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Review

Genetics of thyroid autoimmunity and the role of the TSHR

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ABSTRACT

Graves' disease (GD) and Hashimoto's thyroiditis (HT) make up the autoimmune thyroid diseases (AITD), with classical clinical characteristics arising as a result of environmental factors in people who are genetically predisposed. Three gene regions consistently associated with AITD include the Human Leucocyte Antigen (HLA) region, *CTLA4* and *PTPN22*, which represent general autoimmune risk loci and encode molecules vital for correct immune system function. AITD patients in addition are likely to carry at least one thyroid specific susceptibility locus. Recent genetic studies have refined association of the *TSHR* with GD to within a 40 kb region including intron 1, of the *TSHR* itself, with preliminary evidence to suggest altered mRNA isoform expression. These findings, combined with previous functional data demonstrating that the TSHR A-subunit is the primary autoantigenic region, suggests novel mechanisms for the onset of GD and a potential therapeutic target.

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Contents

1. Introduction

Collectively, autoimmune diseases affect up to 5% of the general population and represent a heterogeneous group of disorders with nearly all major organs targeted (Jacobson et al., 1997; Vyse and Todd, 1996). Graves' disease (GD) and Hashimoto's thyroiditis (HT) make up the autoimmune thyroid diseases (AITD) and are particularly common with a preponderance of about 1% in Western populations (Tunbridge et al., 1977). Both GD and HT possess a strong genetic component with patients often reporting a family history. The AITD UK National Collection of DNA, consisting 2405 GD (2020 females and 385 males) and 400 HT British Caucasian subjects (342 females and 58 males), showed that 47.4% of females and 40.0% of male GD patients and 56.4% females and 51.7% of male HT patients reported a family history of thyroid dysfunction (Manji et al., 2006). Concordance studies in twins suggest that up to 80% of risk can be attributed to genetic factors, leaving approximately 20% for the influence of environmental variables (Brix et al., 1998, 2001). The breakdown in immune tolerance appears to be determined by many disease risk genes, which are modulated by environmental factors. These factors influence many immune system functions, including reactivity of immune cells and mechanisms of antigen presentation, which include the types of antigens presented for processing by the immune system. Interaction between susceptibility genes and environmental factors is likely to be highly complex and is still poorly understood.

In recent years advances have been made in our understanding of the genetics of AITD, particularly GD. Notably, many of the genes identified as conferring susceptibility to the onset of GD are shared among other AIDs, including type 1 diabetes (T1D), rheumatoid arthritis (RA) and multiple sclerosis (MS). This apparent convergence of susceptibility genes increases the risk of autoimmunity

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in general and when combined with disease specific risk factors serve to trigger the autoimmune disease. A fundamental difference between the autoimmune diseases is the type of organ/tissue targeted by the immune system (Marrack et al., 2001). Both GD and HT can be characterised by lymphocytic infiltration of the thyroid with autoantibodies specifically targeting the thyroid stimulating hormone receptor (TSHR), thyroglobulin (Tg) and thyroid peroxidase (TPO). An intriguing debate in autoimmunity is whether autoantigens are simply targeted by a malfunctioning immune system or if they exacerbate the autoimmune problem in individuals possessing other autoimmune susceptibility loci. Recent studies suggest the TSHR, which is the primary autoantigen in GD plays a key role in triggering the onset of GD. This review will examine the genetic evidence and possible disease mechanisms for the role of the TSHR in the onset of GD.

2. Established genetic loci

Three genes/regions have been consistently associated with AITD over many years. These are the HLA gene region, *CTLA4* and *PTPN22*. These genes confer the largest contribution to genetic risk identified to date, with odds ratios (OR) for development of GD equal to or greater than 1.5. All three encode proteins integral to correct immune function, particularly in aspects of T lymphocyte (T-cell) development and activation. Genetic variants within these loci have been associated with multiple autoimmune diseases, suggesting they confer susceptibility to autoimmunity in general. Various other general autoimmune risk loci are also beginning to be uncovered, which require either replication or further validation in additional cohorts, such as IL2Rα/CD25 (Brand et al., 2007), *Tg* (Tomer et al., 1999; Taylor et al., 2006), FCRL3/5 (Simmonds et al., 2006) and CD40 (Tomer et al., 2002; Heward et al., 2004).

3. HLA-region

The HLA-region located on chromosome 6p21, extends over 7.6 Mb and is particularly gene dense with at least 252 genes, most of which are involved in different aspects of immune function (Horton et al., 2004; Mungall et al., 2003). Various regions within the HLA complex have been associated with GD, however extensive LD across the region has made it difficult to decipher the important gene regions harbouring the key aetiological variants. The most important group of genes concerned with AITD are the HLA class I and II genes, which have been consistently associated with GD (Simmonds et al., 2005, 2007; Heward et al., 1998; Ban et al., 2004). The HLA class II genes encode cell surface heterodimers, consisting of α and β chains, which are anchored to the cell surface of antigen presenting cells, such as B cells, macrophages and dendritic cells and are responsible for the binding of exogenous antigens for presentation to $CD4^+$ T cells (Gebe et al., 2002). The HLA class I region contains the HLA-A, HLA-B and HLA-C genes and each encode a single alpha chain composed of three alpha domains, which associate with β2-microglobulin to form an internal receptor that is capable of binding intracellular antigens such as those derived from viruses or bacteria, which are subsequently presented to $CD8^+$ T cells.

Original studies over 30 years ago first demonstrated association of variants within HLA class I, particularly HLA-A and HLA-B with GD (Farid et al., 1976; Bech et al., 1977). Subsequent studies demonstrated stronger associations within HLA class II genes, leading to more focused efforts within this region (Heward et al., 1998; Chen et al., 1999). The strongest GD associations within HLA class II were the *DRB1*03*, *DQA1*0501* and to a lesser extent *DQB1*02*, which together make up the DR3 susceptibility haplotype and a protective DR7 haplotype, consisting of *DRB1*07-DQB1*02-DQA1*0201* (Chen et al., 1999; Heward et al., 1998). More recently Ban et al. (2004) demonstrated an increased prevalence of Arginine at *DRB1* β74 in a GD case-control cohort. Further studies performed at the same time genotyped all alleles within *DRB1*, *DQB1* and *DQA1* in a large GD case-control cohort and by employing logistic regression were able to narrow association to within *DRB1* and *DQA1* and thus exclude an aetiological effect at *DQB1* (Simmonds et al., 2005). Amino acid mapping based on the alleles genotyped at DRB1 identified 13 amino acid positions that were associated with GD, with DRB1 β74 showing strongest evidence for association with GD (Simmonds et al., 2005). The DRB1*03 allele which is part of the predisposing DR3 haplotype encodes an arginine at β74, whereas DRB1*07 part of the protective DR7 haplotype encodes glutamine at β74, suggesting amino acid changes at β74 may drive the associations observed (Simmonds et al., 2005). The strong associations identified with DRB1 and DQA1 combined with the strong LD between class I and II regions previously made it difficult to identify independent associations within class I. However, recent studies by our own group showed for the first time by logistic regression that HLA class I genes, HLA-C and to a lesser extent HLA-B eclipsed associations at DRB1 and DQA1, demonstrating class I genes confer an independent risk to GD (Simmonds et al., 2007). In summary, variants within HLA class I (HLA-C and HLA-B) and HLA class II (DRB1 and DQA1) are likely to interfere with antigen binding and subsequent presentation of antigens to $CD4^+$ or $CD8^+$ T cells. It is possible, that certain HLA class I or II alleles associated with GD such as DRB1 β74 or HLA-C may increase affinity for thyroid autoantigens and so initiate an autoimmune response as seen in GD. Whilst a greater understanding of the HLA system and polymorphism within is likely to open up new hypotheses in the development of AITD and even help identify at risk individuals, it seem unlikely that in the foreseeable future this will lead to the development of novel therapies.

4. CTLA4

CTLA4 is a potent inhibitor of T cell activation, demonstrated by T cell mediated attack of multiple organs, resulting in early death of CTLA4 knock-out mice (Tivol et al., 1995). It is unclear exactly how CTLA4 inhibits T cell activation, however it is known to bind CD80/86 on the surface of antigen presenting cells, which results in a signalling cascade to inhibit activation. *CTLA4* polymorphisms were first associated with GD and have since been linked with other autoimmune diseases (Donner et al., 1997). Earlier studies investigated a limited number of variants, which included a dinucleotide (AT)n repeat within the 3′ untranslated region of exon 3 (Yanagawa et al., 1995), a C/T SNP within the *CTLA4* promoter region −318 bp from the ATG start codon (Braun et al., 1998), an A/G SNP within exon 1 (Ala/Thr position 17) (Heward et al., 1999) and a C/T SNP within the non-coding intron 1 of *CTLA4* (Vaidya et al., 2003). A more comprehensive fine-mapping study genotyped 108 SNPs across 330 kb containing *CD28*, *CTLA-4* and *ICOS* (Ueda et al., 2003). Association was refined to within a 6.1 kb region, just 3′ of CTLA4, with four SNPs, CT60, JO31, JO30 and JO27_1 highly associated with GD (Ueda et al., 2003). The CT60 SNP however revealed strongest association with GD and the associated genotypes of CT60 were linked with reduced mRNA levels of a soluble CTLA4 isoform (Ueda et al., 2003). A recent meta-analysis of 10 studies (4906 GD subjects and controls) supported findings that CT60 is the most associated SNP and calculated a combined OR = 1.49 for CT60 (Kavvoura et al., 2007). However, due to strong LD no one SNP could be differentiated from the other four as being the primary aetiological variant. Further functional studies are now underway to determine the functional role of full length CTLA4 as well as soluble CTLA4 to determine how polymorphisms within the 6.1 kb region may affect the ability of CTLA4 to inhibit T cell activation.

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