

An overview of the pathogenic mechanisms of autoimmune thyroid disorders

Keun Yong Park

Department of Internal Medicine, College of Medicine, Konyang University, Daejeon, Korea

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,¹ and essentially represented by Hashimoto's thyroiditis and Graves' disease, which afflict approximately 2-3% of the population with female predominance.² 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.³

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 familiar occurrence, mainly in female;
- 5) the possibility to produce both experimental autoimmune thyroiditis and, to a lesser extent, Graves, disease in laboratory animals.⁴

Corresponding Author : Keun Yong Park, Department of Internal Medicine, College of Medicine, Kangyang University, 685, Gasuwon-dong, Seo-gu, Daejeon, Korea
TEL: +82-42-600-9169 E-mail: kypark5211@naver.com

Received : July 29, 2014
Revised : July 29, 2014
Accepted : August 1, 2014

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.⁵ 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-thyropoxidase 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.⁶⁻⁷ 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.⁸⁻¹⁰ 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.¹¹⁻¹²

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.¹³⁻¹⁵ Antigen presenting cells(APC), such as dendritic cells (DC), present immunogenic epitopes of Tg to T cells in the context of ClassII major histocompatibility molecules(MHC).^{16,17} 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- γ 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.¹⁶⁻²⁰ CD4+T cells are the major type of lymphocytic cells infiltrating the gland in thyroid autoimmune diseases. CD4+T cells comprise a functionally heterogenous 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 α). 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- β (TGF β) 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.²¹⁻²²

As demonstrated by the group of Prabnakar,²³ 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 β and IL-12 and increased levels of pathogenic Teff, induce and expand Tregs. Tregs produce IL-10 and TGF- β , 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.^{13,14}

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.^{16,24} Moving from these experiments in mice, the group of Schott recently studied TPO- and Tg epitope-specific CD8⁺ 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.²⁵

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

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.²⁷⁻

³⁰ 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.^{31,32}

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.^{33,34}

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

thyroid autoimmunity remains obscure. Similarly, effective prevention strategies still remain to be established and, hopefully, will be the target of future studies.

REFERENCES

- Giulia Cogni, Luca Chio vato. An overview of the pathogenesis of thyroid autoimmunity. *Hormones* 2013;1:19-29.
- Jenkins RC, Weetman AP. Disease association with autoimmune thyroid disease. *Thyroid* 2002;2:977-88.
- Rosalind S, Brown. Autoimmune Thyroiditis in childhood. *J Clin Res Pediatr Endocrinol* 2013;5:45-9.
- Rose NR, Bona C. Defining criteria for autoimmune disease. *Immunol Today* 1993;14:426-30.
- Yoshida A, Hisatome I, Taniguchi S, Shirayoshi Y, Yamamoto Y, Miake J, et al. Pendrin is a novel autoantigen recognized by patients with autoimmune thyroid diseases. *J Clin Endocrinol Metab* 2009;94:441-8.
- Psegnas, Pirozzi G, Poccoli M, Fratir, Santoni A, Palmieri G. p38MADK activation controls are the TLR3-mediated up-regulation of cytotoxicity and cytokine production in human NK cells. *Blood* 2004;104:4157-64.
- Sivori S, Falco M, Della Chiesa M, Carlomagno S, Vitale M, Moretta L, et al. CpG and double-stranded RNA trigger human NK cells by Toll-like receptors: induction of cytokine release and cytotoxicity against tumors and dendritic cells. *Proc Natl Acad Sci USA* 2004;101:10116-21.
- Foley TP Jr, Abbassi V, Copeland KC, Draznin MB. Brief report; hypothyroidism caused by chronic autoimmune thyroiditis in very young infants. *N Engl J Med* 1994;330:466-8.
- Gessl A, Wifing A, Agis H, Steiner G, Czernin S, Boltz-Nitulescu G, et al. Activated Naïve CD4+ peripheral blood T cells in autoimmune thyroid disease. *Thyroid* 1995;5:117-25.
- Wang SH, Baker JR. The role of apoptosis in thyroid autoimmunity. *Thyroid* 2007;17:975-9.
- Bottazzo GF, Pujol-Borrell R, Hanafusa T, Feldmann M. Role of aberrant HLA-DR expression and antigen presentation in induction of endocrine autoimmunity. *Lancet* 1983;2:1115-9.
- Weetman AP. Cellular immune responses in autoimmune thyroid disease. *Clin Endocrinol (Oxf)* 2004;61:405-13.
- Ajjan Ram Kemp EH, Waterman EA, Watson PF, Endo T, Onaya T, Weetman AP. Detection of binding and blocking autoantibodies to the human sodium-iodide symporter in patients with autoimmune thyroid disease. *J Clin Endocrinol Metab* 2000;85:2020-7.
- Yoshida A, Hisatome I, Taniguchi S, Shirayoshi Y, Yamamoto Y, Miake J, et al. Pendrin is a novel autoantigen recognized by patients with autoimmune thyroid diseases. *J Clin Endocrinol Metab* 2009;94:442-8. Epub 2008 Dec 2.
- Feingold SB, Smith J, Houtz J, Popovsky E, Brown RS. Prevalence and functional significance of thyrotropin receptor blocking antibodies in children and adolescents with chronic lymphocytic thyroiditis. *J Clin Endocrinol Metab* 2009;94:4742. Epub 2009 Oct 2223.
- Menconi F, Monti MC, Greenberg DA, Oashi T, Osman R, Davies TF, et al. Molecular amino acid signatures in the MHC class II peptide binding pocket predispose to autoimmune thyroiditis in humans and in mice. *Proc Natl Acad Sci USA* 2008;105:14034-9.
- Yoshida A, Hisatome I, Taniguchi S, Shirayoshi Y, Yamamoto Y, Miake J, et al. Pendrin is a novel autoantigen recognized by patients with autoimmune thyroid disease. *J Clin Endocrinol Metab* 2009;94:442-8.
- Vasu C, Dogan RN, Holterman MJ, Prabhakar BS. Selective induction of dendritic cells using granulocyte macrophage colony stimulating factor, but not fmslike tyrosine kinase receptor 3-ligand, activates thyroglobulin-specific CD4+/CD25+ T cells and suppresses experimental autoimmune thyroiditis. *J Immunol* 2003;170:5511-22.
- Kroemer G, Hirsch F, Conzalez-Garcia A, Martinez C. Differential involvement of Th1 and Th2 cytokines in autoimmune diseases. *Autoimmunity* 1996;24:25-33.
- Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD, et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J Exp Med* 2005;201:233-40.
- Yoshimoto T, Takeda K, Tanaka T, Ohkusu K, Kashiwamura S, Okamura H, et al. IL-12 up-regulates IL-18 receptor expression on T cell, Th1 cells, and B cells: synergism with IL-18 for IFN-gamma production. *J*

- Immunol 1998;161:3400-7.
22. Kong YC, Morris GP, Brown NK, Yan Y, Flynn JC, David CS. Autoimmune thyroiditis: a model uniquely suited to probe regulatory T cell function. *J Autoimmun* 2009;33:239-46.
 23. Gangi E, Vasu C, Cheatem D, Prabhakar BS. IL-10-producing CD4+CD25+ regulatory T cells play a critical role in granulocyte macrophage colony-stimulating factor-induced suppression of experimental autoimmune thyroiditis. *J Immunol* 2005;174:7006-13.
 24. Quaratino S, Badami E, Pang YY, Bartok I, Dyson J, Kioussis D, et al. Degenerate self-reactive human T cell receptor causes spontaneous autoimmune disease in mice. *Nat Med* 2004;10:920-6.
 25. Ehlers M, Thiel A, Bernecker C, Porwol D, Papewalis C, Willenberg HS, et al. Evidence of a combined cytotoxic thyroglobulin and thyroperoxidase epitope-specific cellular immunity in Hashimoto's thyroiditis. *J Clin Endocrinol Metab* 2012;97:1347-54.
 26. Rotondi M, Chiovato L, Tomagnani S, Serio M, Romagnani P. Role of chemokines in endocrine autoimmune diseases. *Endocr Rev* 2007;28:492-520.
 27. Ban Y, Greenberg DA, Concepcion E, Skrabanek, Vilanueva R, Tomer Y. Amino acid substitution in the thyroglobulin gene are associated with susceptibility to human and murine autoimmune thyroid disease. *Proc Natl Acad Sci USA* 2003;100:15119-24.
 28. Rose NR, Bonita R, Burek CL. Iodine: an environmental trigger of thyroiditis. *Autoimmun Rev* 2002;1:97-103.
 29. Brent GA. Environmental exposures and autoimmune thyroid disease. *Thyroid* 2010;20:755-61.
 30. Tomer Y. Genetic susceptibility to autoimmune thyroid disease; past, present, and future. *Thyroid* 2010;20:715-25.
 31. Hasham A, Tomer Y. Genetic and epigenetic mechanisms in thyroid autoimmunity. *Immunol Res* 2012;54:204-13.
 32. Jacobson EM, Huber AK, Akeno N, Sivak M, Li CW, Concepcion E, et al. A CD40 Kozak sequence polymorphism and susceptibility to antibody-mediated autoimmune conditions: the role of CD40 tissue-specific expression. *Genes Immun* 2007;8:205-14.
 33. Burek CL, Talor MV. Environmental triggers of autoimmune thyroiditis. *J Autoimmun* 2009;33:183-9.
 34. Duntas LH. Environmental factors and autoimmune thyroiditis. *Nat Clin Pract Endocrinol Metab* 2008;4:454-60.

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.