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*Review*

# Pathogenesis Markers of Hashimoto's Disease—A Mini Review

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**Abstract**

Hashimoto's thyroiditis (HT) is the most common autoimmune disease involving the thyroid gland. HT often clinically manifest as hypothyroidism due to the destruction of thyroid cells mediated by humoral and cellular immunity. The pathogenesis of HT is a complex process in which environmental factors, hereditary inclination, trace elements immune factors, cytokines, and DNA and miRNA all play an important role. Herein, we summarize the precision factors involved in the pathogenesis of HT and offer an update over the past 5 years to provide a theoretical basis for further investigation of the relevant targets for HT treatment.

**Keywords:** Hashimoto's thyroiditis; autoimmunity; cytokines; pathogenesis; environmental factors; hereditary inclination; trace elements

## 1. Introduction

Hashimoto's thyroiditis (HT) is also known as lymphocytic thyroiditis and chronic autoimmune thyroiditis [1]. HT is a disease characterized by the infiltration and destruction of lymphocytes in thyroid tissues [2], and is the most common autoimmune disease worldwide [3]. Patients with HT develop thyroid antibodies via a number of immune processes. As a result, thyroid tissues are attacked by these antibodies and fibrosis occurs, resulting in the gradual loss of thyroid function [1]. The main clinical manifestation of HT is primary hypothyroidism, which is caused by damage to the thyroid gland [4], and is accompanied by weight gain, constipation, increased sensitivity to cold, and dry skin [5]. HT can cause cardiovascular diseases, such as coronary heart disease [6]. HT is also a risk factor for the development of thyroid cancer [7]. The prevalence of HT is on the rise. Genetic susceptibility, environmental factors, immune factors, cytokines, and vitamin D are all known to have an important role in the pathogenesis of HT [8–10]. Here, we summarize the pathogenesis of HT to identify targets for interventional treatment and to improve the prognosis (Fig. 1).

## 2. Hereditary Inclination

Genetic susceptibility plays an important role in the pathogenesis of HT [8]. Numerous studies have reported a genetic susceptibility to HT. HT is more prevalent in Latin America and less prevalent in Africa and Asians [9].

In the Swedish twin study, the HT concordance was 0.29 and 0.1 for monozygotic and dizygotic twins, respectively, with a heritability of 0.64 [8], the higher concordance among monozygotic twins can be hypothesized to be more heritable and susceptible than dizygotic twins [9].

Recombinant interleukin-2 receptor alpha (IL2RA), human leukocyte antigen (HLA), protein tyrosine phosphatase non-receptor type 22 (*PTPN22*), and cytotoxic T lymphocyte-associated antigen-4 (*CTLA4*) are susceptible sites for HT [11]. These loci have the potential to disrupt T-cell regulation and peripheral immune tolerance, and play an important role in the pathogenesis of HT [11].

HLA-B*46:01 is a prototypical immune response *gene* on the HLA complex, and it was shown by experimental controls that the HLA-B*46:01 gene increased the risk of HT in Han Chinese families [9]. In the thyroid tissue of HT patients, IL-18 is expressed at high levels, which promotes INF-$\gamma$ production and inhibits the proliferation of thyroid cells [12]. Carrying C at position 607 and G at position 137 have high promoter activity and promote the expression of IL-18 protein [13]. It was shown that 137 CG genotype is more frequent in HT patients, the risk of HT was more than 2.237 times higher in individuals with IL18 CG genotype than in individuals with GG genotype, the CA genotype is rare in patients with HT, therefore, it is inferred that the CG genotype is a risk factor for HT and the AC genotype plays a protective role against HT [14].

STAT proteins mediate the pro-inflammatory cytokine IL-6, which in turn affects dysregulated effector T cell responses [15]. Allele A of the STAT3 SNP rs744166 was significantly higher in HT patients than in controls, and compared to the control group, hypothyroidism in this group, demonstrating that allele A increased susceptibility to HT [16].

In a study of Chinese patients with immune thyroid disease, four HT susceptibility locus were identified at the genome-wide level, they were rs1265883 in SLAMF6,

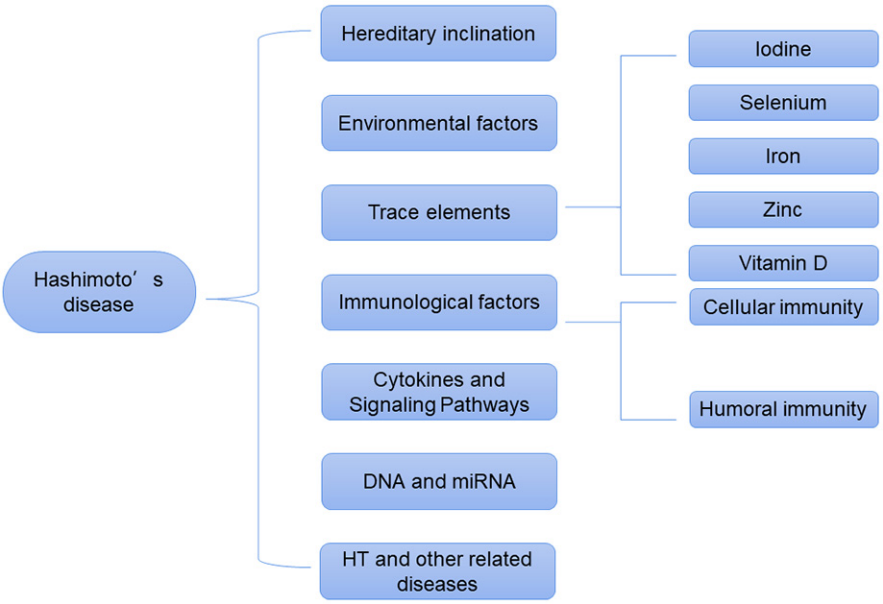


**Fig. 1. Pathogenesis of Hashimoto's disease.**

rs1024161 in CTLA4, rs1521 in the HLA-B region and rs5912838 in GPR174/ITM2A on chromosome X [17] (Table 1, Ref. [9,11,12,17,18]).

**Table 1. Hereditary inclination on HT.**

| High probability | Low probability |
|---|---|
| Latin America [9] | Africa and Asians [9] |
| Identical twins [9] | Dizygotic twins [9] |
| IL2RA, PTPN22 [11] | |
| HLA-B*46:01 [9] | |
| IL18 CG genotype [12] | |
| Allele A of the STAT3 SNP rs744166 [18] | |
| Mutation rs1265883 in SLAMF6 [17] | |
| Mutation s1024161 in CTLA4 [17] | |
| Mutation rs1521 in HLA-B [17] | |
| rs5912838 in GPR174/ITM2A at X chromosome [17] | |

## 3. Environmental Factors

Environmental factors can also influence the pathogenesis of HT [8]. In autoimmune reactive diseases, hygiene without microbial agents has been shown to be strongly associated with the incidence of autoimmune diseases [19]. A study has shown that women born in the summer months will have a 2% higher incidence than the general female population [20]. A range of cigarette smoking and alcohol consumption is protective against HT [21]. Prolonged exposure to stressful situations can also increase the incidence of HT [22]. Specifically, meat is a major nutritional factor that has been shown to increase the risk of thyroid autoimmunity, while plant-based fat-free foods containing fiber and antioxidants reduce the risk of developing HT [23] (Table 2, Ref. [20–23]).

## 4. Trace Elements

### *4.1 Iodine*

Iodine plays an important role in endocrine diseases, especially thyroid diseases. Thyroid epithelial cells take up iodine from the blood and, catalyzed by hydrogen peroxide, iodize thyroid tyrosine molecules, and the iodized products are catalyzed by thyroid peroxidase (TPO) to form T3 and T4 [18]. Studies have shown that increased iodine intake enhances the risk of autoimmune thyroid disease [5]. Both salt iodization schedules and excessive levels of supplementation can cause HT [24]. The current speculated mechanisms may be as follows: (1) Prolonged exposure to high iodine may increase the immunogenicity of thyroglobulin. (2) It activates the autoimmune response and triggers signaling pathways leading to apoptosis, which leads to the destruction of thyroid tissue. (3) Leading to oxidative stress. (4) Inhibition of Tregs impaired peripheral tolerance [18,25].

### *4.2 Selenium*

Selenium is an essential micronutrient that plays an important role in immune-related diseases [26]. The thyroid gland is the largest reservoir of selenium in the body [27]. SELENOS, a family of selenoproteins, is a susceptibility gene for HT that is expressed in thyroid follicular cells and encodes proteins involved in cellular stress and immune inflammatory responses [22]. Selenium supplementation has an immune-stimulating effect, and can inhibit HLA-DR expression in thyroid cells and reduces thyroid autoimmunity [5], as evidenced by increased T-cell proliferation

**Table 2. Environmental aspects on HT.**

| High probability | Low probability |
|---|---|
| Females born in summer [20] | Females born in other seasons [20] |
| Meat [23] | Plant-based foods [23] |
| Prolonged stress [22] | Smoking cigarettes and drinking alcohol in moderation [21] |
| | Residing in a relaxed environment [22] |

and enhanced innate immune cell function [26]. Thus, selenium deficiency is also involved in the pathogenesis of HT. Moreover, there is a link between diet and the development of HT.

### *4.3 Iron*

Iron plays an important role in hemoglobin and myoglobin, and it is involved in many important metabolic processes [28]. TPO can only be activated after binding to repair heme I, which is involved in thyroid hormone synthesis [18], therefore, iron content affects the synthesis of T3T4 [29]. The thyroid-gut axis has recently been found to be closely associated with HT [30], hypothyroidism may lead to digestive abnormalities, impaired intestinal function, and reduced iron absorption. After iron deficiency, it seriously affects the iodine regulation of thyroglobulin and the coupling of iodotyrosine molecules, which leads to the decrease of T3 and T4 production [18], it causes hypothyroidism HT is often associated with autoimmune gastritis [31], there are a large number of anti-parietal cell antibodies in serum. With the increase of disease course, it gradually evolves into severe atrophic gastritis, and gastric acid secretion is greatly reduced [32], causing the body to be unable to effectively absorb iron from food, leading to iron malabsorption [18].

### *4.4 Zinc*

Zinc is a trace element closely related to thyroid metabolism [33]. It promotes the synthesis of hypothalamic thyrotropin-releasing hormone and thyroid stimulating hormone, it is also a structural component of the T3 receptor [33]. It also acts as a thyroid hormone-binding transcription factor that regulates the expression of thyroid hormones [34]. Dietary deficiency of zinc and low serum zinc concentration can lead to changes in thyroid hormone metabolism and even thyroid structure [33]. Zinc deficiency reduces serum free T3T4 levels [30]. And zinc and thyroid function can affect each other, zinc deficiency leads to decreased thyroid function, thyroid insufficiency leads to inadequate zinc absorption [30].

### *4.5 Vitamin D*

Vitamin D deficiency is one of the causes of HT, whereby the greater the vitamin D deficiency, the greater the likelihood of HT [35]. Vitamin D concentrations are positively correlated with serum TNF-$\alpha$, IL-5, and IL-17, cytokines that mediate the cellular immune response to inflammation and are secreted by Th1 cells, in patients with HT [36]. Because cellular immunity is the main pathogenesis element in patients with HT, the relationship between vitamin D and these cytokines suggests that vitamin D is involved in the pathogenesis of HT. Dysbiosis of the gut flora contributes to HT triggers [3] (Table 3, Ref. [5,30,31,35]).

**Table 3. Trace elements aspects on HT.**

| High probability | Low probability |
|---|---|
| High iodine [5] | Low iodine [5] |
| Selenium deficiency [5] | Selenium-rich [5] |
| Iron deficiency [31] | Adequate iron [31] |
| Zinc deficiency [30] | Adequate zinc [30] |
| Vitamin D deficiency [35] | Adequate vitamin D [35] |

## 5. Immunological Factors

Because HT is an autoimmune disease characterized by thyroid-specific autoantibodies, inflammatory infiltration of T and B cells is the main pathogenesis [9]. It is reasonable to assume that in the context of genetic predisposition and environmental factors, errors in innate immune surveillance function produce antibodies against thyroid antigens that can cause both cytotoxic damage to thyroid cells and immune dysfunction, resulting in cellular and humoral immune responses and destruction of thyroid epithelial cells, thus causing disease.

### *5.1 Cellular Immunity*

Some autoreactive T cells escape immune regulatory control and enter the peripheral tissues, which leads to autoimmune disease, where stimulation by peripheral antigens, co-stimulatory factors, or specific cytokines activates T cells, resulting in the formation of different subpopulations of T cells [37]. Th cells and regulatory T cells (Tregs) are important T cells involved in the autoimmune response [38]. Tregs and Th cells are key regulators of inflammation and play an important role in immune tolerance [39]. CD4 is the main marker on the Th surface, with T helper 1 (Th1), T helper 2 (Th2), T helper 17 (Th17), and follicular helper T-cell subsets closely associated with the development of HT [40]. Th17 is capable of secreting IL17, which causes cell infiltration and tissue destruction [41]. Tregs consist mainly of $CD4^+$, $CD25^+$, and FOXP3, the first two markers of immune cells and FOXP3 an autoantigen, all of which are important components of the immune response

[42]. SIRT1-mediated aberrant FOXP3 acetylation activates Tregs, and therefore HT can be treated by modulating SIRT1 [43]. $CD4^+CD25^+$+FOXP3+ Treg subgroups play an important role in autoimmune diseases. In addition, an important role for $CD69^+NKG2D^+$ cells in HT has been identified [44]. The NKG2D receptor is capable of being expressed in $CD4^+$ because the NKG2D receptor is able to downregulate immunity through the mediation of IL-10 and TGF-$\beta$ [45]. In HT patients, $CD4^+CD69^+IL\text{-}10^+$, $CD4^+CD69^+NKG2D^+$, and $CD4^+CD69^+NKG2D^+$IL-10 cells are significantly increased. It can be assumed that $CD69^+$ and $NKG2D^+$ immunosuppression of defective Tregs also contribute to the pathogenesis of HT [44]. The following pathogenic mechanisms have been identified in Tregs: (1) CD25 and FOPXP3 expressed by Tregs suppress immunity by producing factors, such as TGF-$\beta$ and IL-10 [9]. (2) Recent findings have shown altered Treg activity compared to healthy or Down syndrome patients, thus providing evidence that an altered number of Tregs or function contribute to the development of HT [46]. (3) Reduced sensitivity of CD4 cells contributes to the inhibitory effects of TGF$\beta$ [9]. (5) The PD-1/PDL1 pathway is an important immune pathway that is activated at the onset of HT and has therefore been shown to be involved in the pathogenesis of HT [27]. (6) FAS is an apoptotic molecule, the expression of which is increased in HT patients, demonstrating that apoptosis is also part of the pathogenesis of HT [9]. It has been shown that pro-inflammatory cytokines mediate apoptosis in thyroid follicular cells by increasing oxidative stress [47]. (7) T follicular helper (Tfh) cells are a specific subset of $CD4^+$ cells that have an important role in the immune response by helping B cells produce specific antibodies [48]. Tfh can express the chemokine receptor, CXCR5, and the ICOS protein [49]. Increased Tfh cells in HT patients and increased $CD4^+/CXCR5^+/ICOS^{high}$ found in tissues confirm the involvement of Tfh in the pathogenesis of HT [9].

### *5.2 Humoral Immunity*

Antibodies against TG and TPO are present in nearly all HT patients [21]. AbTPO is predictive of hypothyroidism, and patients with high serum AbTPO titers are at increased risk of HT [27]. AbTPO antibodies are capable of producing two types of cytotoxicity (antibody- and complement-dependent cytotoxicity; 44). Indeed, such cytotoxicity destroys thyroid tissue, thus causing thyroid cell death and hypothyroidism [27]. An exosome is a new diagnostic marker with physiologic effects, such as antigen presentation and inflammatory activation [50]. Exosomes are involved in the pathogenesis of autoimmune diseases [51]. In HT patients, exosomes carry TPO and Tg, and deliver the MHC-IITPO/Tg complex to dendritic cells (DCs; 47). DCs accept antigen, bind TLR2/3, and result in an inability of $CD4^+$ cells to differentiate properly through the NF-$\kappa$B signaling pathway [27], thus participating in the pathogenesis of HT [52]. Recently, it has been shown that the thyroid gland of HT patients is infiltrated by IgG4-positive cells, which causes thyroid follicular atrophy and fibrosis [53]. IgG4-positive cells increase and hypothyroidism progresses more rapidly. Thus, IgG4-positive cells are also involved in the development of HT [53]. Sodium iodide symporter (NIS) mediates iodine uptake by the thyroid gland [54], and antibodies to NIS have been found in a small proportion of patients with HT; these antibodies inhibit the outward transport of iodine, thereby inducing HT [9]. Fluctuations in the equilibrium between TSAb and TBAb lead to changes in HT [9].

## 6. Cytokines and Signaling Pathways

The cytokines affecting HT are produced by subsets of Th1, Th2, and Th3 cells that participate in HT cellular and humoral immunity [55]. The main role of Th3 is to synthesize TGF$\beta$ [56]. Th1 is the primary environment for the HT immune response [57]. Th1 regulates late thyroid follicular cells (TFC) function and increases the expression of major histocompatibility complex class II (MHC-II), adhesion factors, and FAS in the pathogenesis of HT. IL-1$\beta$, IFN-$\gamma$, and IL-23 are pro-inflammatory cytokines produced by HT [58]. CAV1 is a plasma membrane microdomain protein that can participate in a variety of signaling pathways [59]. Autophagy maintains cells and organisms in a relatively stable state [60] and causes disease when autophagy-related processes are altered. CAV1 regulates the autophagic process [61]. Light chain 3 (LC3) is associated with autophagic vesicles with specificity, and therefore LC3 is a useful tool for assessing the autophagic process [62]. LC3B-II expression in thyroid cells is reduced after treatment with IL-$\beta$ and IFN-$\gamma$, indicating that autophagic [63] activity is inhibited in HT patients, inhibition of LC3B-II is more pronounced after down-regulation of the CAV1 gene [58], demonstrating that CAV1 causes HT by inhibiting autophagic activity [63]. We therefore hypothesize that downregulation of CAV1 is one of the pathogenic mechanisms of HT. Recent findings suggest that Th17 cytokines are important in the pathogenesis of chronic inflammation [64]. Th17 [65] cytokines are capable of producing IL-22 and IL-17 [66,67], with enhanced expression of IL-22 and IL-17 in HT patients, demonstrating the involvement of these cytokines in the pathogenesis of HT. In addition, T cells are able to enhance the conversion to IL-22 when stimulated by IL-6 [9]. IL-23 [63], a member of the IL-12 family [63,65], has a role in influencing Th17 cell function [68]. IL-17 and IL-23 signaling can also induce inflammatory cytokines, such as TNF and IL-22 [69]. High levels of IL-23 in serum can be detected in 56% of HT patients [70]. It is therefore reasonable to speculate that IL-23, via induction of pro-inflammatory cytokines, causes destruction of thyroid tissue and thus HT develops. Two signaling pathways, CD30-L/CD30 and IL-6/IL-6R, play a role in HT disease [71]. CD30-L/CD30 can expand Th2 subpopulation

and suppress Th1 subpopulation thus positively regulating T cells, protection of organs from cellular immunity [72]. In HT, TLR-3 protein first activates INF regulatory factor (IRF). This leads to the release of Th1-associated cytokine type 1 IFN. It also produces TNF$\alpha$ and IL-6, Th2 and other cytokines related to the pathogenesis of HT through the NK-$\kappa$B signaling pathway [71], In HT, lymphocyte infiltration can downregulate the epithelial expression of CD30-L/CD30 and upregulate the expression of IL-6/IL-6R [71]. Free IL-6 in serum is able to recruit gp80 and bind to it to form a gp80/IL-6 complex, which further activates gp130 [73]. The levels of both free IL-6 and bound gp80/IL-6 complexes are elevated in HT patients [74], so IL-6 is very closely related to the development of HT (Fig. 2). HO-1 and STAT3/PI3K/Akt pathways are involved in this mechanism [75]. The EAT model simulating HT patients was able to cause a significant increase in Akt and STAT3 phosphorylation, thereby attenuating the HT-related cytokines such as IL-17 and TNF-$\alpha$ [75]. In addition, the Notch signaling pathway has been shown to be involved in the pathogenesis of HT [4]. Tregs are able to regulate both Th1 and Th17 subgroups and there is negative cross-regulation between Th1 and Th17. It has been shown that FOXP3+ induces the synthesis of IL-17 by Th17/Treg cells and IL-17 exerts inflammatory effects leading to HT [76]. Notch signaling is thought to play an important role in cellular immunity [77]. It has been shown that Notch is involved in regulating the inflammatory immune response to HT via regulation of Treg/Th17 [42,78]. The increase in Th17 cells and decrease in Tregs in HT patients confirms the involvement of a Treg/Th17 cell axis imbalance in the development of HT [42]. In this process, Notch signaling, i.e., regulating T/B cell production, is also involved in the differentiation of peripheral mature T cells and their subpopulations. The Chinese herbal remedy, Xiaoying Daotan decoction, downregulates Notch expression and upregulates Treg cytokines to suppress the development of HT [42]. Specific HDAC6 inhibitors (HDAC6is) have immunomodulatory properties [79], it can reduce the level of Tg, TPO and IL-17A in serum through PKM2/STAT3 axis, and reduce the thyroid damage caused by HT [80]. HMGB1/TLR9/MYD88 is also one of the pathways in the pathogenesis of HT. Activation of this pathway produces large amounts of inflammatory factors such as TNF-$\alpha$, IL-6, and IL-1$\beta$, which cause impaired thyroid function and lead to organ damage [81] (Fig. 3). Intervention in these pathways. can effectively prevent or control the development of HT [82].

## 7. DNA and miRNA

Environmental factors and genetics act synergistically to determine HT. Inactivation of some genes is associated with DNA methylation. In children and adolescents with HT, DNA methylation has been shown to act on the PTPN22 gene, thereby affecting thyroid function [83]. Some histone alterations affect the expression of some

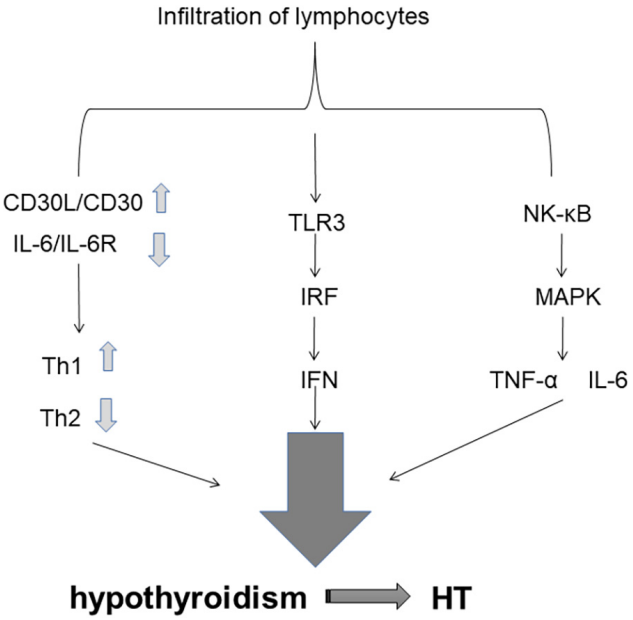


**Fig. 2. Cytokines and Signaling Pathways.**

genes. Tri-methylated histone H3 lysine 4 (H3K4me3) is a marker of gene activation and an overall alteration of H3K4me3 was found in HT patients, with H3K4me3 enrichment in the follicular cells of the thyroid gland of HT patients [84]. These processes are all environment-dependent [21]. The release of genomic DNA from dead cells can activate innate immunity, and it is the H2B histone of DNA that has been shown experimentally to be closely associated with innate immune activation [9]. The miRNA is a novel regulatory gene regulator that is involved in the pathogenesis of many autoimmune diseases [85]. MiR-451 promotes the apoptotic process and accelerates cell death through the expression of caspase-3 [86]. Apoptosis is also a pathogenic mechanism underlying HT. Inhibition of miR-451 expression is effective in reducing the incidence of HT [87]. Thus, miR-451 is an important molecule in the pathogenesis of HT. MiR-296 is overexpressed in HT patients and is capable of causing hypothyroidism, thus miR-296 is also involved in the pathogenesis of HT [87]. The female advantage in HT is associated with inactivation of the X chromosome [88]. FOXE1 is a transcription factor that is involved in the developmental and differentiation processes of the thyroid gland, such as the genes for TPO and Tg [27]. FOXE1 mutations may cause thyroid dysplasia, making the thyroid gland hypothyroid [89]. MAGI3 is a newly identified group of genetic markers that is associated with an increased risk of progression from TPO antibody positivity to hypothyroidism, and implies an association with the pathogenesis of HT [90]. Long non-coding RNAs have recently been recognized as critical for the regulation of genomic expression [91]. Abnormalities in lncRNAs are often associated with immune system diseases [92]. MAFTRR is the transcription product of lncR-

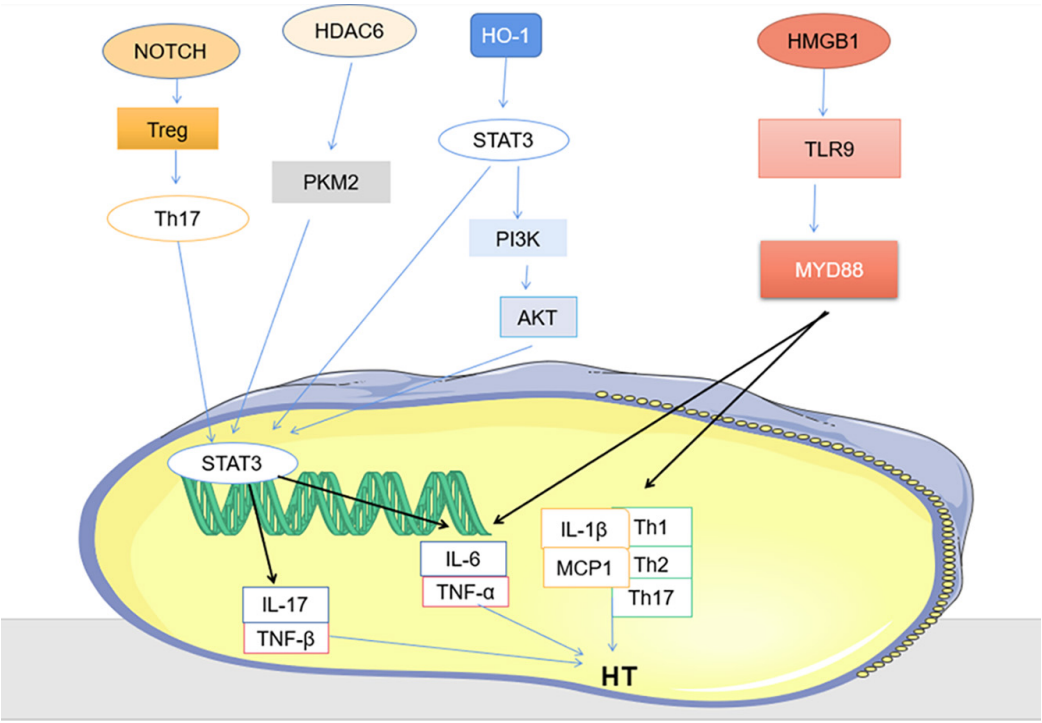


**Fig. 3. Other signaling pathways (PKM2/ STAT3, HMGB1 / TLR9/MYD88 and HMGB1/TLR9/MYD88).**

NAs, a chromatin-associated Th1-specific expression product [93]. Th1 cells are able to activate macrophages and cytotoxic lymphocytes, thus destroying thyroid follicular cells and causing hypothyroidism. MAFTRR has two roles: (1) promoting the differentiation of CD4T cells to Th1 cells and (2) promoting the production of IFN-$\gamma$+ factors in Th1 cells [94]. An increase in MAFTRR transcript levels can lead to an increase in the proportion of Th1 cells and can also increase the transcript levels of IFNG [95]. lncRNAs are able to promote the expression of adjacent genes through epigenetic modifications [96], because of the relative proximity of the MAFTRR to the *MAF* gene, the MAFTRR of HT patients may mistakenly recruit both of the (EZH2 and LSD1) repressor genes into the promoter of the *MAF* gene [93], thereby blocking *MAF* gene transcription [96], thus destroying the thyroid cells and causing hypothyroidism. Increased expression levels of miR-451 were also found in HT patients, but the mechanisms involved have not been clarified [85]. In addition, since pro-inflammatory factors can cause downregulation of miR-141 and upregulation of miR-22 in HT patients, these are positively correlated with disease activity [66] .

## 8. HT and Other Related Diseases

The pathogenesis of HT is further clarified by understanding the familial correlation with other diseases. Six diseases (autoimmune hemolytic anemia, chronic glomerulonephritis, chronic rheumatic heart disease, immune thrombocytopenic purpura, aspergillosis, and Takamatsu disease) are specifically present in the offspring of patients with HT disease in a study of family-associated autoimmune diseases in HT offspring [97]. Arthropathy and connective tissue disease are more common in adults with HT, while type I diabetes and celiac disease are more common in adolescents with HT [63]. Glutamate dehydrogenase is a key autoantigen in type I diabetes, and studies have demonstrated that HLA-II is able to bind TPO and glutamate dehydrogenase, which together lead to the activation of T cells, which may be the pathogenesis of HT [98]. Celiac disease is a chronic autoimmune disease in which specific T-cell antigens can be detected in the mutated peritoneal mucosa of patients with celiac disease. After a number of immune reactions, Th1 cells are stimulated to secrete pro-inflammatory cytokines, such as TNF-$\alpha$ and INF-$\gamma$ [99]. This reaction damages the intestinal mucosa and these pro-inflammatory factors can participate in damaging thyroid cells, thus causing hypothyroidism, again providing valid evidence for INF-$\gamma$ being a key pathway in the development of HT generation.

## 9.Treatment

The most common way to control HT is to take levothyroxine (L-T4) to control the disease [100]. Long-term use of 1.6–1.8 mg per kg to achieve normal levels of thyrotropin in the body [21]. Pregnant women and infants should be treated with liquid L-T4, which is much more bioequivalent than tablets [101]. When the condition is more urgent, prednisone can also be used for shock therapy [102]. Traditional Chinese medicine also plays a significant role in the treatment of HT, Xiaoying Daotan decoction can

effectively down-regulate Notch protein, up-regulate Treg cytokines, down-regulate Th17 cytokines, and reduce immune attack on thyroid gland [42]. It can be used as an effective drug for the treatment of HT. Histone deacetylase 6 specific inhibitor (HDAC6i) inhibitor reduces Th17 cell differentiation by regulating PKM2/STAT3 axis, and successfully reduces thyroid tissue damage [80]. HT is closely related to trace elements and dietary fiber, so appropriate diet, healthy lifestyle, adequate sleep and appropriate vitamin D supplementation can improve the condition [103]. PI3K inhibitor LY294002, Akt inhibitor triciribine or STAT3 inhibitor WP1066 all significantly reduced the severity score of thyroiditis [75], all can be considered as therapeutic agents for HT. Edaravone is a drug that scavenges hydroxyl radicals [104], it acts on the STAT3/PI3K/Akt pathway to effectively improve autoimmune thyroiditis and has become an emerging drug for the treatment of HT [104]. PV-mediated HMGB1 inhibition decreased the expression of pro-inflammatory cytokines and suppressed the HMGB1-TLR9 signaling pathway in, while downregulating the proportion of Th1, Th2 and Th17 cells in splenocyte, provides a potential therapeutic value for HT [81], the lignan component of PV has a strong affinity for the disease protein of HT, and quercetin has a strong affinity for serum thyroid peroxidase (TPO), further confirming that PV can effectively treat HT [100].

## 10. Conclusions

HT is an autoimmune disease caused by a variety of factors, such as environmental factors, genetic susceptibility, and immune factors. The thyroid gland of HT patients is often infiltrated by lymphocytes and fibrosis, and often presents clinically as a painless, diffuse goiter and hypothyroidism. The current treatment for HT is based on thyroid replacement therapy. Among them, the specific mechanism of MicroRNA in relation to the development of HT has not been clarified, the mechanism of elevated MAFTRR in HT patients has not been elucidated, and how MAF damages IFN-$\gamma$ in Th1 cells has not been exhaustively described, so further research is needed regarding the above, and whether other genes are associated with the development of HT. This article summarized the factors that lead to HT. Further investigation of the relevant signaling pathways is needed, however, to provide more effective clinical targets for treatment.

## Availability of Data and Materials

The supporting materials have been included in the article.

## Author Contributions

BJ searched the literature and wrote the article. ZF designed the manuscript. ZF and SW revised the manuscript. All authors read and approved the final manuscript.

## Ethics Approval and Consent to Participate

Not applicable.


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## Conflict of Interest

The authors declare no conflict of interest.

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