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Cutting Edge: The Etiology of Autoimmune Thyroid Diseases

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Abstract Significant progress has been made in our understanding of the mechanisms leading to autoimmune thyroid diseases (AITD). For the first time, we are beginning to unravel these mechanisms at the molecular level. AITD, including Graves' disease (GD) and Hashimoto's thyroiditis (HT), are common autoimmune diseases affecting the thyroid. They have a complex etiology that involves genetic and environmental influences. Seven genes have been shown to contribute to the etiology of AITD. The first AITD gene discovered, HLA-DR3, is associated with both GD and HT. More recently, this association was dissected at the molecular level when it was shown that substitution of the neutral amino acids Ala or Gln with arginine at position beta 74 in the HLA-DR peptide binding pocket is the specific sequence change causing AITD. Non-MHC genes that confer susceptibility to AITD can be classified into two groups: (1) immune-regulatory genes (e.g., CD40, CTLA-4, and PTPN22); (2) thyroid-specific genes—thyroglobulin and TSH receptor genes. These genes interact with environmental factors, such as infection, likely through epigenetic mechanisms to trigger disease. In this review, we summarize the latest findings on disease susceptibility and modulation by environmental factors.

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Introduction

Autoimmune thyroid diseases (AITD) are the commonest autoimmune endocrine diseases [1], and according to one study, AITD are the commonest autoimmune diseases in the USA [2]. Even though both diseases manifest infiltration of the thyroid with thyroid reactive lymphocytes, the end result is two clinically opposing syndromes: Hashimoto's thyroiditis (HT) manifesting by hypothyroidism and Graves' disease (GD) manifesting by hyperthyroidism. In HT, the lymphocytic infiltration of the thyroid gland leads to apoptosis of thyroid cells and hypothyroidism [3]. In contrast, in GD, the lymphocytic infiltration of the thyroid leads to activation of TSH receptor (TSHR)-reactive B cells that secrete TSHR-stimulating antibodies causing hyperthyroidism [4]. GD and HT are complex diseases, and their etiology involves both genetic and environmental influences [1]. Up until 15 years ago, the only known gene for AITD was HLA-DR3. However, with the advent of new genomic tools and the completion of the human genome and the HapMap projects, new non-HLA genes have been identified and their functional effects on disease etiology dissected as well. This review will summarize the major recent advances in our understanding of the genetic and environmental contributions to the etiology of AITD. Future studies will most likely dissect the epigenetic interactions between the AITD susceptibility genes and the environmental triggers of disease.

Genetics and AITD

HLA-DR Gene and Pocket Structure

HLA-DR3 in Caucasians

Located on chromosome 6p21 is the major histocompatibility complex region that encodes for HLA glycoproteins. The HLA region is a highly polymorphic region that contains many immune response genes and has been found to be associated with various autoimmune disorders. The HLA molecule binds a peptide antigen (autoantigen in the cause of autoimmunity) and presents it to the T cell to precipitate the immune response [5].

HLA-DR3, a class II HLA molecule, was the first candidate gene to be associated with AITD in Caucasians (reviewed in 6). It has been identified as a major susceptibly gene in GD, with a positive, though less strong, association with HT. In families with both type 1 diabetes and AITD, HLA-DR3 has been found to be a major genetic contributor [7].

About one half of GD patients are found to have the DR3 allele, compared with only 15–30% of the general population (reviewed in 8). Although the data is controversial, some researchers have found associations of DR3 with GO and with risk for disease relapse [8]. The literature regarding HT is less consistent with reports of associations with DR3 and DR4 in Caucasians, as well as a negative association with DR 1 and 8, suggesting a protective role [9]. This association is not as strong as that with GD owing to the fact that the diagnosis of HT is based on a continuum of clinical or laboratory symptoms. Interestingly, the DR3 allele has also been shown to be associated with GD in a mixed Brazilian population [10]. In other ethnic groups, the HLA associations are with different alleles. For example, HLA-B35 is associated with GD and HLA-DRw53 with HT in the Japanese population; HLA-Bw46 is associated with GD and HLA-DR9 with HT in the Chinese population (reviewed in 8).

The HLA-DR Pocket in GD: the Importance of Arginine at Position 74

While initial studies were critical in identifying the DR3 association with GD and HT in Caucasians, more recent work has focused on the binding pocket of HLA-DR3 as the critical determinant of AITD risk. Specifically, these studies concluded that it is the substitution of the neutral amino acids Ala or Gln for the positively charged Arg at position 74 of the DR beta 1 chain (DRb1–Arg74) resulting in a structural change in the HLA-DR peptide binding pocket that confers the greatest risk for the development GD [11]. Conversely, glutamine at this peptide binding pocket position was found to be protective for GD. This change at pocket 4 of the peptide binding cleft causes a three-dimensional structural alteration in the pocket that most likely allows pathogenic peptides to bind to the HLA molecule and subsequently be recognized by auto-reactive T cells to stimulate the autoimmune response. One potential antigen that might interact with the HLA-DRb1–Arg 74 pocket is thyroglobulin. Indeed, we have found significant interaction between a thyroglobulin gene polymorphism and the HLA–DRb1–Arg 74 pocket variant in predisposing to GD, resulting in an odds ratio of ~16 [12]. Therefore, we hypothesized that this complex interaction in which HLA–DRb1–Arg 74 presents thyroid autoantigens to T cells with the help of a co-stimulatory molecules, possibly CD40 (see below), precipitates thyroid autoimmunity in GD.

The HLA Pocket in HT

More recently, HT was also found to be associated with an HLA–DR pocket-sequence variant; intriguingly, this variant also contains HLA–DRb1–Arg 74. Specifically, the pocket amino acid sequence in humans conferring a risk for HT was found to be the sequence of Tyr-26, Tyr-30, Gln-70, Lys-71, and Arg-74 with the Lys-71 conferring the greatest risk. Similar to the single amino acid substitution in GD, this amino acid sequence also changes the DR pocket structure in a way that most likely results in binding of autoantigenic peptides and their presentation to T cells. A variant with a protective effect for HT has also been discovered, comprising amino acids Leu-26, His-30, Arg-70, Arg-71, and Gln-74 [9].

Immune-Regulatory Genes: CD40, CTLA-4, PTPN22

The CD40 Gene and Graves' Disease

The CD40 molecule, located on chromosome 20q, is crucial to both the innate and adaptive immune responses. It is present on the surface of antigen presenting cells (APCs) including B cells. The T cell–APC interaction results in activation of CD40 as a co-stimulatory molecule. CD40 also plays a critical role in activating B lymphocytes allowing them to terminally differentiate and secrete antibodies (reviewed in 13). It is no surprise that the CD40 gene has been linked to many autoimmune disorders. Whole genome linkage scanning has identified strong linkage of CD40 to GD. The causative variant predisposing to GD is a C/T polymorphism in the Kozak sequence, a nucleotide sequence that is essential for the initiation of translation of the CD40 molecule. Specifically, the CC genotype has been identified in Japanese, Koreans, and Caucasians to be associated with GD [14]. Functional studies demonstrated that the C-allele of this SNP increased

CD40 mRNA translation by ~20–30% when compared with the protective T allele [6]. The increased translation of CD40, driven by the C-allele, increased the levels of CD40 expressed on a B cells, consequently increasing the likelihood of their activation and antibody production [15]. This SNP may also increase translation of CD40 in the target tissue, i.e., the thyroid thereby resulting in cytokine production and activation of resident T cells by bystander mechanisms [6, 13].

The CTLA-4 Gene

The cytotoxic T lymphocyte-associated protein 4, CTLA-4, is a highly polymorphic gene that was first discovered to be associated with risk for AITD by the candidate gene approach. Located on chromosome 2q, under normal circumstances, the CTLA-4 protein acts to suppress T cell activation and subsequent immune response in order to prevent T cell over-activity [6, 13]. CD4+CD25–T cells only express CTLA-4 on their surface after the T cell receptor is activated, and its engagement with its ligand suppresses the ongoing immune response. Decreased or absent CTLA-4 activity permits uninhibited T cell activity and a prolonged, unregulated immune response [16], making CTLA-4 an attractive candidate gene for autoimmunity. Indeed, the CTLA-4 gene has been found to be associated with many other autoimmune diseases.

A microsatellite in 3'UTR of CTLA-4 has been linked to AITD (reviewed in 6, 13); the longer the AT repeat at this site, the less inhibitory activity CTLA-4 has. Other variants of the CTLA-4 gene have been linked to AITD; a G allele substitution at an A/G SNP at position 49 was also found to be associated with AITD conferring a relative risk of ~2 for disease [13]. Additionally, and most recently discovered, an A/G SNP downstream from the 3'UTR, designated CT60, was found also to be associated with GD and has been suggested as the causative variant, albeit this has not been conclusively demonstrated [17]. Unlike other candidate genes, the CTLA-4 gene's association with AITD is not specific to certain ethnic groups or geographic locations (reviewed in 6).

PTPN22 Gene

The protein tyrosine phosphatase-22 (PTPN22) gene encodes for the lymphoid tyrosine phosphatase (LYP), a molecule that, similar to CTLA-4, functions to inhibit T cell activation [18]. A non-synonymous SNP in the PTPN22 gene, R620W, was found to be associated with GD, as well as other autoimmune diseases. This substitution results in a functional change in the LYP protein resulting in activation of T cells, but the mechanism is unclear [13]. Interestingly, this association seems specific for Caucasians and was not found in the Japanese GD population [13].

Copy Number Variants

Copy number variants (CNVs) are large duplications or deletions of a DNA sequence that are inherited. Several CNVs have been reported to be associated with autoimmune disorders [19]. Therefore, we have analyzed the three immune-regulatory genes known to be associated with GD, CD40, CTLA-4, and PTPN22, for the presence of CNVs that are associated with disease. Surprisingly, no CNVs were identified in the CD40 and CTLA-4 genes, while only two subjects out of 190 had a rare PTPN22 CNV. Interestingly, we found significant difference in the CNV analysis when using DNA obtained from fresh blood compared with DNA obtained for Epstein Barr virus-immortalized B cells. Therefore, these results have potential implications for studies of CNV in complex diseases. It is now clear that immortalizing cell lines with EBV creates artificial CNVs and therefore, CNV analysis should only be done on DNA obtained from blood [20].

Thyroid-Specific Genes

Thyroglobulin Gene

The thyroglobulin (Tg) protein is the major thyroidal protein antigen and is a precursor to thyroid hormones. Tg is also a key antigen in AITD as evidenced by the fact that HT is characterized by anti-thyroglobulin antibodies which are detected in 75% of patients [13]. Whole genome linkage studies identified a locus on chromosome 8q24 that was linked with AITD; this locus contained the Tg gene. Sequencing of the Tg gene identified several non-synonymous SNPs that were associated with AITD [21]. Interestingly, we identified a statistical interaction between a SNP in the Tg gene at exon 33 and HLA–DRb1–Arg 74 giving an odds ratio for GD of 16 (reviewed in 13).

TSH Receptor (TSHR) Gene

The TSHR gene is located on chromosome 14q. It was found to be associated with GD both by the candidate gene approach and by whole genome linkage studies [22]. The TSHR gene was a prime candidate gene for GD since GD is caused by autoantibodies that bind to and stimulate the TSH receptor. Several TSHR SNPs have been tested for association with GD, including non-synonymous SNPs in the extracellular TSH receptor domain and in the intracellular domain of the TSHR; all of these gave conflicting results. However, linkage studies demonstrated significant evidence for linkage of GD with a locus on chromosome 14q harboring the TSHR gene [22]. It was later found that non-coding SNPs in intron 1 of the TSHR confer the association with GD [13].

Environmental Factors and AITD

Several environmental and non-genetic triggers have been implicated in the etiology of AITD. These include smoking, stress, iodine intake, medications, bacterial, and viral infections, irradiation, pollutants, and pregnancy. The mechanisms by which certain environmental agents induce thyroid disease could involve interference with thyroid function, direct toxic effects on thyrocytes, or immune stimulation, as well as other effects [23]. It is often difficult to directly link an environmental exposure with thyroid autoimmunity, as disease may be associated with a combination of factors and can manifest over a long period of time. When an environmental exposure triggers AITD in individuals with pre-existing thyroid autoantibodies, this may indicate gene–environment interaction, as the presence of thyroid antibodies is usually a surrogate marker of genetic susceptibility [23].

Iodine

Iodine is one of the most important precipitants of thyroid dysfunction. Although essential for normal thyroid function, excess iodine supplementation can be associated with the onset of thyroid autoimmunity. Potential mechanisms by which iodine can induce autoimmunity in the thyroid include direct stimulation of immune responses to the thyroid, increased immunogenicity of highly iodinated Tg, and direct toxic effects of iodine on thyrocytes via free oxygen radicals generation [24]. Observational studies have demonstrated increased incidence of autoimmune thyroiditis in regions with increased iodine consumption compared with regions of low consumption [24]. In a 5-year follow-up study in China of a large cohort of 3,018 subjects, the incidence of subclinical hypothyroidism and autoimmune thyroiditis was higher in those individuals with median urinary iodine concentration greater than 243 (micrograms per liter; 25]. Moreover, among 300 patients with non-toxic goiter from iodine-replete areas in Greece, 60% had positive thyroid autoantibodies. An increased prevalence of Hashimoto's thyroiditis was also observed after correction of iodine deficiency [26]. Iodine associated thyroid autoimmunity, however, may be a transient phenomenon. Kahaly et al. followed a group of patients with endemic goiter that received iodine for 6 months and another group that received T4. High titers of thyroid antibodies were found in 19% of the patients receiving iodine. After iodine was withdrawn, Ab levels decreased significantly, and after a 4-year follow-up, these levels had normalized in four of the patients [27].

Using an animal model, Burek et al. showed that the incidence of thyroiditis in NOD.H2^{h4} mice increased when excess iodine was added to their drinking water [28]. NOD. H2^{h4} mouse is a spontaneous model of autoimmune thyroiditis that resembles the human disease. In this model, an increased expression of intracellular adhesion molecule-1 was observed on thyrocytes which was upregulated by iodine consumption [28].

Medications

Several medications may play a role in the development of AITDs. IFNα, interleukin-2, lithium, amiodarone, and highly active antiretroviral therapy (HAART) are the agents most commonly associated with thyroid dysfunction [29].

Amiodarone

Amiodarone is an iodine-rich drug used in individuals with certain tachyarrythmias. The incidence of amiodarone-induced thyroid dysfunction, either thyrotoxicosis or hypothyroidism, is approximately 15–20% [30]. The development of thyroid disease depends upon iodine intake, with thyrotoxicosis occurring more frequently in iodine-deficient areas and hypothyroidism more often encountered in iodine-sufficient areas [30, 31]. Amiodarone-induced thyrotoxicosis (AIT) can be further divided into type 1 AIT (iodine-induced hyperthyroidism), and type 2 AIT (destructive thyroiditis), with type 1 being more common in those with pre-existing thyroid disease, such as latent GD. Differentiating between these subtypes is important as it can affect treatment decisions. Amiodarone can exert effects on the thyroid via different mechanisms including inhibition of type 1 5'deiodinase activity and inhibition of thyroid hormone entry into peripheral tissues. This results in an overall decreased concentration of T3 in individuals receiving long-term therapy. Amiodarone may also have direct cytotoxic effects on the thyroid which is possibly worsened by desethylamiodarone, the main amiodarone metabolite. In normal and autoimmune rat models exposed to amiodarone, changes described at the cellular level included distortion of thyroid architecture, apoptosis, necrosis, formation of inclusion bodies, and macrophage infiltration [31, 32].

The effects of thyroid hormones on the heart are mediated via nuclear T3 receptors. Amiodarone exerts an inhibitory effect on the binding of T3 to thyroid hormone receptors (TR's) alpha-1 and beta-1 in vitro and on the expression of particular T3-dependent genes in vivo [33]. There are a number of T3-responsive genes in the heart that encode for proteins involved in cardiac contractility. Amiodarone decreases heart rate and alpha myosin heavy chain expression (mediated by TR alpha-1) and increases sarcoplasmic reticulum calcium-activated ATP-ase and beta myosin heavy chain expression (mediated via TR beta-1). A microarray analysis of 8,435 genes in the left ventricular

myocardium of rats showed a significant similarity in expression profiles between hypothyroid and amiodarone treated rats [34].

Highly Active Antiretroviral Therapy

Inconsistent results have been reported on thyroid function in HIV patients receiving HAART. It has been proposed that thyroid-specific autoimmunity can occur upon immune restoration with HAART. Suppression of HIV RNA causes a re-population of T cells with an increase in memory and naïve CD4 cells. This immune restoration may trigger AITD. Chen et al. reported 17 patients who developed AITD following 17 months of HAART, with GD occurring in 15 of these patients [35]. These findings also supported an earlier retrospective study in which five HIV patients without pre-existing thyroid disease were diagnosed with GD after 20 months on HAART. TPOAb and TSHRAb were detected after CD4 cells had increased significantly while on HAART therapy [36]. These findings suggest that HIV patients receiving HAART should be carefully monitored for symptomatology of GD, and thyroid function testing should be routinely performed in these patients [35, 37].

Interferon-alpha

Interferon-alpha (IFNα) is commonly used as a therapeutic agent in the management of several disorders, including hepatitis C (HCV) and has also been associated with the onset of thyroid autoimmunity. IFNα may enhance immune responses via increased expression of perforin in NK cells and T cells, as well as suppression of Th2 and enhancement of Th1 immune responses. Studies have also shown an upregulation of MHC expression and cytokine-mediated cytotoxic actions at the level of the thyroid [29, 38]. Females tend to carry a higher risk for developing AITD during IFNα therapy. The presence of thyroid antibodies prior to treatment confers a higher risk of thyroid dysfunction [38, 39]. In more than 50% of individuals, thyroid abnormalities resolve once IFNα has been withdrawn, with permanent disease more likely to occur in those with prior autoantibody positivity [40]. Screening therefore should be performed in all patients prior to commencing IFNα therapy and regularly during therapy [39].

Infections

Several infections have been implicated in the pathogenesis of AITD including *Helicobacter pylori*, *Borrelia burgdorferi*, *Yersinia enterocolitica*, Coxsackie virus, and retroviruses. Furthermore, recent studies have substantiated a strong association between AITD and HCV. Seasonal and geographic variations also support infection as a trigger of AITD (reviewed in 29, 41). Possible mechanisms by which infections may trigger thyroiditis include release of sequestered antigens by cell destruction or apoptosis, exposure of cryptic epitopes, molecular mimicry, or via a bystander mechanism resulting in activation of resident T cells. The molecular mimicry hypothesis proposes that sequence similarities between viral/bacterial proteins and self-proteins can induce a cross-over immune response to self-antigens, with a breakdown of self-tolerance, resulting in autoimmunity. The bystander mechanism suggests that infections of certain tissues can induce local inflammation via cytokine secretion, thereby activating resident T cells [41, 42]. Although infections may promote AITD, they can also be partially protective, as suggested by the hygiene hypothesis. According to this hypothesis, the immune system builds tolerance to repeated infectious exposures, and this may explain a lower prevalence of thyroid Abs in those of lower socioeconomic class [42].

Bacterial Infections

Data regarding the role of the spirochete, *B. burgdorferi*, and the enterobacter, *Y. enterocolitica*, in triggering thyroid autoimmunity remain inconclusive. Some reports have suggested molecular mimicry that may explain an association between both of these pathogens and AITD [29, 43–45]. In a study by Benvenga et al., regions of homology were probed between thyroid autoantigens and proteins of *Borrelia* and *Yersinia*. The study also looked for binding motifs to HLA-DR molecules and associated binding of the DR–peptide complex to the T cell receptor [43]. Significant homologies were found for 16 *Borrelia* proteins (five with TSHR, two with Tg, three with TPO, and six with NIS), and 19 *Yersinia* proteins (four with TSHR, two with Tg, two with TPO, and 11 with NIS). The number of motif copies was found to be greater in the regions of homology of thyroid autoantigens with *Yersinia* than those with *Borrelia*, with the commonest being HLA-DR3, DR-4, and DR-7. Since DR3 and DR4 confer an increased risk for the development of AITD, these in silico data may suggest that, in genetically susceptible individuals, *Borrelia* and *Yersinia* proteins may have the potential to trigger thyroid autoimmunity [43]. However, these data remain to be confirmed.

Viral Infections: Hepatitis C

Among infectious agents the most solid data supporting an association with AITD exist for the hepatitis C virus [46]. Indeed, thyroid dysfunction has been identified in individuals with HCV, without concomitant use of IFNα.

Many studies have revealed increased titers of anti-thyroid antibodies (TPO and Tg) without clinical thyroid

dysfunction in hepatitis C patients. In a study performed in France, the prevalence of laboratory and/or ultrasound abnormalities of the thyroid, suggestive of latent autoimmune thyroiditis, was higher in patients with chronic HCV who had not received IFNα therapy compared with controls [47]. Antonelli et al. demonstrated that the percentage of patients with positive thyroid antibodies (TPO and Tg) was significantly higher in HCV patients when compared with controls and patients with HBV [40]. Moreover, HCV and IFNα therapy together may have a synergistic effect in inducing thyroid dysfunction [48].

There are several proposed mechanisms by which HCV can trigger AITD. One mechanism may be related to a generalized autoimmunity initiated by the virus. There is increased production of interferon-gamma in hepatocytes and lymphocytes of HCV-infected patients, and this can direct the immune system towards Th1 responses. HCV may also share partial sequences with thyroid tissue antigens (microsome and thyroglobulin), potentially triggering AITD by molecular mimicry [49]. The frequency of AITD may also be higher in patients with a mixed subtype infection. Further studies are awaited, however, to clarify the association between HCV genotypes and the development of AITD. Another possible mechanism is direct HCV infection of thyroid cells. Recent studies have described the presence of HCV virions within thyroid follicular cells [50]. Furthermore, we have shown that HCV E2 proteins can bind to CD81 molecules on thyroid cells and upregulate the pro-inflammatory cytokine IL-8. This can have a significant effect on the thyroid environment and lead to thyroid autoimmunity by bystander activation mechanisms [41, 51].

Environmental Toxins (for a recent review See 23)

Many environmental pollutants, including polyaromatic hydrocarbons, perfluorinated chemicals, phthalates, and bisphenol A, have been shown to be toxic to thyroid cells and promote the onset of AITD [23]. These chemicals are widely used in various industrial and consumer products and may specifically have thyroid-disrupting properties [48, 52]. Polyaromatic hydrocarbons, including polychlorinated biphenyls (PCBs) and polyhalogenated biphenyls (PBB), are organic compounds produced from coal and found in air and water, and they can possibly trigger thyroiditis. PBBs are commonly used compounds in products including adhesives, lubricants, and flame retardants, while PCBs are found in plasticizers. A high prevalence of hypothyroidism was observed in individuals exposed to PBB with an associated elevation in antimicrosomal Abs and anti-thyroglobulin Abs [53].

Bisphenol A (BPA) is commonly used to manufacture plastic products, including can linings and clear plastic bottles. BPA may bind to the thyroid hormone receptor and act as an antagonist to T3, inhibiting its transcriptional activity. Moriyama et al. showed that the inhibition of T3 transcriptional activity occurred through interaction with nuclear corepressor proteins [54]. Another study revealed that when BPA was fed to pregnant rats, there was a significant increase of total T4 in the pups 15 days postpartum [52]. However, definitive data in humans are lacking.

In view of the evidence that many of these chemicals can interfere with thyroid function, there is a growing concern about their effects on neurological development during embryonic life [23, 52]. Exposure during pregnancy, for example, which itself is a risk factor for AITD, can have hazardous effects on the developing fetus in which normal thyroid hormone levels are crucial for normal growth and brain development. It is important, therefore, to be aware of environmental triggers of AITD and to monitor thyroid functions closely in susceptible women during pregnancy [23, 29].

Epigenetics: the Interface between Genes and Environment in Disease Etiology

While it is clear that genetic and environmental factors interact to precipitate thyroid autoimmunity, the nature of this interaction is still unclear. One potential mechanism for gene–environment interaction in complex diseases, which has emerged in recent years, is through epigenetic effects. Epigenetic effects are defined as heritable effects on gene expression that are not coded in the DNA sequence. However, more recently, the term epigenetics has been broadened to include any non-DNA sequence encoded effects on gene expression whether inherited or not. The classical epigenetic factors include DNA methylation, histone modifications (usually acetylation, de-acetylation, and methylation) and micro-RNAs [55, 56]. In several autoimmune diseases including type 1 diabetes [57], systemic lupus erythematosus [58] and rheumatoid arthritis [59] epigenetic changes have been shown to play a role in the etiology of disease, and epigenetic factors are likely to be involved in other autoimmune diseases including AITD [60]. Epigenetic changes are likely to be important in AITD. As mentioned before, infections have been shown to play an important role in triggering AITD [41]. A likely mechanism by which AITD can be triggered by infections in susceptible individuals is through epigenetic effects. Indeed, epigenetic modifications have been observed following viral infections such as HIV [61].

Conclusions

We have gone a long way since the identification of HLA-DR3 as the first AITD susceptibility gene. At least seven

non-HLA genes have been identified, and the mechanisms by which they induce disease and their interactions with environmental factors are being deciphered. The AITD, including GD and HT, are complex diseases. Their etiology involves common as well as distinct immune pathways. Likewise, the susceptibility genes for AITD include genes predisposing to both GD and HT (e.g., CTLA-4, PTPN22) as well as genes distinct for GD (e.g., CD40) and HT (12q locus) [22]. Functional studies have unraveled some mechanisms by which variants in these genes predispose to disease. For example, the HLA-DR pocket variant containing arginine at position 74 likely confer susceptibility to disease by enabling the presentation of pathogenic Tg peptides [62, 63]. Future research will focus on the epigenetic interactions between AITD susceptibility genes and environmental triggers of disease. Dissecting these mechanisms will enable us to modulate these epigenetic interactions and design new, mechanism-based therapies for AITD.

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