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THE ETIOLOGY OF AUTOIMMUNE THYROID DISEASE: A STORY OF GENES AND ENVIRONMENT

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Abstract

Autoimmune thyroid diseases (AITD), including Graves' disease (GD) and Hashimoto's thyroiditis (HT) are prevalent autoimmune diseases, affecting up to 5% of the general population. Autoimmune thyroid diseases arise due to complex interactions between environmental and genetic factors. Significant progress has been made in our understanding of the genetic and environmental triggers contributing to AITD. However, the interactions between genes and environment are yet to be defined. Among the major AITD susceptibility genes that have been identified and characterized is the HLADR gene locus, as well as non-MHC genes including the CTLA-4, CD40, PTPN22, thyroglobulin, and TSH receptor genes. The major environmental triggers of AITD include iodine, medications, infection, smoking, and possibly stress. Recent data on the genetic predisposition to AITD lead to novel putative mechanisms by which the genetic-environmental interactions may lead to the development of thyroid autoimmunity.

INTRODUCTION

The two major autoimmune thyroid diseases (AITD) include Graves' disease (GD) and Hashimoto's thyroiditis (HT), both of which are characterized pathologically by infiltration of the thyroid by T and B cells, reactive to thyroid antigens, biochemically by the production of thyroid autoantibodies, and clinically by abnormal thyroid functions (hyperthyroidism in GD and hypothyroidism in HT) (reviewed in (1; 2)). Additional variants of AITD include post-partum thyroiditis (reviewed in (3–5)), drug induced thyroiditis, such as interferon induced thyroiditis (IIT) (6), thyroiditis associated with polyglandular autoimmune syndromes (reviewed in (7; 8)). While the exact etiology of thyroid autoimmunity is not known, it is believed to develop when a combination of genetic susceptibility (9; 10) and environmental encounters leads to breakdown of tolerance. While several major genes and environmental factors contributing to the etiology of AITD have been identified, their interactions are still not understood.

METHODOLOGICAL ADVANCES

Recent advances in genetic methods enabled significant progress in the identification of complex disease genes. Complex disease genes can be identified by linkage analysis or by association studies. Classically linkage studies were most powerful for screening the entire

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genome while association studies were mostly utilized for candidate gene analysis. However, genome wide associations (GWAS) have become a reality and proved to be a powerful tool for gene mapping.

Linkage analysis

The principle of linkage analysis is based on the premise that if two genes or polymorphisms are close together on a chromosome they will co-segregate in families. The likelihood that a recombination will occur between them during meiosis is inversely related to the distance between them. Therefore, if a polymorphic marker is close to a disease susceptibility gene, its alleles will co-segregate with the disease in families. The measure of the likelihood of linkage between a disease and a genetic marker is the LOD (logarithm of odds) score (11). The LOD score is the base-10 logarithm of the odds ratio in favor of linkage. According to widely accepted guidelines, in complex diseases a LOD score of >1.9 is suggestive of linkage, while a LOD score of >3.3 indicates significant linkage in studies using the parametric approach. Linkage is confirmed if evidence for linkage is replicated in two separate data sets (12).

Association analysis

Association analysis is highly sensitive and may detect genes contributing $<5\%$ of the total genetic contribution to a disease. Association analyses are performed by comparing the frequency of the allele studied (e.g. HLA-DR3) in a dataset of patients and in ethnically matched controls. If the allele tested is associated with the disease it will appear significantly more frequently in patients than in controls. The probability of having the disease in an individual positive for the allele compared with an individual negative for the allele is estimated by the relative risk (13). There are at least two possible explanations for the existence of an association between an allele and a disease: 1) the associated allele itself is the genetic variant causing an increased risk for the disease; 2) the associated allele itself is not causing the disease but rather a gene in linkage disequilibrium with it (14).

Candidate gene analysis

Candidate genes are genes which are selected by virtue of their physiological functions, as possible contributors to disease etiology. If a candidate gene causes a disease, then markers inside or flanking this gene will be associated and linked with the disease. The candidate gene approach enabled the identification of several AITD susceptibility genes (e.g. CTLA-4, see below).

Whole genome screening

Whole genome screening is a powerful tool, as it enables scanning the entire human genome for a disease gene without any prior assumptions on disease pathogenesis. Whole genome screening by linkage is performed by testing a panel of markers which span the entire human genome for linkage with a disease in a dataset of families in which the disease aggregates. Since linkage spans large distances one can scan the entire human genome by linkage using approximately 400–500 polymorphic markers at an average inter-marker distances of 10–20 Mb (15). If one or more markers in a certain locus show evidence for linkage with the disease this locus may harbor susceptibility gene for the disease studied. Linked regions can then be fine mapped and the genes identified (16).

Up until recently whole genome scanning was possible only using linkage because the linkage intervals needed between markers are 10–20 Mb while for genome-wide screening by association analysis one would need to employ approximately 500,000 markers at much shorter distances (approximately < 50 Kb). The completion of the HapMap project (17) has

made whole genome scanning by association studies feasible (18). The HapMap project genotyped more than one million single nucleotide polymorphisms (SNPs) spanning the entire human genome in four ethnically distinct human populations and tested these SNPs for linkage disequilibrium (LD) (17). The HapMap analysis demonstrated that the human genome is highly organized into discrete linkage disequilibrium blocks (LD blocks) which are flanked by recombination hot spots, or areas at which recombinations are much more likely to occur. Recombinations are much rarer at the LD blocks with all the markers in each block in tight LD. This enabled the utilization of tag-SNPs (each SNP representing an entire linkage disequilibrium block) to test the entire human genome for association with disease. Moreover, microarray-based genotyping technology, enabled the typing of up to 500,000 SNPs in a single experiment. Thus, today it is possible to scan the entire human genome using densely spaced SNPs.

In summary, recent advances have made it possible to efficiently identify complex disease genes. As a result it became apparent that most complex diseases are influenced by numerous genes which interact with each other and with environmental factors. Using both the candidate gene approach and whole genome linkage studies, 6 AITD susceptibility genes have been identified and confirmed, HLA-DR, CD40, CTLA-4, PTPN22, thyroglobulin and TSH receptor.

THE HLA-DR GENE LOCUS

Genetic studies

The major histocompatibility complex (MHC) region, encoding the HLA glycoproteins, consists of a complex of genes located on chromosome 6p21 (19). HLA class II genes were the first genes to be tested in AITD. While initial studies analyzed different HLA-DR and DQ alleles in AITD (10), more recent studies focused on the specific peptide binding pocket sequences and 3-D structures that predispose to disease (20; 21). GD is associated with HLA-DR3 in Caucasians (reviewed in (22)). The frequency of DR3 in Caucasian GD patients was 40–50% and in the general population approximately 15–30%, resulting in an odds ratio (OR) for people with HLA-DR3 of up to 4.0 (23). Among Caucasians, HLA-DQA1*0501 was also shown to be associated with GD (24; 25), but it appears that the primary susceptibility allele in GD is indeed HLA-DR3 (HLA-DRB1*03) (26).

Data on HLA alleles in HT have been less definitive than in GD. Earlier studies showed an association of goitrous HT with HLA-DR5 (RR=3.1) (27) and of atrophic HT with DR3 (RR=5.1) in Caucasians (28). Later studies in Caucasians reported weak associations of HT with HLA-DR3 (29; 30) and HLA-DR4 (31). Recently, we have shown that a specific amino acid signature of HLA-DR is strongly associated with HT across HLA-DR alleles (see below).

Mechanisms

Over the past 3 decades the mechanisms by which HLA class II proteins confer susceptibility to autoimmunity have been dissected. T cells recognize and respond to an antigen by interacting with a complex between an antigenic peptide and an HLA class II molecule (mostly DR and DQ) (reviewed in (32)). The various HLA class II alleles have different affinities for peptides. Thus, peptides formed from proteolysis of autoantigens (e.g. thyroglobulin) are recognized by T cell receptors on cells which have escaped tolerance. Thus, certain HLA-DR alleles may permit the autoantigenic peptide to fit into the antigen binding groove inside the HLA molecule, and to be recognized by the T-cell receptor, while others may not (33). This could determine if an autoimmune response to that antigen will develop. The best studied disease for structural-functional correlations between HLA class II pocket variants and peptide binding is type 1 diabetes (T1D) (34). It was found that the

amino acid residue at position 57 of the DQ β chain plays a key role in the genetic susceptibility to T1D (35). Lack of Asp at this position at both DR alleles is strongly associated with T1D (36). Structural analysis of DQ molecules has shown that lack of Asp57 on the DQ β chain may predispose to T1D by causing significant alterations in the pocket structure (37; 38). Crystal structure of the HLA-DQ molecule demonstrated that when Asp is present at position 57 of the DQ β chain it forms a salt bridge with the arginine at DQ α 76 making pocket 9 (P9) electrostatically neutral. In contrast, lack of the negatively charged Asp at DQ β 57 makes pocket P9 positive, and enables insulin peptides to form a salt bridge with Arg at DQ α 76 (37; 39). Thus, lack of Asp at DQ β 57 will permit immunogenic islet cell peptides (e.g. insulin peptides) to fit into the HLA-DQ peptide binding pocket and to be recognized by the T-cell receptor (37; 39). In contrast, the presence of Asp at DQ β 57 will prevent insulin peptides from fitting in the pocket, and hence will prevent them from being presented to T-cells (33).

Similar genetic-structural studies were performed by us in AITD. We recently identified arginine at position 74 of the HLA-DR β 1 chain (DR β -Arg-74) as the critical DR amino acid conferring susceptibility to GD (20). In contrast, the presence of glutamine at position 74 of the DR β 1 chain was protective. These data were replicated in an independent dataset (40). Position 74 of the DR β chain is located in pocket 4 (P4) of the DR peptide binding cleft. Structural modeling analysis demonstrated that the change at position 74, from the common neutral amino acids (Ala or Gln) to a positively charged hydrophilic amino acid (Arg), significantly modified the three dimensional structure of the P4 peptide-binding pocket (20). This could alter the peptide binding properties of the pocket favoring peptides which can induce GD (20; 41).

Similarly, we have identified a pocket HLA-DR amino acid signature that conferred strong risk for HT resulting in an odds ratio of 3.7 (21). This pocket amino acid signature resulted in a unique pocket structure that is likely to influence pathogenic peptide binding and presentation to T-cells. Thus, both GD and HT are associated with specific DR pocket sequence and structure, strongly suggesting that alterations in peptide binding to HLA-DR play a major role in the etiology of both GD and HT, as has been shown in type 1 diabetes (42).

THE CTLA-4 GENE

Genetic studies

The cytotoxic T lymphocyte-associated factor 4 (CTLA-4) gene is a major negative regulator of T cell activation (43). CTLA-4 may play a role in autoimmunity as CTLA-4 activation has been shown to suppress several experimental autoimmune diseases including murine lupus (44), collagen-induced arthritis (45), experimental autoimmune glomerulonephritis (46), and diabetes in NOD mice (47). Thus, it was postulated that CTLA-4 polymorphisms which reduce its expression and/or function might predispose to autoimmunity.

DeGroot and colleagues were the first to show an association between CTLA-4 and autoimmunity (48). Their study showed a significant association between a microsatellite in the 3'UTR of CTLA-4 and GD. Since this original publication CTLA-4 was shown in numerous studies to be linked and associated with both GD and HT (49–54). Several CTLA-4 polymorphisms have been investigated, and the most consistent associations were found with 3 variants, an AT-repeat microsatellite at the 3'untranslated region (3'UTR) of the CTLA-4 gene [(AT) n] (48; 51); an A/G SNP at position 49 in the signal peptide resulting in an alanine/threonine substitution (A/G49) (50; 55–58); and an A/G SNP located downstream and outside of the 3'UTR of the CTLA-4 gene (designated CT60) (53). The

association between AITD and CTLA-4 has been consistent across different ethnic groups (48; 51; 55;59–63).

CTLA-4 was shown to confer susceptibility to the production of thyroid antibodies (TAb) alone without clinical disease (64–66). Further analysis by our group showed that the involvement of CTLA-4 in the genetic architecture of AITD is more complex than originally thought. While the main contribution of CTLA-4 is to the propensity to develop TAb, CTLA-4 may play a role in the susceptibility to high levels TAb and clinical AITD when interacting with other loci (67). Moreover, both the G allele (previously reported to be associated with AITD) and the A allele (reported to be protective) of the A/G49 SNP may predispose to disease when interacting with different loci (67).

Mechanisms

It is still not known which CTLA-4 variant is the causative variant and by what mechanism it confers susceptibility to autoimmunity. To identify the causative variant functional studies are needed as all associated variants are in tight linkage disequilibrium. Mechanistically, a polymorphism that reduced CTLA-4 expression/function would be expected to augment T-cell activation, and potentially, lead to autoimmunity. The A/G49 SNP causing a Thr to Ala substitution in the signal peptide, was reported to cause mis-processing of CTLA-4 in the ER resulting in less efficient glycosylation and diminished surface expression of CTLA-4 protein (68). Kouki et al (69) have shown an association between the G allele of the A/G49 SNP and reduced inhibition of T cell proliferation, results which were later replicated by us (54). However, this association could be due to a direct effect of the A/G49 SNP on CTLA-4 expression/function, or due to the effects of another variant in linkage disequilibrium with the A/G49 SNP. Further studies demonstrated that when a T-cell line, devoid of endogenous CTLA-4, was transiently transfected with a CTLA-4 construct harboring either the G or the A allele of the A/G49 SNP there was no difference in CTLA-4 expression/function (70). These data suggest that A/G49 is not the causative SNP, but rather is in linkage disequilibrium with the causative variant. Functional analysis of the CT60 SNP in a small number of patients suggested that the GG (disease susceptible) genotype was associated with reduced mRNA expression of the soluble form of CTLA-4 (53). However, a recent large study did not find an association between CT60 genotypes and soluble CTLA-4 mRNA expression levels (71). Another CTLA-4 variant that could affect CTLA-4 functionality is the 3'UTR (AT)_n. Indeed, carriage of the longer repeats (associated with disease) was associated with reduced CTLA-4 inhibitory function (72). Moreover, the long repeats were associated with significantly shorter half life of CTLA-4 mRNA compared to the short repeats (73). The region of CTLA-4 3'UTR in which the AT-repeat is located contains three AUUUA motifs which may affect mRNA stability (74). This could provide an attractive mechanism for the association between the short alleles of (AT)_n and AITD, as well as other autoimmune diseases.

THE CD40 GENE

Genetic studies

CD40 is expressed primarily on B-cells and other antigen presenting cells (APC's (APC's) (75), and plays a fundamental role in B-cell activation inducing, upon ligation, B-cell proliferation, immunoglobulin class switching, antibody secretion, and generation of memory cells (76; 77). Using a combination of linkage and association studies we and others have identified CD40 as a major susceptibility gene for GD (78–84). Sequencing the entire CD40 gene led to the identification of a C/T polymorphism, at the 5'UTR of CD40 (79), with the CC genotype of this SNP strongly associated with GD (79; 81–84). One study did not find the association, possibly due to ethnic differences among populations (85).

However, a meta-analysis showed a highly significant association between the CC genotype and GD (83). Moreover, we have recently shown that the association of the CC genotype was stronger in the subset of GD patients that had persistently high levels of thyroid antibodies after treatment (86).

Mechanisms

How can the CC genotype predispose to GD? Functional studies demonstrated that the CD40 Kozak SNP influences CD40 translational efficiency. The C-allele of the polymorphism increases the translation of CD40 mRNA transcripts, by 20–30% compared to the T-allele (87; 88). Therefore, it is possible that increased CD40 expression driven by the C allele contributes to disease etiology by lowering the threshold of autoreactive B-cells for activation to thyroidal antigens (87). Another possibility is that the C-allele enhances CD40 expression on thyrocytes (89; 90). CD40 signaling in thyrocytes can result in cytokine secretion (e.g. IL-6 (89)) and activation of resident T-cells in the thyroid by bystander mechanisms (86).

Since CD40 is a major APC and B-cell co-stimulatory molecule, the question arises whether the CD40 Kozak SNP could play a role in other autoimmune conditions? Association studies in Hashimoto's thyroiditis (79) and type 1 diabetes (91), both cell mediated autoimmune diseases with strong Th1 component, showed no association. However, a recent study has shown that the C allele of the CD40 Kozak SNP was strongly associated with high IgE levels in asthma (88).

THE PROTEIN TYROSINE PHOSPHATASE-22 (PTPN22) GENE

Genetic studies

The lymphoid tyrosine phosphatase (LYP), encoded by the protein tyrosine phosphatase-22 (PTPN22) gene, like CTLA-4, is a powerful inhibitor of T cell activation (92). A tryptophan/arginine substitution at codon 620 (R620W) of PTPN22 was found to be associated with AITD including both GD (93), and HT (94), as well as with other autoimmune diseases (95–98). Unlike CTLA-4 which was associated with AITD across ethnic groups, the PTPN22 gene shows significant ethnic differences in associations. This is most probably due to the absence of the susceptible variant in certain ethnic groups. As an example, the tryptophan variant of the protein tyrosine phosphatase-22 (PTPN22) gene is very rare in the Japanese and, therefore, PTPN22 does not seem to contribute to autoimmunity in the Japanese (99).

Mechanisms

Mechanistically, the disease associated tryptophan variant makes the protein an even stronger inhibitor of T cells, as it is a gain-of-function variant (100). One possible explanation for this surprising finding is that a lower T cell receptor signaling would lead to a tendency for self-reactive T cells to escape thymic deletion and thus remain in the periphery.

THYROGLOBULIN

Genetic studies

Thyroglobulin (Tg) is a 660 kDA homodimeric protein that serves as a precursor and storehouse for thyroid hormones (101). Tg is one of the main targets of the immune response in AITD and all AITD phenotypes are characterized by the development of Tg antibodies. Mouse models have provided additional evidence for the importance of Tg in the development of thyroid autoimmunity. The mouse model for Hashimoto's thyroiditis,

murine experimental autoimmune thyroiditis (EAT), can be induced, in genetically susceptible mice, by immunization with thyroglobulin (102)).

Recently, Tg gene was established as a major AITD susceptibility gene (103–108). Linkage studies mapped an AITD locus to the Tg gene region on chromosome 8q24 (15; 103; 109). Further detailed sequencing analysis of the Tg gene identified three amino acid substitutions that were significantly associated with AITD, A734S, V1027M, and W1999R (110).

Mechanisms

One attractive mechanism is by which amino acid variants in Tg could predispose to AITD is by altering Tg peptide presentation by APC's to T-cells within HLA class II molecules. Such a mechanism would imply that there exist an interaction between Tg variants and HLA-DR variants predisposing to AITD. Indeed, we have shown that the W1999R variant had a statistical interaction with the Arg74 polymorphism of HLA-DR, resulting in a high odds ratio of 15 for GD (111). This statistical interaction may imply a biological interaction between Tg and HLA-DR. For example, the Tg peptide repertoire generated in individuals with the R allele of W1999R (associated with AITD) could be pathogenic, while DR β -Arg74 could optimally present these pathogenic Tg peptides to T-cells.

TSH RECEPTOR GENE

Genetic studies

The hallmark of GD is the presence of stimulating thyrotropin (TSH) receptor antibodies (1), and, therefore, the TSHR was an attractive candidate gene for GD. Prior to the completion of the human genome project and the availability of detailed SNP maps three missense SNPs of the TSHR have been examined for association with GD (112), D36H, P52T, and D727E. However, studies of these SNPs gave inconsistent results with some showing associations (113; 114), and others not (115–118). However, one group in Japan consistently reported associations of the TSHR with GD in the Japanese (60; 63). More recently it was found that non-coding SNPs of the TSHR are associated with GD (119; 120). The most consistent association has been with an intron 1 SNP (121; 122).

Mechanisms

It is usually easier to postulate potential mechanisms for missense SNPs. The mechanisms by which intronic SNPs may predispose to disease are much more challenging to study. Therefore, it is still not know how the intron 1 SNP of the TSHR could predispose to GD. Potential mechanisms include alterations in TSHR gene expression and/or splicing (123). Indeed, several splice variants of the TSHR gene have been reported (123; 124).

THE ROLE OF ENVIRONMENTAL FACTORS

A recent twin study estimated that 79% of the liability to the development of GD is attributable to genetic factors (125). Therefore, about 20% of the liability to develop GD is due to non-genetic factors. Among the non-genetic factors postulated to precipitated AITD are iodine (126; 127) (Table 1), medications such as amiodarone and interferon alpha (128) (Table 2), infections (129), Smoking (Table 3), and stress (Table 4).

One of the most intriguing environmental triggers of autoimmune thyroid diseases is infection. Indeed, there is evidence that infectious agents may trigger AITD (reviewed in (130)). For example studies have shown seasonality (131) and geographic variation (132) in the incidence of GD. Moreover, Valtonen et al. found serological evidence for a recent bacterial or viral infection in 36% of newly diagnosed GD patients and in only 10% of controls (133). Several infectious agents have been implicated in the pathogenesis of AITD

including *Yersinia enterocolitica* (134–137), Coxsackie B virus (138), retroviruses (139–143), *Helicobacter pylori* (144; 145). However, by far the strongest association of AITD with an infectious agent is with hepatitis C virus (HCV) (146). While some earlier studies did not show a clear association between hepatitis C and thyroid autoimmunity (147), more recent studies have shown a clear association (148–150). In two studies from France of patients with hepatitis C infection who had not received IFN alpha therapy, the incidence of thyroid antibodies and/or dysfunction was significantly higher in the patients than in the controls (148; 151). Overall, in most studies examining the frequency of thyroid disorders in hepatitis C patients approximately 10% of the patients had positive TAB's prior to initiation of interferon therapy (152–156). A recent very large studies that controlled for dietary iodine and treatment demonstrated that both hypothyroidism and thyroid autoimmunity were significantly more common in patients with hepatitis C compared to controls (150)(32). Moreover, pooling of data from all studies on HCV infection and thyroid autoimmunity demonstrated a significant increase in the risk of thyroiditis in HCV patients (157).

What are the mechanisms by which infectious agents can trigger AITD? Two main theories have been proposed for the induction of autoimmunity by infectious agents (158): (1) the molecular mimicry theory suggests that sequence similarities between viral proteins and self proteins can induce a cross-over immune response to self antigens (159); (2) the bystander activation theory proposes that viral infection of a certain tissue can induce local inflammation (e.g. by cytokine release), resulting in activation of autoreactive T-cells that were dormant or suppressed by peripheral regulatory mechanisms (160). While evidence for molecular mimicry between *Yersinia* proteins and thyroid antigens exists (161), these data have not been confirmed. Recent data favor the bystander activation as the predominant mechanism by which viral agents trigger autoimmunity in autoimmune thyroiditis (162). Recently, we have shown that the HCV virus can activate cytokine secretion by thyroid cells (163). We examined whether the HCV receptor, CD81, was expressed and functional on human thyroid cells. We found significant levels of CD81 mRNA and protein on human thyroid cells in primary cultures. Moreover, incubation of human thyroid cells with HCV envelope glycoprotein E2 resulted in E2 binding to thyroid cells and activation of IL-8 secretion (163). Hence, it is possible that HCV can trigger autoimmune thyroiditis by infecting the thyroid resulting in release of pro-inflammatory mediators such as IL-8, and induction of thyroid autoimmunity by bystander activation mechanisms. Indeed, two recent studies have shown that HCV is present in the thyroid of infected individual (164; 165). Moreover, it is possible that even if HCV does not infect thyroid cells viral proteins that are shed for virions or that are part of non-infectious virions can also trigger an inflammatory response resulting in thyroid autoimmunity by bystander mechanisms.

CONCLUSIONS

The AITD are complex diseases that are postulated to be caused by the combined effects of multiple susceptibility genes and environmental triggers. Significant progress has been made in the past decade in mapping the AITD susceptibility genes and understanding the mechanisms by which they confer risk for disease. The AITD susceptibility genes identified so far can be divided into two broad groups: (1) immune modulating genes and (2) thyroid specific genes. The first group includes the HLA-DR, CD40, CTLA-4, and PTPN22 genes, while the second group includes the Tg and TSHR genes. It is clear that additional genes contribute to the genetic susceptibility to AITD, as well as to the different phenotypes of AITD, disease severity, and, possibly, response to therapy. In addition, several environmental factors have been associated with the etiology of AITD, notably, dietary iodine, infections, smoking and certain medication. How the susceptibility genes and environmental triggers interact to cause AITD is still not known.

Intriguingly, all AITD susceptibility gene identified so far participate in the immunological synapse and/or the signaling pathways activated by the immunological synapse. This finding suggests that inherited abnormalities in the immunological synapse contribute to the breakdown of tolerance in AITD. Possibly, this breakdown in tolerance may be triggered by a bystander mechanism, whereby an insult to thyroid tissue (as a result of infection, medications, or iodine) can trigger a local inflammatory reaction which then activates resident T-cells. These T-cells could then cause an autoimmune reaction to the thyroid in genetically susceptible individuals.

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Table 1
Selected studies on the association between dietary iodine and autoimmune thyroid disease

Study (ref)	Associated AITD	Number of Patients	Number of Controls	Design	Findings
Zois et al. 2006 (166)	HT	29 children	NA	Epidemiological	Following 29 children for 5 years after eliminating iodine deficiency, anti-TPO and TG antibodies increased in frequency and level, and TSH levels increased.
Laurberg et al. 1999 (167)	HT/GD	569,108 (persons×years studied)	NA	Epidemiological	In areas of low iodine intake, hyperthyroidism was more common than hypothyroidism, conversely, in areas where there was high iodine intake, hypothyroidism was more common.
Laurberg et al. 1991 (168)	GD	220 (East- Jutland) and 162 (Iceland)	NA	Population based	The incidence of GD was significantly higher in Iceland, an area of high iodine intake, compared to East-Jutland, an area of low iodine intake. This was most marked in the younger age groups.
Papanastasiou et al 2000 (169)	HT	40	N/A	Prpspective	All patients with goiter received 1 ml of iodized oil (480 mg iodine); 7 patients developed TAB's, and FNA revealed ' lymphocytic infiltration in 10 cases before and 27 cases after iodine injection
Pederson IB, et al. 2007 (170)	HT	535,831	NA	Population based	Iodization results in an increase in the incidence rate of hypothyroidism, primarily in young and middle aged subjects.
Pederson IB, et al. 2006 (171)	GD	535,831	NA	Population based	Iodine fortification results in an increase in the incidence rate of hyperthyroidism, mostly in young individuals
Papanastasiou L, et al 2000 (169)	GD/HT	40 (total)	NA	Population based	Administration of iodine oil intramuscularly resulted in the onset of transient thyroid autoimmunity.
Teng et al. 2006 (172)	HT	3018	N/A	Population based	The prevalence of autoimmune thyroiditis was 1.3% in areas of excessive iodine intake and 0.2% in areas of deficient iodine intake

Table 2

Selected studies on the association certain medications and thyroid autoimmunity.

Study (Ref)	Medication/Treatment	Associated AITD	Number of Patients	Findings
Reviewed in Tomer Y. et al. 2006 (6)	IFN-alpha	GD/HT	NA	Clinical disease (GD, HT, or destructive thyroiditis) was seen in 5–10% of those that received IFN-alpha for treatment of hepatitis, and thyroid autoantibodies appeared in 10–40%.
Trip MD. et al. 1991 (173)	Amiodarone	GD/HT	58	Euthyroid patients treated with amiodarone for arrhythmias had an incidence of thyrotoxicosis of 12.1% and an incidence of hypothyroidism of 6.9%.
Coles AJ. et al. 1999 (174)	Campath-1H (anti-CD52)	GD	37	12/27 multiple sclerosis patients treated with campath-1H developed Graves' disease compared the incidence of only 1–2% in untreated multiple sclerosis patients and those treated with IFN-beta 1 b.
Knysz et al. 2006 (175)	Antiretroviral	GD	1	27 years old HIV patient was treated with Stavudine, lamivudine, amprenavir, and ritonavir. Two years later she had high T4 and low TSH, with thyroid enlargement and eyelid retraction.
SklarC. et al. 2000 (176)	Irradiation for Hodgkin's disease	GD/HT	1791	Of the 1791 Hodgkin's patients assessed, 34% had been diagnosed with at least one thyroid abnormality. Hypothyroidism was the most common disturbance with a relative risk of 17.1. Hyperthyroidism was seen in 5% of survivors giving an 8 fold greater incidence than reported in the controls.

Selected studies on the association between smoking and autoimmune thyroid disease (note that we did not include studies on the well-known association between Graves' ophthalmopathy and smoking).

Table 3

Study (Ref)	Associated AITD	Number of Patients	Number of Controls	Type of Study	Findings
Vestergaard P. 2002 (177)	GD	data from 25 previous studies	NA	Meta-analysis	Smokers that had quit smoking were associated with a lower risk to GD than current smokers.
Yoshiuchi K. et al. 1998 (178)	GD	228	228	Matched case/control	Smoking was associated with GD in women.
Heidberg T. et al. 2000 (179)	GD	132	132	Twin case/control	Smoking is associated with an increased risk of developing clinically overt thyroid disease.
Vestergaard P. et al. 2002 (180)	GD/HT/TNG	516/628/348	516/628/348	Matched case/control	There is an increased risk of GD, HT, and TNG with ever smoking compared to never smoking in women but not men.
Prummel M. et al. 1993 (181)	GD/HT/TNG	200/75/100	200	Case/control	Smoking was associated with GD and with more severe eye disease. Smoking was not associated with HT
Belin et al. 2004 (182)	TAb	15,592	NA	Population based	Smoking was associated with decreased frequency of thyroid autoantibodies and elevated TSH

Table 4
Selected studies on the association between stress and autoimmune thyroid disease

Study (Ref)	Associated AITD	Number of Patients	Number of Controls	Type of Study	Findings
Mantos-Santos A. et al. 2001 (183)	GD	31	31	case/control	GD patients had a significantly greater number of negative and positive stressful life events compared to the control group.
Winsa B. et al. 1991 (184)	GD	208	372	case/control	GD patients claimed to have had more negative life events in the 12 months preceding diagnosis. Negative life event scores were also significantly higher.
Boscarino J. 2004 (185)	GD/HT	2490	NA	epidemiological	Chronic post traumatic stress disorder is associated with common autoimmune diseases including GD and HT.
Yoshiuchi K. et al. 1998 (178)	GD	228	228	matched case/control	Stressful life events were associated with GD in women.