression of Fas receptors which lead to programmed cell death of the thyrocytes. Cytokines released by thyrocytes contribute to migration and activation of pathogenic (proinflammatory) Th17 lymphocytes, at the same time diminish the expression of regulatory T cell (Treg). In addition, the microenvironment in the infiltrated thyroid is conductive to the differentiation of proinflammatory Th22 lymphocytes, and infiltrating B cells triggered by Th2 cytokines release autoantibodies which may contribute to further thyrocyte destruction by the ADCC mechanism. Solid arrows indicate stimulatory actions, T-ended lines indicate inhibitory activities, and dashed arrows indicate cell differentiation. Thicker lines mean stronger effects.

(e.g. granzyme B) in the thyroid, ultimately leading to the apoptosis of thyroid cells [44–46]. In addition, in ATD the thyrocytes express Fas and FasL molecules and proinflammatory IFN-γ and IL-1B cytokines may enhance Fas expression in human thyrocytes [5]. Whole schematic of pathogenesis of autoimmune process in ATD including a network of immune cells, cytokines and thyrocytes is shown in Fig. 1.

Autoantibodies, especially anti-TPO IgG1, can destroy thyrocytes by inducing antibody-dependent cell-mediated cytotoxicity (ADCC). As a result, destroyed thyrocytes release cytokines such as IL-6, IL-1β, IL-8, which additionally initiate inflammation by attracting more lymphocytes to the thyroid. Also, anti-TPO antibodies promote the production of proinflammatory cytokines by T-lymphocytes and phagocytic cells, by facilitating binding of TPO/anti-TPO complexes to Fcγ-receptors on antigen-presenting cells [5].

7. Conclusion

Autoimmune thyroid disease is a complex autoimmune process that can be triggered by a specific environmental factors while presenting simultaneously with a genetic predisposition and decreasing function of T regulatory lymphocytes. This leads to impairment in the immune tolerance of autoantigens and consequently the destruction of the thyroid gland and hypothyroidism. Despite the large-scale research and discovery of new subpopulations of lymphocytes, cytokines, chemokines and their functions in the human body, the etiology of ATD in many aspects remains a mystery. Studies indicate high levels of Th17 and Th22 cells, but we are still uncertain as to their role in the development of ATD. The role of NK cells in etiopathogenesis of ATD can be pleiotropic. On one hand they suppress autoreactive B and T lymphocytes and can neutralize autoimmunity associated with infection, but on the other hand their strong cytotoxic effect on infected cells can lead to the release of autoantigens and the production of autoreactive lymphocytes. In the autoimmune thyroid diseases, there is an increased number of CD4$^+$ T cells that exhibit impaired expression of the genes essential for the development of regulatory T lymphocytes. In ATD patients decreased Treg levels have been noticed and, what is commonly known, this can contribute to development and escalation of autoimmunity.

Conflict of interest

Not declared.

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