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PII: S1568-9972(20)30220-2

DOI: https://doi.org/10.1016/j.autrev.2020.102649

Reference: AUTREV 102649

To appear in: *Autoimmunity Reviews*

Received date: 15 March 2020

Accepted date: 21 March 2020

Please cite this article as: M. Ralli, D. Angeletti, M. Fiore, et al., Hashimoto's thyroiditis: An update on pathogenic mechanisms, diagnostic protocols, therapeutic strategies, and potential malignant transformation, *Autoimmunity Reviews* (2020), https://doi.org/10.1016/j.autrev.2020.102649

Hashimoto's thyroiditis: an update on pathogenic mechanisms, diagnostic protocols, therapeutic strategies, and potential malignant transformation

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Abstract

Hashimoto's thyroiditis, characterized by thyroid-specific autoantibodies, is one of the commonest autoimmune disorders. Although the exact etiology has not been fully elucidated, Hashimoto's thyroiditis is related to an interaction among genetic elements, environmental factors and epigenetic influences. Cellular and humoral immunity play a key role in the development of the disease; thus, a T and B cells inflammatory infiltration is frequently found. Histopathologic feature of the disease includes lymphoplasmacytic infiltration, lymphoid follicle formation with germinal centers, and parenchymal atrophy. Moreover, the occurrence of large follicular cells and oxyphilic or Askanazy cells is frequently associated to Hashimoto's thyroiditis. Clinically, Hashimoto's thyroiditis is characterized mainly by systemic manifestations due to the damage of the thyroid gland, developing a primary hypothyroidism. Diagnosis of Hashimoto's thyroiditis is clinical and based on clinical characteristics, positivity to serum antibodies against thyroid antigens (thyroid peroxidase and thyroglobulin), and lymphocytic infiltration on cytological examination. The mainstream of treatment is based on the management of the hypothyroidism with a substitution therapy. A relationship between Hashimoto's thyroiditis and a possible malignant transformation has been

proposed in several studies and involves immunological/hormonal pathogenic links although specific correlation is still debated and needs to be further investigated with prospective studies.

Keywords: Hashimoto's Thyroiditis, Autoimmunity, Hypothyroidism, Autoimmune thyroid disorders

1. Introduction

Hashimoto Thyroiditis (HT), also called chronic lymphocytic or autoimmune thyroiditis, is an autoimmune thyroid disease characterized by increased thyroid volume, lymphocyte infiltration of parenchyma, and the presence of antibodies specific to thyroid antigens. HT is considered, together with Graves' Disease (GD), an autoimmune thyroid disorder (AITD) whose frequency has increased considerably in the recent years [1-3]. HT is currently the leading cause of hypothyroidism [1, 4]; moreover, patients with HT are more likely to be affected by cardiovascular diseases and malignant neoplasms [5, 6].

HT was first described by a Japanese physician, Haraku Hashimoto, in 1912 [7]. He found that thyroid tissue was infiltrated by lymphocytes with increased volume of the gland, naming this disease as "struma lymphomatosa". Hashimoto's struma lymphomatosa was not considered a specific clinical entity until 1931, when Allen Graham [8] described the condition as an autonomous pathology. In 1956, Rose and Witebsky [9, 10] demonstrated that rabbit immunization with extracts of rabbit thyroid induced histologic modification on thyroid tissue similar to HT, identifying anti-thyroglobulin antibodies in the serum. In the same year, Roitt, Doniach et al [11] isolated anti-thyroglobulin antibodies from the serum of patients with HT and stated that patients with HT may have an immunological reaction to thyroglobulin, concluding that Hashimoto's goiter should be considered an autoimmune disease of the thyroid gland.

2. Epidemiology

Incidence of HT rapidly increased in the last 3 decades [12]. Currently, HT is one of the most common thyroid diseases and its incidence is 0.3-1.5 cases per 1000 people [13]. More than 10% of women display positive antibody and around 2% show clinical manifestations [14]; men present one-tenth of this prevalence [15] . The white race shows a higher incidence than black, while HT is rare in Pacific Islanders [16]. Disease prevalence increases with age [16].

Although the reasons of female gender prevalence are still unknown, possible explanations could be found in the role of female sex hormones, as demonstrated in animal models of many autoimmune diseases [17, 18], or following the inactivation of chromosome X and fetal microchimerism [19]. In a recent study on 490 patients affected by HT, no significant differences in chromosome X inactivation were observed compared to normal subjects, but four other meta-analysis showed that chromosome X inactivation may be relevant [20]. If microchimerism played a significant role, HT should have been more frequent in women with multiple pregnancies. However, a study of 4.6 million Danes revealed only a irrelevant increase of autoimmune diseases in women with a previous pregnancy, compared to those who did not have children [21]. The pathogenesis of HT has also been associated with climate conditions, since Siberian women have higher thyroid peroxidase (TPO) antibody title than general population [22].

Last, HT may have a higher prevalence in some conditions such as myasthenia gravis (MG) and systemic sclerosis. A recent meta-analysis from Song et al on 39 studies showed reliable evidence that HT, along with other thyroid disorders, have a higher prevalence in patients with MG and identified MG as a risk factor for thyroid autoimmunity [23]. In a meta-analysis conducted on 46 studies by Yao et al, the authors found a considerably high prevalence of autoimmune thyroid conditions in subjects with systemic sclerosis, and that this condition is associated with increased risks of thyroid pathologies [24]. Although the pathogenic mechanisms of the associations between thyroid autoimmunity and these conditions are not clear, it has been hypothesized that immune defects, hormones, genetic and environmental factors may play a central role in poly-autoimmunity [25].

3. Etiology

Although still largely unknown, pathogenesis of HT is related to genetic influences, environmental triggers and epigenetic effects [26].

3.1 Genetic susceptibility

A genetic susceptibility to HT disease has been shown in epidemiological studies that focused on familial predisposition [27]. Brix et al showed in Danish twins that monozygotic twins exhibited a concordance rate of more than 50%, while dizygotic twins showed absence of any concordance [28]. Moreover, data from the same study regarding thyroid autoantibodies showed an high concordance rate for monozygotic twins that was nearly 80%, when compared to dizygotic ones (40%) [28].

Several genes have been shown to be involved in HT pathogenesis, including genes of immune response and thyroid function. Among the genes that control the immune response, a relevant role is played by those coded in the Human Leukocyte Antigen (HLA) complex; thus, it has been showed that the HLA-B* 46:01 gene is associated with the development of HT, as demonstrated in Chinese children is a case-control and family-based study [29]. In another study of 444 Japanese patients with HT, some genes (*HLA-A* 02:07* and *HLA-DRB4*) were shown to increase the chance of illness while others favored protection [30].

Current literature established the involvement of many other immunoregulatory genes that control the immune response, in addition to those in the HLA complex. Single nucleotide polymorphisms (SNPs) regarding the *CTLA-4, PTPN22, CD14, CD40* and *IL2R genes* have been associated to the development of HT [31]. A meta-analysis by Ji et al regarding a specific polymorphism involving A49G in *CTLA-4 gene* has demonstrated an increased risk of HT for white race subjects and for Eastern Asia population [32].

Studies have focused on possible polymorphism of the group of genes that encode for the cytokines involved in HT pathogenesis and progression; however, no significant results have been reported so far [33, 34]. A major study of 202 Tunisians patients with HT revealed the association with an *IL1RN* VNTR polymorphism, [33] while another study of 182 Chinese patients with HT showed the importance of the rs763780 polymorphism in *IL17F[34]*.

Studies regarding Graves' disease (GD) have focused the attention on the lack of regulatory T cells (Treg) that may induce a thyroid lymphocyte infiltration, associated with hypothyroidism in an animal model of GD [35, 36]. This observation suggests that Treg cells in humans may determine a natural progression from the hyperthyroidism of GD to the hypothyroidism of HT [37]. Regulatory B cells (Breg) also seem to be involved in HT, although their role has not been completely understood and further studies are needed [38].

Chemokines also play a role in HT and other autoimmune thyroid disorders. In a recent study, Ferrari et al investigated the modulation of the secretion of chemokines CXCL8 and CXCL10 in cell cultures of thyroid follicular cells in GD, concluding that CXCL10 could be associated with the initial phase of GD, while CXCL8 could be associated with a later chronic phase of the disease [39].

Furthermore, selenoproteins (SEP) are important for the thyroid hormone deiodination and selenium deficiency could be considered a predisposing factor as dietary environmental element [40, 41], as it will be further discussed in the paragraph on environmental triggers. In a study on a Portuguese population including 481 subjects, HT susceptibility has been associated to a polymorphism in the promoter region of the selenoprotein S gene (SEPS1) [42].

3.2 Environmental triggers

Environmental factors could play an important role, as demonstrate recent epidemiological changes, and development of HT may not be only due to an innate predisposition but may be a consequence of environmental factors that have changed rapidly. Moreover, as demonstrated in homozygous twins, the disease only clinically accounts in about 50% of the subjects, thus in genetically predisposed subjects some environmental factors could cause an autoimmune reaction against the thyroid.

As observed in several autoimmune disorders, the presence of more hygienic environment without microbial agents may be associated with an high incidence of allergic and autoimmune diseases,

including HT [43]. Many studies have shown that the excess of iodine in the diet may determine the onset of HT in predisposed individuals. A study of iodoprophylaxis on volunteers in a region of Italy with iodine deficiency revealed a doubled occurrence of anti-thyroid antibodies with a quadrupled incidence of HT during the observation period [44].

Insufficient selenium intake with diet may result in a worsening of HT. Selenium intake in Europe showed a decrease of 50% in the last 30 years. Nevertheless, the administration of selenium supplements did not show an improvement in thyroid morphology but only a reduction in levels of TPO autoantibodies, as demonstrated in recent meta-analysis [45].

Another dietary component that could have a role in HT is vitamin D, whose serum levels are related to exposure to the sun. Although lower serum levels of vitamin D were observed in subject with HT, these might be related to metabolic changes in hypothyroidism, especially because thyroid dysfunction is inversely related to the severity of vitamin D levels [46]. A recent study confirmed that it should be taken into account in future research [47].

Novel anticancer regimens such as interferon-α and tyrosine kinase inhibitors have been associated to thyroid diseases including HT [48].

The role of smoking and alcohol in the etiopathogenesis of HT is still controversial and no clear evidence is available so far, although it seems that a moderate consumption of alcohol may be protective against HT and other autoimmune diseases [49, 50].

The observation that Hepatitis C virus may cause a worsening of HT has suggested a possible mechanism of molecular mimicry between viral and self-antigens. However, so far, all attempts to find viruses in thyroid patients with HT did not give reliable results. Human Herpesvirus 6 has been shown to be active in some studies in HT patients and demonstrated a strong tropism for thyroid follicular cells (TFCs). However, these studies only included a relatively small number of patients and require further validation [51, 52].

3.3 Epigenetics factors

Current research has shown that genetic and environmental factors act synergically in determining HT through modulation of epigenetic factors [53-57]. Epigenetic factors may regulate gene expression and phenotype, resulting in the onset of disease in absence of DNA structure alterations [58].

Epigenetic factors involved in the onset of the disease are numerous, although methylation, histone modifications, and RNA interference through non-coding RNAs are the most frequent [58]. HT is characterized by lymphocytic infiltration in the thyroid, followed by the infiltration of T and B cells into the thyroid gland. It has been hypothesized that autoantibodies and B cell dysfunction represent the primary immune reactions in autoimmune thyroid disorders, and aberrant functions of T cell subsets also play important roles in breaking the immune homeostasis and starting the autoimmune cascade against thyroid tissues (**Figure 1**) [55].

The methylation of DNA can determine the inactivation of certain genes, while some histone alterations induce the activation of other genes; however, the action of these epigenetic mechanisms can be variable and influenced by environmental factors [58, 59]. Moreover, non-coding RNAs including microRNAs can also control the expression of specific genes [60, 61].

Evidence suggests that female preponderance in HT may be due to X chromosome inactivation, considered a major epigenetic feature in which one X chromosome is silenced [55]. This suggests that the functioning of the genes can be altered by epigenetic mechanisms and result in the onset of autoimmune disorders; therefore, epigenetic factors could play a fundamental role together with genetic and environmental factors in determining autoimmune diseases [54, 55, 62].

This growing evidence suggests that environmental factors can induce epigenetic modifications that, in genetically susceptible individuals, may produce autoimmunity thyroid diseases including HT [63, 64].

4. Pathogenic Mechanisms

Pathogenesis of HT is strictly related to autoantibodies with a relevant lymphocytic infiltrate, including of B and T cells in the thyroid tissue [65, 66]. It is believed that one of the first events in HT pathogenesis is a functional alteration of B cells with formation of autoantibodies. In addition, T cell dysfunction is associated with the breakdown of immune homeostasis against thyroid tissue [65, 66]. Therefore, it could be hypothesized that cellular and humoral immunity is associated to the pathogenesis of HT.

4.1 Cellular immunity

In HT patients, CD8+ T cells against thyroglobulin and TPO were found [67]. However, only a small number (2-3%) of CD8+ cells are specific to TG/TPO, so most of them are not specific to thyroid antigens. Moreover recent studies established that cell death in autoimmune thyroiditis is not only due to cytotoxicity but also to apoptosis processes [68].

A specific population-specialized CD8+ cells, termed "Suppressor T cells" have been considered able to inhibit harmful immune responses. It has been hypothesized that in HT there is an alteration in the function of T cell suppressors against specific antigens of thyroid cells [69]. Some of the functions of T suppressor cells seem to be carried out by the T regulator cells (Treg) [70]. These cells can attenuate the immune response by direct or indirect contact with the production of cytokines such as growth factor (TGF)-Beta and Interleukin 10 [70, 71]. Some studies have demonstrated an alteration in the number and function of Treg cells in HT [72, 73].

The role of Treg cells has been focused in a recent study [36] that analyzed the rate and the expressions of Helios and PD-1 in HT patients, exploring the relationship of these with thyroid function and specific autoantibodies in peripheral blood mononuclear cells of HT patients and healthy patients. In particular, Helios is considered as an important mediator for Treg cells since it can upregulate Foxp3 expression. It has been acknowledged that Treg-coexpressing Foxp3 and Helios phenotype exhibited a superior suppressive abilities than CD4+CD25+ Treg [74]. Moreover, PD-1 delivers inhibitory signal to prevent immune damage when binding to its ligands PD-L1 [75].

Helios and PD-1 may also exert vital function in regulating Treg cell peripheral tolerance and autoimmunity. Interestingly, a recent study based on flow cytometry analysis detected the percentage of Treg cells was remarkably lower in HT patients with an inverse correlation to thyroid function when compared with healthy controls. The levels of Treg, aTreg, and Helios-expressing aTreg cells were all negatively correlated with antithyroid antibodies, confirming that the deficiency of Treg frequency and aberrant expressions of Helios and PD-1 may possibly contribute to the immune damage to the thyroid in HT [36, 76] (**Figure 2)**.

4.2 Humoral Immunity

The production of specific antibodies to thyroid tissue is one of the most important features of HT. In the great majority of HT patients, there are specific autoantibodies for TG and TPO [77]. In addition, the anti-TPO antibody assay is useful in predicting a condition of hypothyroidism [78]. Recently, a variant of HT called IG4 thyroiditis has been identified and is part of a systemic autoimmune disease characterized by the presence of IG4-positive cells [79].

Some studies have found an increase of serum levels of Th1 cells [80, 81] and IL-17 and IL-22 cytokines in HT [82]. IL-12 cytokine has been shown to be increased in 56% of patients with HT [83].

A recent study [84] suggested that circulating exosomes play an active role in the pathogenesis of HT. Exosomes have the capability to transfer bioactive molecules into other cells thus affecting biological activity and are involved in several cellular process as antigen presentation, inflammatory activation, autoimmune disorders and tumor metastasis (5,6). Specific HT-exosomes might present antigens to dendritic cells (DC) and bind TLR2/3, causing DC activation via the NFκB signaling pathway, leading to an imbalance in CD4+ T lymphocyte differentiation and potentially contributing to HT onset. [85] A similar process has been demonstrated in systemic lupus erythematosus; however, further studies are required to confirm this hypothesis in patients with HT.

HT is often associated with other autoimmune disorders, indicating a possible common poly-autoimmune etiology. In a large prospective study on 3209 patients with GD, Ferrari et al evaluated the association of this thyroid disorder with other autoimmune conditions. A significant percentage (16.7%) of GD patients had another associated autoimmune disease such as vitiligo, autoimmune gastritis, rheumatoid arthritis, polymyalgia rheumatica, multiple sclerosis, and celiac disease. In some patients, three or more associated autoimmune disorders were diagnosed [86].

5. Histopathology

Histopathological characteristics of HT include lymphoplasmacytic infiltration, fibrotic tissue presence, lymphatic follicular formation, parenchyma atrophy and presence in lymphoid follicles of large cells with eosinophilic granule in the cytoplasm called Hurtle cells [87]. Hypothyroidism is due to the destruction of thyroid cells [88].

Histopathological features of HT are not unique, although several different variants of HT have been identified through clinical and histological features, such as fibrotic and atrophic [89, 90], Riedel thyroiditis [91, 92] and IG4 thyroiditis [93, 94].

In the *fibrous variant*, thyroid tissue is completely replaced by fibrous tissue. However, fibrosis never extends beyond the thyroid capsule as is the case for malignant thyroid neoplasms [15].

In the *fibrous atrophy variant*, the thyroid gland is reduced in volume with large quantities of fibrous tissue and atrophy of the thyroid tissue [88, 95]. TSH antibody receptors can be detected in a small percentage of cases [96].

Riedel's thyroiditis was so named by the name of its discoverer Bernhard Riedel [92], and was later considered as a local manifestation of a systemic disease called multifocal fibrosclerosis [91]. The main histological features are the presence of abundant fibrotic tissue extending beyond the thyroid capsule in the absence of neoplastic cells [15].

IgG4 thyroiditis has been proposed recently as another variant of HT [94]. This variant is characterized by high concentrations in thyroid tissue and serum of IG4. Probably, this variant

represents a local manifestation of a systemic disease called Immunoglobulin G4-related disease (IG4-RD) [97].

The growing interests on IG4-related disease provided recently a simplified classification [98], where HT is divided into IgG4-positive and IgG4-negative groups, based on immunohistochemistry for IgG4 and IgG. Patients in the IgG4-positive group were significantly younger than those in the IgG4-negative HT group, and displayed a significantly higher degree of fibrosis of thyroid parenchyma. Immunohistochemical expression score for TGF-b1 was higher in IgG4-positive group than in IgG4-negative, suggesting that this new classification might have relevant clinical implications for the management of HT [99].

6. Symptomatology

Symptomatology of HT is characterized by local and systemic manifestations. Local symptoms are due to the compression of the anatomical structures of the neck, including dysphonia following the involvement of the recurrent laryngeal nerve, dyspnea due to compression of the trachea, and dysphagia consequent to compression of the esophagus.

Systemic symptoms are more common and are due to primary hypothyroidism that occurs almost always in HT and involves most organs and tissues with significant variability [100], although often preceded by subclinical manifestations [101, 102].

Non-specific rheumatic manifestations associated with undifferentiated inflammatory arthropathy have been recently observed in patients with HT [103, 104].

Several clinical variants of HT have been described, and include painless thyroiditis, painful thyroiditis, postpartum thyroiditis, and Hashimoto's encephalopathy.

Painless thyroiditis is so named because the patient does not feel any pain in the neck and its main feature is represented by a transient phase of hypothyroidism that return to euthyroidism [105].

Painful Thyroiditis is so called because of the progressive, acute and intolerable pain in one lobe or the whole thyroid. It is a rare variant of HT that mostly affect women with a sex ratio of 10 to 11:1 [106].

Postpartum thyroiditis is so called because it manifests six months after delivery and is clinically identical to the painless thyroiditis. The favorable course of these two clinical forms is probably due to transient autoimmune disorders [105].

Hashimoto's encephalopathy is one of the most relevant clinical variants of HT [107] due to its association with encephalopathy as first described by Brain in 1966 [108]. Later, many other clinical cases were identified [109]. The most frequent symptoms include subacute cognitive deterioration, myoclonus, change in behavior, and seizures [110]. Clinically, this condition responds well to corticosteroid therapy, and seems to be supported by alpha enolase autoantigens [107, 111-114]. The search for anti-alpha enolase antibodies is useful for the diagnosis and treatment of Hashimoto's encephalopathy but does not allow a connection between thyroid and encephalic disease [115].

7. Diagnosis

The diagnosis of HT is based on clinical symptoms, anti-thyroid antibodies and histological features.

Serum anti-TPO antibodies are considered the most important feature of HT and are present in about 95% of patients [100]. Instead, anti-thyroglobulin antibodies are present in a lower (60-80%) percentage of cases and therefore are less reliable for diagnosis [116]. It appears that anti-thyroglobulin antibodies may be the expression of an initial immune response, whereas anti-TPO antibodies may be the result of a later immune response as if there was an immune escalation [117].

Cytological examination is not routinely performed, but only when a thyroid nodule is present with a suspicion of malignant transformation. Moreover, HT ultrasonographic characteristics could make difficult the nodule identification and aspiration, although not associated with non-diagnostic and

indeterminate cytological rates [118]. The presence of lymphocytes in contact with thyroid cells is considered the most important element to make a differential diagnosis between HT and thyroid tumors [119] (**Figure 3**).

Radiologic evaluation of HT includes mainly sonographic examination, where specific features are considered a decreased echogenicity, heterogeneity hypervascularity and presence of hypoechoic micronodules with echogenic rim [120].

8. Treatment

The main purpose of HT treatment is the control of hypothyroidism and consists of oral administration of a synthetic hormone, the Levo-Thyroxine 4 (L-T4) [121], at a dosage of 1.6-1.8 micrograms per kilo. The substitution therapy must be prolonged for a lifetime to achieve normal circulating thyrotropin (TSH) levels. In selected cases, L-T4 treatment may be not required and only clinical observation is needed.

The role of glucocorticoids been questioned, as they may regulate the thyroiditis and acutely improve thyroid function, although the risks associated with the high dose and long treatment are considered to outweigh the benefit [122]. However, a short-term use of prednisolone may have a longer-term benefit in IgG4-disease subgroup [123].

The additional role of a specific diet for the management of HT has been questioned in recent years [124]. It has been postulated that an excessive iodine intake induces thyroid autoimmunity by increasing the immunogenicity of thyroglobulin in genetically predisposed subjects [125]. Thus, an high iodine supplementation in HT should be discouraged, as possibly dangerous, although an appropriate supplementation should be proposed in pregnancy to a total intake of 250g/day [122].

Selenium plays a key role in human thyroid hormone homeostasis, as several selenoproteins are involved in thyroid function, although efficacy of selenium supplementation in HT patients is debated [126]. Oral administration of selenium in the form of seleno-methionine would be beneficial in HT patients with selenium deficiency and should protect the thyroid gland from the

autoimmune reaction [127]. However, the literature is discordant [128]. A systematic review and meta-analysis by Wichman et al [129] showed a reduction of serum TPO-Ab levels and serum Tg-Ab; however, no significant correlation between the baseline selenium levels and the decrease in serum TPO-Ab level was demonstrated. A more recent systematic review and meta-analysis regarding the efficacy of oral administration of selenium revealed no effect of selenium supplementation on TSH levels, health-related quality of life [130] or thyroid ultrasound, in levothyroxine substitution-untreated individuals, and sporadic evaluation of clinically relevant outcomes in levothyroxine substitution-treated patients [131].

The association between vitamin D deficiency, HT pathogenesis and thyroid hypofunction has been demonstrated in several studies [126, 132, 133]. Since the low cost and the minimal side-effect of oral vitamin D supplementation, screening for vitamin D deficiency and supplementation may be recommended for patients with HT, with monthly monitoring of calcium and 25[OH]D levels, when clinically required [126].

The role of surgery for HT is limited for cases with a compression of cervical anatomical structures or in the presence of a nodule with malignant transformation characteristics [13, 134]. However, thyroidectomy performed in HT patients is burdened with a greater number of complications compared to other thyroid disorders [135]. As a future perspective, thyroid gland transplantation has also been proposed to correct hypothyroidism but needs to be validated by further studies [136].

9. Malignant transformation

Occurrence of HT is frequently found in thyroid glands resected for a neoplastic process. The association of HT and papillary thyroid cancer (PTC), firstly reported by Dailey in 1955 [137], has been widely debated. Controversy exists whether HT predisposes patients to the development of PTC, since this association may be considered a chance occurrence of two relatively common diseases or may be indicative of a cause and effect relationship, or at least a predisposing factor. This relationship has been postulated since chronic inflammation may lead to the development of a

neoplastic transformation, as demonstrated for other tissues. Moreover, the prolonged elevated levels of TSH in HT patients may stimulate follicular epithelial proliferation, thereby promoting the development of PTC [138-140] (**Figure 4**).

Several studies have investigated this association; however, results are dissimilar among studies. Interestingly, ambiguous data regarding this association may be due to a potential selection bias, as the majority of the publications in the past decades were retrospective analyses of patients undergoing thyroidectomy[138]. In the last years, the relationship between HT and PTC has been achieved by fine-needle aspiration cytology (FNAC) data, that are more representative of a typical population of patients with HT [138]. Data obtained from FNAC showed that the average prevalence of PTC in patients with HT was 1.20%, with an average risk ratio of 0.69, compared with the studies based on thyroidectomy data, where the average prevalence was about 27 % and risk ratio was and 1.59 [138, 141]. These data confirmed a higher risk reported in studies of thyroidectomy specimens, compared to studies of patients undergoing FNAC. Studies regarding FNAC show no significant increase of PTC in patients with HT, although FNAC specimens may be limited by a lack of definitive histological pathology. To date, evidence favoring a causal relationship between HT and PTC is inconsistent, and a validated criterion to identify HT patients at a higher risk of developing PTC is required, although a causative relationship between HT and PTC could not be excluded.

Despite PTC, occurrence of Non-Hodgkin primary thyroid lymphoma has been strongly associated with HT, as considered the only recognized risk factor, with a risk of about 60 times higher in patients HT[90]. Thyroid lymphoma accounts approximately 5% of all thyroid neoplasms, with a female predominance and histologically are mainly characterized by B cell phenotype, although a T-cell phenotype may also occur [90].

10. Conclusions

Although many genetic and environmental factors that could trigger an autoimmune response have been identified, the exact pathogenic mechanisms of HT are still unknown. Recently, the significance of epigenetic factors in HT etiopathogenesis has been highlighted, but further studies are necessary to accurately understand their role. The treatment of HT, which currently focuses on clinical symptoms of the disease, should in the future act on the autoimmune mechanism that causes the destruction of the thyroid parenchyma and the consequent hypothyroidism. A better understanding of epigenetic modifications and autoimmune pathogenic mechanisms could contribute to a more accurate diagnosis of HT, a more adequate choice of treatment approach, and a more precise prediction of treatment outcomes.

Conflict of Interest of all authors

the authors report no conflict of interest

Funding source

the authors report no funding sources for this article

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Figure 1. Loss of immune tolerance results in autoimmunity during the development of autoimmune thyroid diseases. Naive CD4+ T cells can be activated by dendritic cells (DC) or other antigen-presenting cells and they can differentiate into various subsets which are characterized by different cytokines and specific transcription factors. The balance of those immune cells is necessary for the maintenance of immune homeostasis. Under normal conditions, T cell subsets have normal functions, and there is immune homeostasis in human body, which can maintain the immune tolerance and avoid unwarranted immune attacks to thyroid tissues. Some genetic factors and environmental factors can result in the dysfunctions of these T cell subsets, B cells, and antigen-presenting cells, which may break up the immune homeostasis and cause thyroid autoimmunity. *From Wang B, Shao X, Song R, Xu D, Zhang JA. The Emerging Role of Epigenetics in Autoimmune Thyroid Diseases. Front Immunol. 2017 Apr 7;8:396 [55]*.

Figure 2. Thyroid autoimmunity produces two opposite pathogenetic processes and clinical outcomes. A: During Hashimoto's thyroiditis, self-reactive CD4+ T lymphocytes recruit B cells and CD8+ T cells into the thyroid. Disease progression leads to the death of thyroid cells and hypothyroidism. Both autoantibodies and thyroid specific cytotoxic T lymphocytes (CTLs) have been proposed to be responsible for autoimmune thyrocyte depletion. B: In Graves' disease, activated CD4+ T cells induce B cells to secrete thyroid-stimulating immunoglobulins (TSI) against the thyroid-stimulating hormone receptor (TSHR), resulting in unrestrained thyroid hormone production and hyperthyroidism. *From: Stassi G, De Maria R. Autoimmune thyroid disease: new models of cell death in autoimmunity. Nat Rev Immunol 2002, 2(3):195-204 [76]*.

Figure 3. (A) Histologic section of papillary thyroid carcinoma (left) and Hashimoto thyroiditis background (right). (B) Hashimoto thyroiditis showing effacement of thyroid architecture by diffuse lymphocyte infiltration and residual thyroid follicles. *From: Nam YJ, Kim BH, Lee SK, Jeon YK, Kim SS, Jung WJ, Kahng DH, Kim IJ. Co-occurrence of papillary thyroid carcinoma and mucosa-associated lymphoid tissue lymphoma in a patient with long-standing hashimoto thyroiditis. Endocrinol Metab 2013, 28(4):341-5 [142]*.

Figure 4. The relationships between Hashimoto thyroiditis (HT) and papillary thyroid carcinoma (PTC) with their immunological/hormonal pathogenic links. The left part shows the relevance of environmental factors and genetic background in thyroid carcinogenesis. Radiation may cause PTC development by RET-PTC oncogene rearrangements and more rarely with point BRAF mutations. Increased TSH levels due to nonautoimmune thyroid failure induced by radiation play an important role both in promotion and progression of PTC. The right part displays the complex relation

between HT and PTC. Multiple factors related to thyroid autoimmunity (serum anti-thyroid autoantibodies, inflammatory molecules, free radicals with secondary RET/PTC rearrangements), genetic/environmental conditions, and high TSH values (consequence of autoimmune thyroid failure) are involved. *From: Boi F, Pani F, Mariotti S. Thyroid Autoimmunity and Thyroid Cancer: Review Focused on Cytological Studies. Eur Thyroid J. 2017 Jul; 6(4): 178–186 [140]*.

Highlights

- Hashimoto's thyroiditis is one of the commonest autoimmune disorders.
- Hashimoto's thyroiditis is related to an interaction among genetic elements, environmental factors with an epigenetic influence.
- Diagnosis of Hashimoto thyroiditis is based on clinical features, presence of serum antibodies against thyroid antigens and cytological examination.
- The mainstream of treatment is based on the management of the hypothyroidism with a substitution therapy.

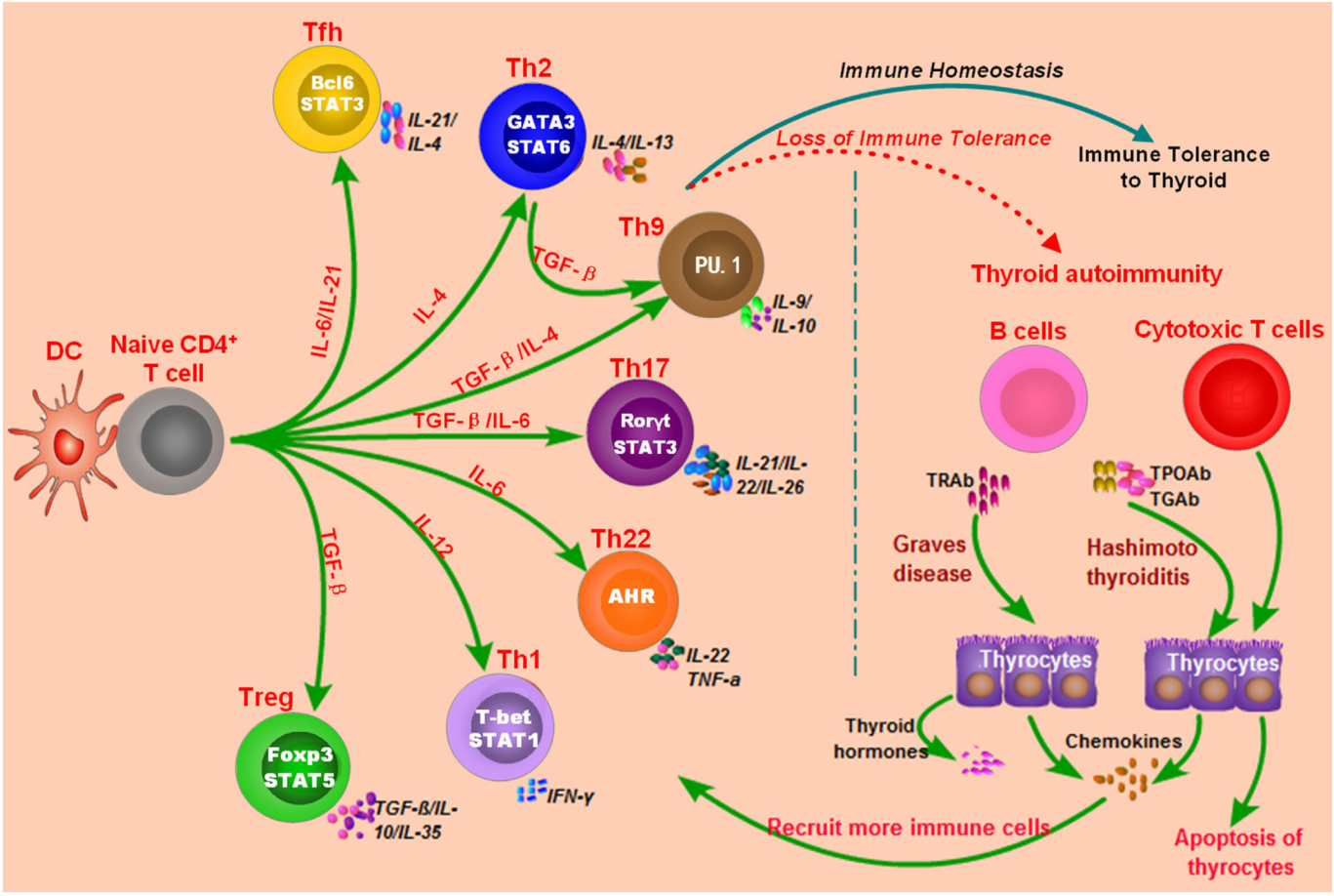
Tfh
Bcl6
STAT3
IL-21/
IL-4
Th2
GATA3
STAT6
IL-4/IL-13
Immune Homeostasis
Loss of Immune Tolerance
Immune Tolerance
to Thyroid
Th9
PU. 1
IL-9/
IL-10
TGF-β
Thyroid autoimmunity
DC
Naive CD4+
T cell
IL-6/IL-21
IL-4
TGF-β /IL-4
TGF-β /IL-6
B cells
Cytotoxic T cells
Th17
Rorγt
STAT3
IL-21/IL-
22/IL-26
TRAb
TPOAb
TGAb
IL-6
IL-12
TGF-β
Graves
disease
Hashimoto
thyroiditis
Th22
AHR
IL-22
TNF-a
Th1
T-bet
STAT1
IFN-γ
Thyrocytes
Thyrocytes
Treg
Foxp3
STAT5
TGF-ß/IL-
10/IL-35
Thyroid
hormones
Chemokines
Recruit more immune cells
Apoptosis of
thyrocytes

Figure 1

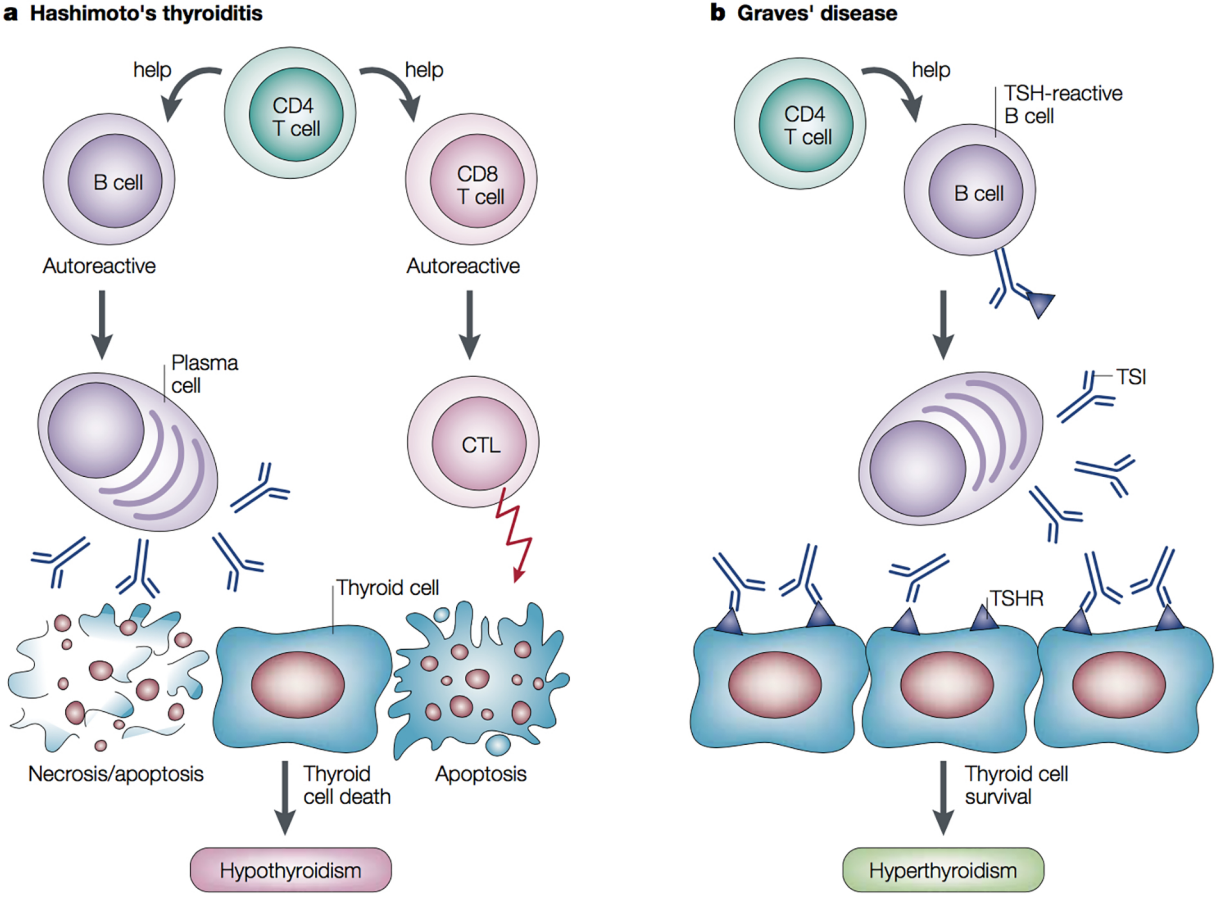
a Hashimoto's thyroiditis
help
CD4 T cell
help
B cell
CD8 T cell
Autoreactive
Autoreactive
Plasma cell
CTL
Thyroid cell
Necrosis/apoptosis
Thyroid cell death
Apoptosis
Hypothyroidism
b Graves' disease
help
CD4 T cell
TSH-reactive B cell
B cell
TSI
TSHR
Thyroid cell survival
Hyperthyroidism

Figure 2

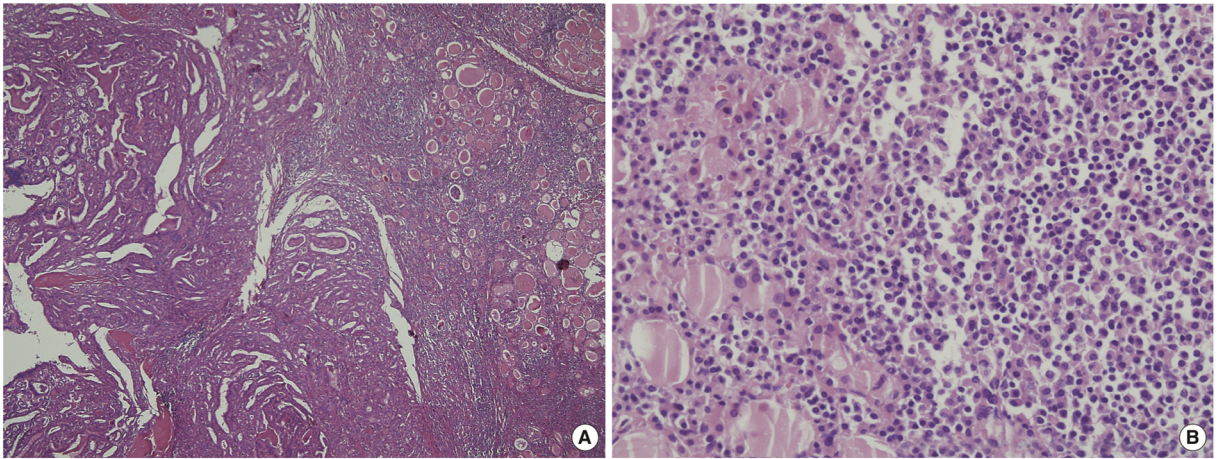

Figure 3

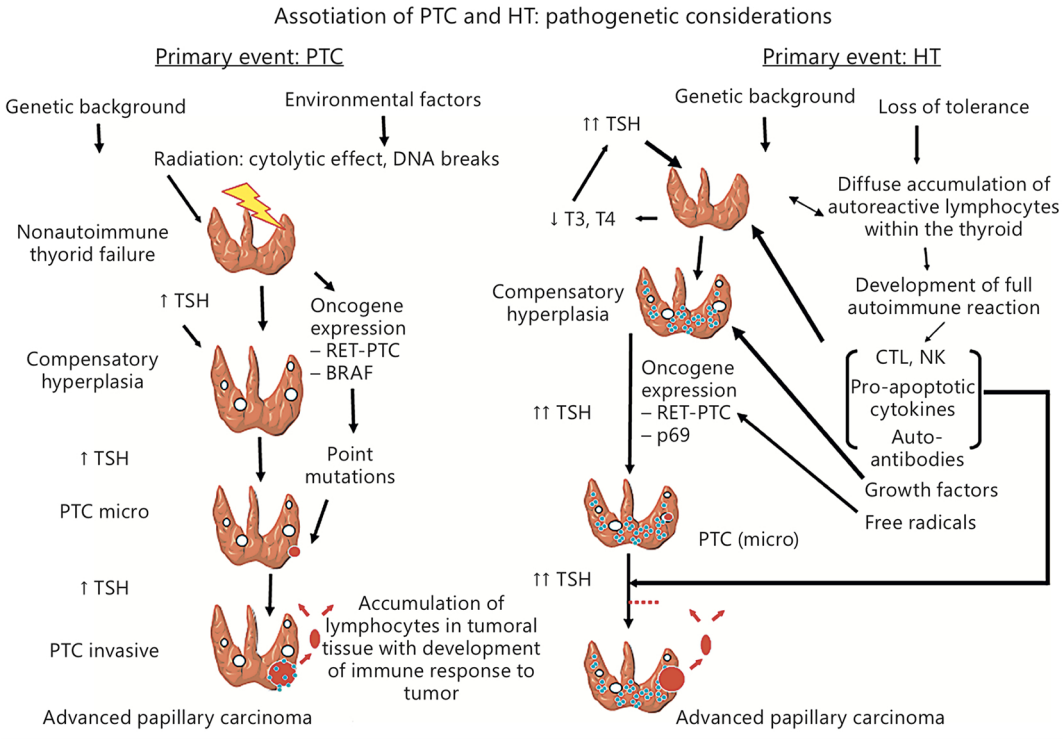
Assotiation of PTC and HT: pathogenetic considerations
Primary event: PTC
Genetic background
Environmental factors
Radiation: cytolytic effect, DNA breaks
Nonautoimmune thyorid failure
↑ TSH
Oncogene expression – RET-PTC – BRAF
Compensatory hyperplasia
↑ TSH
Point mutations
PTC micro
↑ TSH
PTC invasive
Accumulation of lymphocytes in tumoral tissue with development of immune response to tumor
Advanced papillary carcinoma
Primary event: HT
Genetic background
Loss of tolerance
↑↑ TSH
↓ T3, T4
Diffuse accumulation of autoreactive lymphocytes within the thyroid
Development of full autoimmune reaction
Compensatory hyperplasia
CTL, NK
Pro-apoptotic cytokines
Auto-antibodies
Oncogene expression – RET-PTC – p69
↑↑ TSH
Growth factors
Free radicals
PTC (micro)
↑↑ TSH
Advanced papillary carcinoma

Figure 4