European Review for Medical and Pharmacological Sciences 2014; 18: 3611-3618

Autoimmune thyroid disease: mechanism, genetics and current knowledge

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Abstract. – Recent epidemiological studies recognized a steady increase in the incidence of different autoimmune endocrine disorders, including autoimmune thyroid disease (AITD). The etiology of AITD is multifactorial and involves genetic and environmental factors and apparently with a strong preponderance in females. There are mainly two types of AITD, Graves' disease and Hashimoto's disease and both of these show strong association in age groups above 45-50 years. Among environmental factors smoking and alcohol have significant effects, both protective as well as for aggravating the disease, even though the precise nature of these effects are not clearly known. There are elevated levels of circulating antibodies against the thyroid proteins, mainly thyroid oxidase, thyroglobulin and thyroid stimulating hormone receptor, in patients with Graves' disease or Hashimoto's disease. Linkage and association studies in AITD identified several major genes that are relevant for the onset of AITD, including the thyroid-specific genes, thyroglobulin and thyroid-stimulating hormone receptor and also many immune-regulatory genes. In this review we addressed many aspects of AITD including disease mechanisms, involved thyroid antigens, environmental factors and genetic factors.

Key Words:
Autoimmune thyroid disease, Graves' disease, Hashimoto's disease.

Introduction

In the recent years there has been a steady increase in the incidence of different autoimmune endocrine disorders, including type 1 diabetes mellitus and also autoimmune thyroid disease (AITD)[1]. Even though causes for this increase are not precisely known, the significance of problem is evident. The etiology of AITD is multifactorial and involves genetic and environmental factors. AITD has a complex etiology and is due to the development of autoimmunity against thyroid Figure 1 antigens against a particular genetic background facilitated by exposure to environmental factors Thyroid is more frequently targeted than any other organ by autoimmune responses. The AITDs are prototypical organ specific autoimmune diseases, but the underlying mechanisms that trigger these autoimmune responses are not clearly known. The prevalence of subclinical AITD, as judged by the presence of antithyroid antibodies, but in the absence of any symptomatic clinical disease, may be even higher[2].

Prevalence of the two major autoimmune thyroid diseases (AITDs), Graves disease (GD) and Hashimoto's thyroiditis (HT), which are characterized by thyrotoxicosis and hypothyroidism, respectively, is estimated to be 5%[3]. The major autoantigens in Hashimoto's disease are thyroid peroxidase (TPO) and thyroglobulin (Tg), but these antibodies (TPO-Ab and Tg-Ab) also occur in ~70% of Graves' disease patients. Similarly, while thyroid-stimulating hormone receptor (TSHR) is the major autoantigen in Graves' disease, these antibodies also occur in few patients with Hashimoto's disease[4]. Both the AITDs are characterized by lymphocytic infiltration of the thyroid and the production of thyroid autoantibodies[5]. Environmental factors including infection, diet, iodine, and smoking seem to contribute significantly to AITD[6]. Considering that AITD is related to immune system, initially only major histocompatibility complex (MHC) class II genes were thought to predispose to AITD. However, later studies confirmed several non-MHC susceptibility genes to contribute to the etiology of AITD. While certain genes are common to AITD and other autoimmune diseases[7], some genes are unique for GD or HT, and some are common to both diseases.

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Gender Differences in AITD

AITD is much more common among women than in men, with a female:male ratio ranging from 5:1 to 10:1 (Figure 1). The biological explanation for the gender difference is not entirely clear except for some recent clues[4]. The post partum thyroiditis is often seen prior to permanent autoimmune hypothyroidism[8] and in fact post partum period carries a high risk for the onset of Graves' disease[9]. Apparently, the formation of maternal regulatory T-cells (Treg) early in pregnancy leads to a decrease in the circulating thyroid antibodies during pregnancy, in order to maintain a state of tolerance to fetal alloantigens to prevent fetus rejection[10]. After delivery, thyroid antibodies rebound with a transient rise. Fetal microchimerism is considered to be an important factor for the high probability of parity as a risk factor for AITD. As fetal cells appear in the maternal circulation by the first trimester, their persistence in maternal tissues leads to fetal microchimerism. Maternal immune responses against fetal antigens can trigger autoimmune diseases like AITD. In fact, fetal microchimerism was noticed in blood and thyroid tissues from women with either Hashimoto's or Graves' disease[11]. Thus, parity at least partly explains the female preponderance of AITD. Besides parity, X-chromosome inactivation can also significantly contribute to the high incidence of AITD in females. It is known that one of the two X chromosomes is inactivated in early embryonic stage in females. Inactivation of the same X chromosome in more than 80% of cells is called 'skewed X-chromosome inactivation' (XCI)[12] and can lead to loss of immunological tolerance to X-linked antigens might and, thus, induce autoimmunity, including AITD[13].

Clinical Aspects of AITD

Hashimoto's thyroiditis, also known as chronic autoimmune thyroiditis[14], is more common in iodine sufficient (e.g., USA) or excess (e.g., Japan) countries. In this condition, the thyroid gland is generally non-tender and firm, and is often enlarged with an irregular texture. Atrophy is often noted in the gland with diffusely infiltrated lymphocytes. The prevalence of Hashimoto's thyroiditis is as high as 40% in elderly women[15]. Nearly 50% of the patients diagnosed by anti-TPO antibodies have euthyroid, while majority of the other patients have subclinical (mild) hypothyroidism characterized by normal free T4 levels and elevated serum TSH and only a small minority have severe hypothyroidism. It is estimated that the presence of anti-TPOAb predicts the development of overt hypothyroidism at a rate of approximately 2.5% per year[16]. On the other hand, among the people with elevated TSH and positive TPOAb, about 4.5% per year develop overt hypothyroidism. Subacute or destructive thyroiditis is an inflammatory condition of thyroid, characterized by a self-limited release of preformed thyroid hormone causing hyperthyroidism, resulting in thyroid hormone depletion (hypothyroidism). Thyroid function may or may not return to normal[17].

Serum Antibodies in AITD

The major autoantigens in Hashimoto's disease are thyroid peroxidase (TPO) and thyroglobulin (Tg) and in Graves' disease TSHR is the major autoantigen, even though there is overlapping presence of these antibodies in both types of patients[4].

Thyroid autoantibodies: Thyroid microsomal antibody was one of the first thyroid autoantibodies to be recognized and this antibody was found to target TPO[18] and the anti-TPO antibodies are considered diagnostic of both the AITDs[19]. TPO is a trans-membrane protein located in the apical membrane of thyrocytes, where it conducts the synthesis of thyroid hormones.

Thyroid-stimulating hormone receptor antibodies: The discovery of a long-acting thyroid stimulator (LATS) in Graves' disease, which is distinct from TSH, led to the discovery of au-

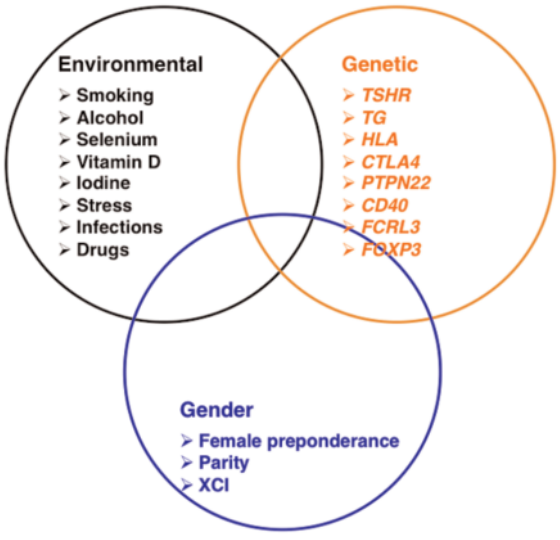

Figure 1. The multifactorial etiology of autoimmune thyroid disease: A Venn diagramatic depiction.

toantibodies against the TSHR[20]. Anti-TSHR antibodies are currently classified further into stimulating, blocking and neutral antibodies, on the basis of their ability to bind with different types of epitopes (e.g. conformational, linear) as well as the diversity of their biological actions[21]. Stimulating TSHR antibodies cause the hyperthyroidism of Graves' disease; even though TSHR blocking antibodies are found in some patients with Hashimoto's thyroiditis their role is uncertain.

Thyroglobulin-specific antibodies: The Tg-specific antibodies are found in most patients with Hashimoto's thyroiditis (> 90%) and also present in low titers in the sera of Graves' disease patients (40-70%)[22]. TgAb are also found in ~20% of clinically euthyroid individuals in the general population, probably suggestive of possible sub-clinical AITD.

Pendrin antibodies: Pendrin conducts the transport of iodide from the apical membrane of the thyrocyte into the follicular lumen and facilitates the organification of iodide. Sequence variations in the Pendrin gene were found to be associated with thyroid autoimmunity[23]. Antipendrin antibodies were found in 97.5% of Hashimoto's patients as well as in 74% of Graves' patients but none in the controls[24].

Environmental Factors

Among the several environmental factors, infection, diet, iodine, medications and smoking appear most important[6].

Smoking: Smoking is a well-established risk factor for Graves' disease and this risk disappears in few years following cessation of smoking. The OR for Graves' disease is 3.30 in smokers and this drops significantly in ex-smokers reaching the level of never smokers (1.41)[25]. However, new evidence is derived from large cross-sectional population-based surveys and from prospective observational studies, showing the protective effects of smoking against AITD. For example, in NHANES III the prevalence of TSH is lower in smokers than in nonsmokers (2.6 vs 5.5%)[26]. Evidence also points to reduce risk of developing TPO-Ab/Tg-Ab and autoimmune hypothyroidism in a dose-dependent manner in current smokers, but this protection is lost few years following smoking cessation. The reason for the increased risk for Graves' disease in smokers is currently unknown and the possibility for the involvement of nicotine, which is known to cause a shift from pathogenic Th1 and Th17 responses to protective Th2 responses. In fact, anatabine, a structural analogue of nicotine is known to reduce the incidence and severity of experimental autoimmune thyroiditis[27].

Alcohol: A population based study in Denmark indicated protective effects of alcohol consumption against the development of AITD. Alcohol is also known to protect against other autoimmune diseases such as rheumatoid arthritis and type I diabetes[4]. It has been suggested that moderate alcohol consumption has a beneficial effect on the immune system and this may be instrumental in its protective effect on AITD[28]. On the other hand, alcohol can also exert direct toxic effects on the thyroid gland, which, however, is difficult to reconcile with its protective effects and these differences may relate to the quantity of consumption and also other precipitating factors.

Selenium: Among all the body tissues, the thyroid gland contains more selenium. Selenium is an essential cofactor for the important redox regulatory enzymes, glutathione peroxidases and thioredoxin reductases that protect thyrocytes from oxidative damage. A deficiency of selenium is known to be associated with poor immune function[29] and may promote the initiation or progression of thyroid autoimmunity. Accordingly, selenium supplementation has proven to prevent deterioration of mild Graves' ophthalmopathy[30] and the post partum surge of TPO-Ab and thyroid dysfunction[31].

Medications: Besides iodine, selenium and smoking various medications such as amiodarone, alumtuzumab, iplimumab, propranolol, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, highly active antiretroviral therapy (HAART), interferon alpha and other cytokines have been shown to influence total and free T3 levels[32] and also to contribute to AITD[17, 33].

Amiodarone is an iodine-rich drug and is commonly used in patients with certain forms of tachyarrythmias. Approximately 15-20% of the cases of either thyrotoxicosis or hypothyroidism are likely due to amiodarone-induced thyroid dysfunction[34]. There are two types of amiodarone-induced thyrotoxicosis (AIT) and differentiating between these is necessary for proper treatment decisions. Type 1 AIT, which is iodine-induced hyperthyroidism, is more common in patients with pre-existing thyroid disease, such as latent GD. Type 2 AIT is destructive thyroiditis. There are multiple mechanisms by which amio-

darone causes thyroid dysfunction. Amiodarone inhibits type 1 5'deiodinase, resulting in decreased generation of T3 from T4 and increased rT3 production, which has lower clearance[35]. This drug also blocks thyroid hormone entry into peripheral tissues, leading to an overall reduced T3 levels in individuals on long-term amiodarone therapy[36]. Amiodarone and its main metabolite desethylamiodarone are known to directly induce cytotoxicity on the thyroid causing distortion of thyroid architecture, apoptosis, necrosis, formation of inclusion bodies, and macrophage infiltration[36,37]. Besides the above, amiodarone has been shown to inhibit the interaction between T3 and thyroid hormone receptors a1 and b1 thereby compromising the T3-dependent gene expression *in vivo* and this has a major impact on heart muscle where the expression of many proteins involved in cardiac contractility is dependent on thyroid hormone receptors[38]. AIT is a difficult condition to diagnose and treat, and discontinuation of amiodarone is usually recommended.

Infections: Antibodies from patients infected with *Yersinia enterocolitica* (YE) can inhibit the binding of TSH to thyroid membranes whereas antibodies from Graves' disease can inhibit the binding of TSH to YE outer membranes. This could be the reason for the relationship between the pathogenesis of AITD and infection with YE. There is also cross-reactivity between YE outer membrane proteins and epitopes of TSHR antibodies. Besides YE infection, gut microbiota are implicated in triggering Hashimoto's thyroiditis. It has been speculated that the profound changes in gut microbiota brought about by smoking cessation can lead to the loss of the protective effect of current smoking for Hashimoto's disease. Thyroid autoimmunity has been described in Turkish patients with Familial Mediterranean Fever even though the underlying causes are not known[39].

Viral infections and AITD: Among various infectious agents strong evidence exists that supports an association of AITD with the hepatitis C virus[40,41]. Individuals infected with HCV and not yet on IFNα therapy, do show thyroid dysfunction. Elevated levels of thyroid antibodies are often seen in patients with untreated HCV infection and without clinical thyroid dysfunction[42]. In fact, IFNα therapy in HCV patients can lead to a synergistic effect on thyroid dysfunction[43]. Besides HCV, enteroviruses have also been detected in thyroid tissue of subjects with Hashimoto's thyroiditis[44]. Interestingly, a significantly higher percentage of HCV patients display positive thyroid antibodies than the patients with HBV infection[45,46]. It has been proposed that HCV infection of human thyrocytes causes the production of proinflammatory cytokines, which in turn enhance the autoimmune response and subsequent AITD. HCV E2 proteins were shown to bind to CD81 molecules on thyroid cells and upregulate the pro-inflammatory cytokine IL-8, which can alter the thyroid environment and lead to thyroid autoimmunity by bystander activation mechanisms[47]. Also, in hepatocytes and lymphocytes of HCV patients, there is an elevated production of interferon-γ, which can direct the immune system towards Th1 responses. Additionally, it has been suggested that HCV shares partial sequences with thyroid tissue antigens (microsome and thyroglobulin), thus, potentially triggering AITD by molecular mimicry[48].

Genetic Factors

Both family studies as well as twins based studies support a strong genetic influence on AITD etiology[49]. Studies on twins show a significantly higher concordance rate among monozygotic twins than among dizygotic twins for both Graves' disease[50] and Hashimoto's thyroiditis[51]. These studies indicated that nearly 80% of the risk for Graves' disease is hereditary[52]. In fact, linkage and association studies in AITD identified several major genes for AITD, including both thyroid-specific genes [thyroglobulin (Tg) and thyroid-stimulating hormone receptor (TSHR)] and immune-regulatory genes. The immune-regulatory genes predisposing to AITD are shared with other autoimmune diseases.

Thyroid Antigens as AITD Susceptibility Genes

TSHR gene: Graves' disease results from the production of TSHR stimulating antibodies, which activate elevated thyroid hormone synthesis and secretion, leading to clinical thyrotoxicosis. TSHR antibodies are present in all patients of GD, and the disease severity directly correlates with blood TSHR antibody levels. Besides this, injecting animals with TSHR antibodies transfers disease, and transfer of antibodies from mothers with GD to newborns also transfers GD[53]. The completion of the Human Genome Project along with the discovery of dense maps of single nucleotide polymorphisms (SNPs) revealed that the TSHR gene is strongly associated with GD and that most of the causative SNPs are located with-

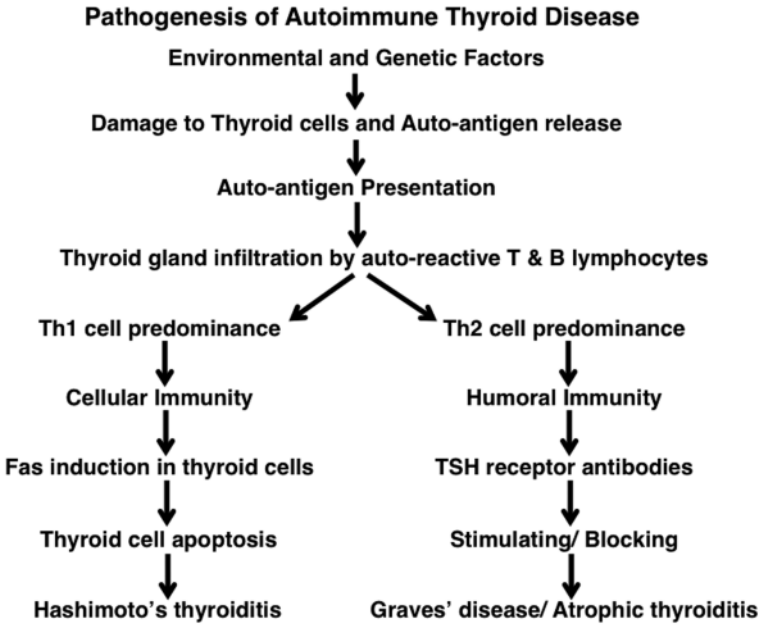

Figure 2. Flow-chart of events involved in the pathogenesis of autoimmune thyroid disease.

in intron 1[54]. Reduction of TSHR expression because of the SNPs in the thymus, enables TSHR-targeting autoreactive T cells to escape deletion in the thymus and leads to disease later in life (Figure 2).

Thyroglobulin gene: Inasmuch as Tg constitutes ~80% of total thyroid content, and as Tg can leak into the circulation and is exposed to the immune system, Tg is an important candidate gene for AITD. Besides, the best model of human autoimmune thyroiditis is induced by immunizing mice with Tg[55], as Tg may be the earliest disease trigger[56]. That Tg may be an AITD susceptibility gene came from linkage studies showing a significant linkage peak on chromosome 8q at the Tg gene region[57]. Sequencing of the Tg gene identified amino acid variants that are significantly associated with AITD and one such SNP in exon 33, showed significant statistical interaction with a human leukocyte antigen (HLA)-DR variant containing an arginine at position β74 (HLA-DRβ1-Arg74), together conferring a high risk for AITD[58]. However, a direct link between the Tg SNPs and the pathogenic Tg peptides is not yet established.

Immune response genes as AITD susceptibility genes: Genetic screens identified HLA locus as the first such association with both GD and HT[59] and in particular, HLA-DR3 was found to confer the strongest risk of all GD susceptibility genes identified and also to predispose for HT. As mentioned above, presence of arginine at position 74 of the HLA-DR β-chain is essential for the development of AITD, and a substitution mutation of this arginine residue with glutamine is protective from AITD[60].

Another important immune response AITD susceptibility gene is CD40, which plays a key role in the cross talk between antigen-presenting cells (APCs) and T cells. CD40 normally provides a crucial signal for proliferating, differentiating, and switching to the production of immunoglobulin G in B-lymphocytes[61]. Because of its role in B-cell function, and as GD is a B cell-mediated autoimmune disease, CD40 is a unique GD susceptibility gene[61,62]. Upregulation of CD40 by SNP, rs1883832, can effectively lower the threshold for B cell activation leading to the onset of autoimmune disease. Activation of CD40 in thyrocytes has been shown to enhance cytokine (e.g., IL6) secretion followed by the activation of resident T cells, leading to a local inflammatory response and autoimmunity and both these mechanisms contribute to GD[61,62].

Besides HLA-DR and CD40, three other genes involved in T cell activation and regulation Figures 1 and 2 are found to be associated with AITD, viz., cytotoxic T lymphocyte–associated antigen 4 (CTLA-4), protein tyrosine phosphatase nonreceptor type 22 (PTPN22), and CD25[5]. While several polymorphisms in the CTLA-4 gene were known to be associated with

AITD, only some of these lead to reduced CTLA-4 function[63] and there are more recent evidences implicating the reduced CTLA-4 function in the onset of AITD[64]. A SNP at position 1858 in PTPN22 (that encodes the lymphoid tyrosine phosphatase) that results in the mutation of tryptophan-620 to arginine (R620W) of this phosphatase is associated with AITD[65]. Also, CD25 gene, which encodes for interleukin-2 receptor α-chain (IL-2Rα) is associated with GD[66].

In the first genome-wide association study of GD conducted in China, 1,536 GD patients and 1,516 control subjects were genotyped for approximately 660,000 SNPs[67]. In this mega study, the investigators confirmed many of the previously identified GD loci, and also mapped on chromosomes 6q27 and 4p14, two new GD loci, which contain several genes; however, the identity of GD conferring gene(s) in these loci is still unclear[67].

Conclusions

AITD, which is of two types, Graves' disease and Hashimoto's disease, has much higher prevalence among women than in men and this in part related to pregnancy. Predominantly, autoimmune reaction against thyroid gland proteins, thyroglobulin, TPO and TSHR triggers AITD. As expected, AITD incidence is influenced significantly by geographical, environmental and genetic factors and also ageing. Recent advances in genome-wide association studies (GWAS) identified many SNPs in gene loci that are strongly associated with AITD, even though the precise cause and effect relationship between specific gene function and the disease have not been defined.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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