

# An overview of the pathogenic mechanisms of autoimmune thyroid disorders

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Objectives, recent epidemiologic studies in humans suggest an increased prevalence of thyroiditis associated with the excessive administration of iodine. More than three times of recommended daily intake of iodine was observed among people in North America. These people generally presented higher level of anti-thyroglobulin antibody, anti-thyroperoxidase antibody, serum thyroid-stimulating hormone and exacerbation of lymphocytic infiltration in thyroid, which indicated the overconsumption of iodine could induce hypothyroidism and enhance the autoimmune response. However, the precise mechanism of excessive iodine intake induced autoimmune thyroid disease remains largely unknown.

Over half a century has elapsed since the 1956 identification of thyroglobulin antibodies and the devising of the first experimental model of autoimmune thyroiditis. Since then an incredible amount of experimental work has led to an ever deeper understanding of the nature of thyroid auto-antigens, the main immune mechanisms responsible for Hashimoto's thyroiditis and graves' disease, their genetics, and their environmental risk factor. Yet, in the majority of genetically predisposed people the individual trigger of thyroid autoimmunity remains obscure. Similarly, effective prevention strategies still remain to be established and, hopefully, will be the target of future studies.

**Key Words:** Autoimmune, Pathogenic mechanism, Thyroid disorders

Autoimmune thyroid diseases are a group of heterogeneous disorders characterized by abnormal lymphocytic activation directed against self-tissues,<sup>1</sup> and essentially represented by Hashimoto's thyroiditis and Graves' disease, which afflict approximately 2-3% of the population with female predominance.<sup>2</sup> In pediatrics, autoimmune thyroid disease is the most common thyroid disorder, the most common age at presentation is adolescence, but the disease may occur at any time, rarely even in children under one year of age.<sup>3</sup>

They fulfill all the required criteria for autoimmune diseases including.

- 1) infiltration of the thyroid by lymphocytes, which are auto-reactive to thyroid antigens;
- 2) presence of circulating thyroid auto-antibodies;
- 3) immunological overlap with other autoimmune diseases;
- 4) a story of familial occurrence, mainly in female;
- 5) the possibility to produce both experimental autoimmune thyroiditis and, to a lesser extent, Graves, disease in laboratory animals.<sup>4</sup>

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The three main thyroid auto-antigens, which were identified several decades ago, are thyroglobulin, the organ-specific enzyme thyroid peroxidase, and the TSH-receptor. More recently, autoantibodies to pendrin, an iodide transporter located at the apical pole of thyroid follicular cells, were identified in the majority of patients with Hashimoto's thyroiditis and Graves' disease.<sup>5</sup> And recent epidemiologic studies in humans suggest an increased prevalence of thyroiditis associated with the excessive administration of iodine. More than three times of recommended daily intake of iodine was observed among people in North America. These people generally presented higher level of anti-thyroglobulin antibody, anti-thyroperoxidase antibody, serum thyroid-stimulating hormone and exacerbation of lymphocytic infiltration in thyroid, which indicated the overconsumption of iodine could induce hypothyroidism and enhance the autoimmune response.<sup>6-7</sup> However, the precise mechanism of excessive iodine intake induced autoimmune thyroid disease remains largely unknown.

## BASIC MECHANISMS IN THE DEVELOPMENT OF THYROID AUTOIMMUNITY

Because of the importance of T-cells in immune regulation, much attention has focused on this lymphocyte subpopulation to explain the breakdown in tolerance and the clinical manifestations seen in autoimmune thyroid disease.<sup>8-10</sup> Consistent with their playing a fundamental role,

an increased proportion of activated T-helper(Th) (CD4+) cells can be demonstrated in the circulation of a majority of patients with autoimmune thyroid disease and this is thought to lead to a cascade of immune-mediated events.<sup>11-12</sup>

Most of our current knowledge on the basic mechanisms of thyroid autoimmunity derives from data obtained studying experimental models of autoimmune disease, mainly in mice. Experimental autoimmune thyroiditis (EAT) in mice can be induced by immunization with mouse Tg emulsified in complete Freund's adjuvant.<sup>13-15</sup> Antigen presenting cells(APC), such as dendritic cells (DC), present immunogenic epitopes of Tg to T cells in the context of Class II major histocompatibility molecules(MHC).<sup>16,17</sup> Costimulatory signals are also required, which may result in either activation or down-regulation of T cells. Based on the type of cytokines secreted by these DCs, a Th1, Th2, or a Th17 immune response can be initiated. Th1 cells predominantly secrete IFN- $\gamma$  and IL12, whereas Th2 cells secrete IL4 and IL10. Th17 cells secrete IL17. Th1 and Th17 cells have been shown to infiltrate the thyroid, resulting in chronic inflammation and eventually death of the thyrocytes in EAT.<sup>16-20</sup> CD4+T cells are the major type of lymphocytic cells infiltrating the gland in thyroid autoimmune diseases. CD4+T cells comprise a functionally heterogeneous population of T effector cells(Teff), being responsible for the development of thyroiditis and a smaller population(10%) of T regulatory cells(Tregs), which express CD25(The IL-2 receptor  $\alpha$ ). Tregs are critical for maintaining peripheral tolerance and are identified by their expression of Foxp3,

a transcription factor which is necessary and sufficient for Treg development. These cells typically secrete the cytokines IL-10 and Transforming Growth Factor- $\beta$  (TGF $\beta$ ) to induce tolerance. Neonatal thymectomy (at 3 days) and irradiation result in a multi-organ autoimmune disease, thus providing evidence for natural Tregs. The role of these cells is to prevent the development of organ-specific autoimmunity. Tregs are kept at a basal state of activation by low levels of circulating auto-antigen; the homeostatic level is sufficient to prevent the development of autoimmunity, but the clonal balance between Tregs and auto-reactive T cells could be overcome by immunogenic stimuli, such as the administration of mTG and adjuvant.<sup>21-22</sup>

As demonstrated by the group of Prabnakar,<sup>23</sup> treatment of mTg primed mice with granulocyte-macrophage-colony stimulating factor (GM-CSF) induces semi-matured tolerogenic DCs that are characterized by reduced levels of pro-inflammatory cytokines such as IL-1 $\beta$  and IL-12 and increased levels of pathogenic T<sub>H</sub>1, induce and expand Tregs. Tregs produce IL-10 and TGF- $\beta$ , two regulatory cytokines, which, by counteracting the role of pro-inflammatory cytokines, result in the suppression or prevention of EAT.

In addition to cell-mediated immune mechanisms, AITD is characterized by the secretion of antibodies (Abs) to a variety of thyroid-specific antigens, most notably thyroglobulin (Tg), and thyroid peroxidase (TPO) but also to a lesser extent the TSH receptor, the sodium iodide symporter (NIS), and most recently pendrin.<sup>13,14</sup>

Experimental evidence in mice demonstrated that, apart

from Tg, TPO is also a major antigen in chronic autoimmune thyroiditis. Indeed, transgenic, TAZ10, mice expressing a human T cell receptor specific for a cryptic TPO epitope, spontaneously develop chronic autoimmune thyroiditis. This thyroid autoimmunity model is Major Histocompatibility Complex (MHC II) restricted, but occurs independently from mature B cells and antibodies.<sup>16,24</sup> Moving from these experiments in mice, the group of Schott recently studied TPO- and Tg epitope-specific CD8<sup>+</sup> T cells in patients with HT, who were investigated both at the time of diagnosis and after a long-lasting disease. To this end, they synthesized six different human leukocyte antigen (HLA)-A2 restricted, TPO- or Tg- specific tetramers. The frequency of peripheral TPO- and Tg- specific CD8 positive T cells was significantly higher in HLA A2 positive HT patients (2.8+9.5%) compared with HLA-A2 negative HT patients (0.5+0.7%), HLA A2 positive non-autoimmune goiter patients (0.2+0.4%), and HLA-A2-positive healthy controls (0.1+0.2%). The frequency of Tg-specific T cells (3.0%) was very similar to that of TPO specific CD8-positive T cells (2.9%). Subgroup analyses revealed a steady increase of the number of epitope-specific CD8-positive T cells from 0.6+1.0% at initial diagnosis up to 9.4+18.3% in patients with long lasting disease. Analyses of the number of thyroid-infiltrating cells as well as the cytotoxic capacity revealed a similar picture for TPO- and Tg- specific T cells. These data demonstrate that both TPO- and Tg-specific CD8-positive T cells are involved in the disease process of HT. Interestingly enough, Tg-specific T cells were elevated in the peripheral blood at the time point of clinical disease manifestation, whereas

a reverse distribution was observed in the thyroid aspirates. This phenomenon may suggest a role of Tg-specific T cells at disease initiation. During disease progression, TPO-specific T cells would acquire an incremental role due to epitope spreading. Taken together, this study supports the view that in HT a combined TPO- and T-specific cytotoxic immune response does occur.<sup>25</sup>

In the last few years, evidence was also accumulated supporting the concept that IFN- $\gamma$  inducible chemokines, such as CXCL10, play an important role in the initial stages of thyroid autoimmunity. When stimulated by IFN- $\gamma$ , thyroid follicular cells secrete CXCL10, which in turn recruits into the thyroid Th1 lymphocytes expressing CXCR3 and secreting IFN- $\gamma$ , thus establishing a loop which reinforces and maintains the autoimmunity process.<sup>26</sup>

## LOSS OF SELF-TOLERANCE TO THE THYROID IN HUMANS

### ROLE OF GENETICS

The role of genetics is suggested by the high frequency of autoimmune thyroid diseases affecting family members and by a significantly higher concordance of autoimmune thyroid diseases in monozygotic (HT=55%; GD=35%) compared to dizygotic (HT=0%; GD=35%) twins. The fact that concordance is not 100% in monozygotic twins indicates that environmental factors also play an important role in the etiology of autoimmune thyroid disease. Indeed, it is assumed that autoimmune thyroid

diseases are caused by the combined effects of multiple susceptibility genes and environmental factors which affect both the thyroid and the systemic immune system.<sup>27-</sup>

<sup>30</sup> Several susceptibility genes have been identified by whole candidate gene analysis, genome linkage studies genome-wide association studies, and whole genome sequencing techniques. These genes are classified as non-specific immune-related genes and thyroid-specific genes.<sup>31,32</sup>

### ROLE OF THE ENVIRONMENT

As recently reviewed by Duntas, an array of environmental factors have been inculcated for their stimulatory effect in thyroid autoimmunity. Some of these factors, such as iodine excess, selenium deficiency, tobacco smoking and, possibly, industrial pollutants, exert their effects mainly at a population level. Infective agents, immune-modulatory drugs, and stress are probably more relevant for the individual development of autoimmune thyroid disease.<sup>33,34</sup>

## CONCLUSIONS

Over half a century has elapsed since the 1956 identification of thyroglobulin antibodies and the devising of the first experimental model of autoimmune thyroiditis. Since then an incredible amount of experimental work has led to an ever deeper understanding of the nature of thyroid autoantigens, the main immune mechanisms responsible for Hashimoto's thyroiditis and graves' disease, their genetics, and their environmental risk factor. Yet, in the majority of genetically predisposed people the individual trigger of

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## Peer Reviewers' Commentary

Over half a century has elapsed since the 1965 identification of thyroglobulin antibodies and the devising of the first experimental model of autoimmune thyroiditis. Since then an incredible amount of experimental work has led to an ever deeper understanding of the nature of thyroid auto-antigens, the main immune mechanisms responsible for Hashimoto's thyroiditis and grave's disease, their genetics, environmental risk factor. Effective prevention strategies still remain to be established and hopefully, will be the target of future studies. In this review, easy to clean and the pathogenesis autoimmune thyroid disorders is thought to be the primary outpatient care will help a lot.