Genetic control of T cell immune tolerance mechanisms and susceptibility to autoimmune disease

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Abstract

The majority of human autoimmune diseases have a complex aetiology with strong genetic and environmental components. The genetic component of disease susceptibility is generally highly polygenic, with multiple loci acting synergistically, and genetically heterogenous, with diverse sets of polymorphic loci capable of driving the same autoimmune reaction. The genetics of autoimmunity is further complicated by the division of genetic susceptibility into general autoimmune propensity polymorphisms and disease-specific polymorphisms. Despite the complexity of autoimmune genetics at the locus level, it appears that a limited number of conserved mechanistic pathways are affected by genetic polymorphisms. The conserved tolerance pathways subverted by autoimmune polymorphisms are being unravelled by the analysis of mouse models of autoimmunity. These models have identified three key fragile links in the T cell tolerance pathway - antigen presentation and the apoptotic response in the thymus, \textit{cis}- and \textit{trans}-acting peripheral suppression of autoreactive T cells, and the target organ response to autoimmunity.
The genetic epidemiology of autoimmune diseases

The common autoimmune diseases cluster within families, indicating a genetic basis for disease susceptibility. The genetic component of disease susceptibility, based on monozygotic twin concordance for disease, is around 20-50% for most prevalent autoimmune diseases (Table 1), indicating a strong additional influence of environmental and developmental factors in determining disease outcome.

As autoimmune diseases share a common basic aetiology, that of inappropriate activation of the immune response towards self-antigens, it is unsurprising that they also share common genetic components of susceptibility. There are three main lines of evidence supporting the existence of genetic factors that contribute towards general autoimmune disease susceptibility.

1) There is a large amount of clinical data that multiple autoimmune diseases cluster in the same patient population (Table 2). For example, patients with type 1 diabetes (T1D) have elevated risks of developing autoimmune thyroid disease (AITD) \(^1\), Sjogren’s syndrome \(^2\) and Coeliac disease \(^3\), among others. This may indicate a primary genetic defect predisposing the proband to multiple autoimmune diseases, or alternatively it may represent a genetic defect causing a single primary autoimmune disease that later catalyses multiple secondary autoimmune diseases.

2) Autoimmune diseases as a broad classification show tighter familial clustering than specific autoimmune diseases. Numerous studies have demonstrated that the first degree relatives of patients with a particular autoimmune disease have a greater risk of developing autoimmune conditions beyond that which the proband was effected with (Table 3). For example, the first degree relatives of T1D probands in Columbia have a 2.3% risk of developing T1D, but a 6% risk of developing an alternative autoimmune disease, giving an overall 8.3% risk of developing any autoimmune condition \(^4\).

3) Genetic association studies have been performed for multiple common autoimmune diseases and several loci have been consistently associated with more than one autoimmune disease (Table 4). While ascertainment bias exists for many of these associations and some show little effect in the larger population, the clustering of association is striking. For example, polymorphisms in \(IL2RA\) have been associated with T1D \(^5\), AITD \(^6\), multiple sclerosis (MS) \(^7\) and rheumatoid arthritis (RA) \(^8\). Likewise the \(PTPN22\) locus has been associated with T1D \(^8,9\), AITD \(^10\), systemic lupus erythematosus (SLE) \(^11\), RA \(^8,12\), and Crohn’s disease \(^8\). \(HLA\) is more complicated, as the locus is consistently associated with autoimmune disease (in many cases as the strongest single genetic contributor) but different alleles are largely associated with specific diseases \(^13\).

Together these data indicate that the genetic component to autoimmune disease includes both general autoimmune susceptibility loci and organ-specific autoimmune susceptibility loci. In this model of the genetics of autoimmunity, general autoimmune susceptibility loci result in a susceptibility to immune tolerance failure and hence
predispose the individual to developing a range of autoimmune diseases. By contrast, organ-specific autoimmune susceptibility loci direct the pathogenicity of immune tolerance failure towards a specific antigen group or anatomical location. This accounts for the existence of shared and unique gene associations in the mapping studies (Table 4). It also proposes an explanation for why autoimmune disease in general clusters in families (Table 3), yet the most common autoimmune disease manifestation in an autoimmune monozygotic twin pair is for both individuals to develop the same disease (Table 1).

Recent advances in mouse models of autoimmunity have begun to unravel the mechanistic understanding of how genetic defects can contribute to both general autoimmune susceptibility and organ-specific autoimmune susceptibility. For the general autoimmune susceptibility mechanisms, the Non-obese diabetic (NOD) mouse strain has highlighted the potential role defects in thymic negative selection can play in allowing autoreactive T cell clones to enter the periphery. The Foxp3 knockout mouse has demonstrated the importance of Foxp3+ regulatory T cells in maintaining peripheral tolerance by trans-mediated suppression of autoreactive T cells, and the sanroque mutant mouse illustrates the requirement for autoreactive effector T cells to have innate restraints on activation. Each of these pathways represents likely mechanisms that are altered during human autoimmunity, with multiple minor effects acting synergistically to produce immune tolerance failure. In addition, Aire knockout mice have illustrated the manner in which organ-specific tolerance defects can occur through reduced thymic expression of the target antigen and NOD mice indicate the potential for organ-intrinsic defects in resistance to autoimmunity to play a role in susceptibility.

**Generalised genetic defects in central tolerance mechanisms**

The first form of immunological tolerance to be experimentally established was the clonal deletion of T cells that recognise self-antigens with a high affinity during T cell differentiation 14. This process of thymic negative selection relies on the differential ‘wiring’ of immature thymocytes compared to mature T cells, with strong interaction with MHC bound to self-peptide causing apoptosis through the upregulation of Bim 15, 16. Despite the firm establishment of thymic negative selection as a key immune tolerance mechanism, until recently it was not considered a likely contributor to tolerance against organ-specific antigens and therefore a poor candidate for a defective mechanism during autoimmune disease. Even after the initial assumption that organ-specific genes were not present in the thymus was proven incorrect 17, 18, the efficiency of the negative selection process to act through trace quantities of proteins was not fully appreciated.

NOD mice are a well-established model of autoimmune diabetes. One of the interesting aspects of the NOD model is that NOD mice show the same general autoimmune susceptibility that is demonstrated by familial studies in human cohorts. NOD mice spontaneously develop multiple autoimmune disorders, sialitis and dacryoadenitis in addition to T1D, and are susceptible to additional autoimmune diseases when modified by experimental challenge or genetic alteration 19-29. For example, replacement of the
T1D MHC susceptibility allele, $H2^{d7}$, with $H2^{h4}$ prevents T1D but results in spontaneous AITD. Susceptibility to multiple autoimmune diseases has been genetically mapped in NOD mice, with similar results to human studies - highly polygenic control of disease susceptibility with partially overlapping sets of loci involved.

The NOD mouse therefore represents a model where the mechanistic basis for a general genetic propensity to autoimmune disease can be unravelled. One of the promising candidates for such a broad mechanistic defect in immune tolerance is the resistance of NOD thymocytes to undergoing negative selection in response to self-antigen. This trait has been observed in vitro and in vivo for both MHC class II-restricted and MHC class I-restricted T cells. The defect in negative selection is T cell-intrinsic and is observed at all stages of maturation with an approximately ten-fold reduction in the apoptotic response to a fixed amount of antigen presentation. This resistance to negative selection has been mapped by us and others, and while there are differences in the genomic linkage patterns that can probably be attributed to the different models used, in each case prominent linkage was observed to regions known to contribute to autoimmune diabetes in NOD mice. The precise mechanism by which NOD thymocytes are resistant to negative selection has not yet been fully determined, however factors likely to play a role in the resistance are reduced levels of surface T cell receptor (TCR) expression during early stages of thymocyte maturation, poor upregulation of the key apoptotic mediator Bim, and a global defect in the initiation of the negative selection transcriptome.

Currently it is unknown whether an analogous genetic defect is present in human populations and the answer to this question probably awaits further elucidation of the mechanism of negative selection in thymocytes. There are, however, suggestions from a range of monogenic autoimmune disorders that central tolerance defects could contribute to autoimmune susceptibility in humans. These are the partial T cell immunodeficiencies, which can be caused by mutations in a range of genes including $RAG1$, $RAG2$, $DCLRE1C$, $IL7RA$, $RMRP$, $IL2RG$, $ADA$, $ZAP70$ and $LIG4$. Some of these genes are involved in TCR somatic recombination, some in TCR signalling, some in cytokine signalling and some in basic metabolic processes. The common thread, however, is that severe loss-of-function causes complete T cell immunodeficiency, while moderate loss-of-function causes partial T cell immunodeficiency with autoimmunity or immune dysregulation. A number of mouse models have recently been developed to mimic this partial T cell immunodeficiency, such as partial loss-of-function alleles of $Rag1$, $Rag2$, and $Zap70$.

An analysis of the genetic mechanism by which $Zap70$ hypomorphic alleles can produce autoimmune outcomes was performed by crossing a minor loss-of-function allele ($Zap70^{mrd}$) to a severe loss-of-function allele ($Zap70^{mrt}$) to produce a mouse strain with $Zap70$ activity in the critical range ($Zap70^{mrd/mrt}$). The spontaneous development of immune dysregulation in these mice, but not in either parental strain, demonstrates that the crucial factor in the development of autoimmunity is the degree of impairment rather than the particular allelic variant involved. The immune dysregulation in these
mice is intrinsic to effector T cells, indicating that the impact on negative selection is greater than the impact on effector T cell activation. As a similar phenotype is observed in partial loss-of-function Rag1 and Rag2 mutant mice, it is possible that a common causality is involved, suggesting that the level of T cell immunodeficiency is able to impact the efficiency of thymic negative selection.

The mechanism by which partial T cell immunodeficiency may alter the efficiency of thymic negative selection is just starting to be unravelled. Thymic micro-architecture depends on crosstalk between thymocytes and the epithelium using the lymphotixin (LT) pathway. In mice where the LT pathway is crippled, the structure of the thymic epithelial cell network is disturbed, as is the expression of chemokines involved in the migration of thymocytes. These combined factors alter the efficiency of negative selection even without altering the thymic expression of the self-antigen involved. It is therefore possible that partial immunodeficiency, by limiting the number of mature thymocytes and hence LT production, disrupts the normal thymic micro-architecture and reduces the efficiency of negative selection. Additional, or alternative, factors involved may be a restriction in the TCR repertoire of Foxp3+ regulatory T cells or the increased activation potential of effector T cells due to the lymphopenic environment overriding intrinsic restraints on activation, tolerance mechanisms that are treated in more detail in following sections.

While these mouse studies were led by clues from monogenic autoimmune conditions, it is likely that minor levels of T cell immunodeficiency, insufficient to cause autoimmunity alone, are able to act in concert with additional genetic factors to result in autoimmunity. This hypothesis explains the association of a number of gene loci involved in determining the size of the T cell repertoire with common autoimmune diseases. For example, the gain-of-function PTPN22 allele associated with T1D, RA, SLE, AITD and Crohn’s disease and the SH2D2A allele associated with RA and MS (see Table 4) result in a reduction in TCR signalling. Interestingly, moderate loss-of-function alleles of IL7RA can precipitate autoimmunity due to partial T cell immunodeficiency, while an allele of IL7RA which likely gives a two-fold increase in soluble IL-7RA is associated with MS and T1D. Potentially, this allele contributes to autoimmune susceptibility by reducing effective IL-7 serum levels and creating a degree of T cell immunodeficiency. Therefore, in a variety of way genetic defects in the efficiency of negative selection are likely to be playing a role in human susceptibility to autoimmune disease.

Generalised genetic defects in trans-acting peripheral tolerance mechanisms

Research into another monogenic autoimmune disease, Immune dysregulation, Polyendocrinopathy, Enteropathy and X-linked syndrome (IPEX), has revealed a key mechanism of immunological tolerance. Both IPEX and the murine equivalent, Scurfy, are fatal multi-organ autoimmune syndromes caused by loss-of-function mutations in the gene Foxp3. The necessity of Foxp3 for immune tolerance is caused by the role of Foxp3 in coordinating the lineage differentiation of regulatory T cells (T_R) from the naïve T cell pool. In the absence of Foxp3+ T_R self-reactive T cells undergo
uncontrolled activation and mediate autoimmunity. It is thought that the majority of Foxp3+ T_R are generated in the thymus as a consequence of moderate-affinity recognition of self-antigen. However, Foxp3 can also be induced in the periphery under a number of different tolerogenic contexts. Expression of Foxp3 results in the upregulation of a broad set of genes that confer T_R suppressor activity, proliferative capacity, metabolic fitness and suppression of alternative T cell lineages. After commitment to the T_R lineage cells require antigen-specific stimulation in order to initiate their suppressive capacity.

As a crucial mediator of peripheral immune tolerance, T_R are a candidate for genetic impairment in the common autoimmune diseases. Genetic factors that reduce the commitment, homeostasis or function of Foxp3+ T_R would lower the threshold for activation of autoreactive T cells. One of the known requirements for Foxp3+ T_R is IL-2 signalling. Mice deficient in Il2, Il2ra and Il2rb show severe immunopathology due to a trans-acting (phenotypic dominant) immune tolerance mechanism. In both Il2 and Il2ra deficient mice Foxp3+ cells are generated at lower levels in the thymus. In the periphery, T_R cells deprived of IL-2 signalling have a reduced metabolic fitness and proliferative capacity when in competition, but reach near-normal absolute numbers and are still able to suppress in vitro assays and high affinity autoreactive T cells in vivo. The IL-2-deprived T_R are not, however, efficient at suppressing low affinity autoreactive T cells in vivo, which are capable of undergoing proliferative expansion and driving autoimmune disease. In NOD mice the Il2 locus is variant and shows two-fold lower production of IL-2. This loci is linked to the susceptibility to T1D and enhanced proliferation of autoreactive T cells. Critically, the IL-2 pathway is also intimately connected with human autoimmunity, with loci associations between IL2 and T1D and MS, IL2RA and T1D, RA, MS and AITD, and IL2RB and T1D and RA. It is likely that these associations are limiting the supply of IL-2 to Foxp3+ T_R and thereby decreasing the regulatory suppression of low affinity autoreactive T cells. Partial immunodeficiency (described above) may also act to induce immunodeficiency by limiting the production of Foxp3+ T_R in the thymus, as successive waves of thymocyte maturation are required to upregulate the necessary cofactors for Foxp3 induction.

As well as the quantity of Foxp3+ T_R, reductions in the suppressive capability of the cell type could lead to autoimmunity. Two mediators of trans-acting dominant tolerance, soluble CTLA4 (sCTLA4) and IL-10, are produced in abundance, but not exclusively, by T_R and have suppressive properties. Both loci have been associated with multiple autoimmune diseases, indicating a role in generalised tolerance mechanisms. CTLA4 is a high affinity ligand for B7.1/B7.2, which can out-compete CD28 and produce negative signalling. A ligand-independent form of CTLA4 (liCTLA4) exists that probably acts to dampen basal T cell activation without B7.1/B7.2 stimulation. In the NOD mouse, where the Cita4 locus is one of the strongest diabetogenic genomic regions, a splice variation decreases production of liCTLA4 and thus probably creates an effector T cell-intrinsic defect in tolerance (covered in greater detail below). Another form of CTLA4 can be produced which does not act in an effector T cell-intrinsic manner, sCTLA4. sCTLA4 in the serum can
blockade available B7.1/B7.2, reducing the capacity of autoreactive T cells to become activated, and can also stimulate IDO production by dendritic cells, precipitating tryptophan metabolism and T cell suppression. Recombinant sCTLA4 (CTLA4-Ig) is in use as a therapeutic for autoimmune diseases due to these properties. It is therefore notable that the autoimmune susceptibility allele of CTLA4 associated with multiple diseases contains a splice variant that reduces the production of sCTLA4. Another immunomodulatory product, produced by Tr1 and T_R, is IL-10. IL-10 is particularly important in maintaining T cell tolerance at the mucosal sites, and both II10-deficient mice and mice with a Foxp3-specific abatement of IL-10 show immune dysregulation in the gut and lung. The association of IL10 promoter polymorphisms with autoimmune disease may therefore represent impairment in production of this tolerance mediator by T_R and other regulatory cell types.

Defects in regulatory cell types beyond Foxp3^+ T_R may also be involved in general susceptibility to autoimmunity. Invariant Natural Killer T (iNKT) cells, for example, have regulatory properties and can inhibit autoimmune disease in mouse models of MS (experimental autoimmune encephalomyelitis, EAE) and T1D. Both the EAE-prone SJL strain and the T1D-susceptible NOD strain have a numerical and functional defect in iNKT cells. In NOD mice the defect is caused by multiple loci, several of which colocalise with diabetogenic loci, and transfer of additional NKT cells inhibit autoimmunity. It is likely that a similar genetic contribution to autoimmune susceptibility occurs in humans, as T1D patients show reduced numbers of iNKT cells with reduced production of the effector cytokine IL-4.

**Generalised genetic defects in cis-acting effector T cell tolerance mechanisms**

Beyond the trans-acting tolerance mechanisms described above, effector T cells also have intrinsic cis-acting mechanisms that limit activation. One of the most important cis-acting tolerance mechanisms is the intrinsic maintenance of the quiescent naïve T cell state unless the cell is licensed to enter effector lineages. The association of multiple cytokine pathway genes with autoimmune disease, including STAT4, TNFA, IL12B, IL23R, IL10 and IFIH1 (Table 4), is likely to reflect subtle alterations in the ease with which a naïve autoreactive T cell is able to transition into a pathogenic effector cell. While different effector T cell lineages have been associated with different autoimmune diseases, here we concentrate on the mechanisms by which naïve T cells are normally restrained from inappropriately entering the Th17 and T_{F H} lineages.

Th17 cells are a newly described subset of CD4^+ T cells that secrete IL-17 and other pro-inflammatory cytokines. Many of the roles previously ascribed to Th1 cells during the pathogenesis of autoimmune mouse models such as EAE and Collagen-Induced Arthritis (CIA) respectively are now thought to be mediated by Th17 cells as Il17^−/− mice are resistant to EAE and CIA. Follicular B helper T cells (T_{F H}) are a subset of effector T cells distinct from Th1, Th2 and Th17 lineages. Among their key characteristics they express CXC-chemokine receptor 5 (CXCR5), allowing them to respond to CXCL13 produced by follicular stromal cells and migrate to the follicles. T_{F H} cells also express high levels of the Inducible T Co-Stimulator (ICOS) and IL-10,
allowing them to provide B cell help once they have entered the follicle. Both Th17 and Tfh cells are powerful immune mediators and therefore inappropriate entry of autoreactive T cells into the lineage can predispose an individual to autoimmunity.

Generation of Th17 cells is directed by a milieu of cytokines including IL-6, IL-21, IL-23 and TGFβ turning on the Th17 master regulator, RORγt. Initially it was reported that differentiation of Th17 cells required only TGFβ and IL-6, however it has since become apparent that Th17 cells can be induced in the absence of IL-6 provided IL-21 is present. IL-6 initiates the STAT3-dependant production of IL-21, which, in conjunction with RORγt, allows the expression of the IL-23 receptor on the T cell surface. It is essential to note that while TGFβ and IL-6 can drive the differentiation of Th17 cells, it is only in the presence of IL-23 that these cells can express their full compliment of pro-inflammatory cytokines and become pathogenic. IL-23-deficient mice do not develop EAE, while IL-23 over-expressing mice have an increased susceptibility to EAE. It is therefore interesting that the IL23R locus is associated with ankylosing spondylitis, Crohn’s disease and psoriasis, while IL12B (a component of IL-23) is linked to psoriasis. The linkage of allelic variations in IL23R and IL12B to multiple autoimmune diseases is highly suggestive of a genetic dysfunction in the normally tightly regulated process of Th17 induction.

The role of Tfh cells in autoimmune disease is exemplified by studies of the sanroque mouse strain. The sanroque mouse recapitulates the hallmark features of the human autoimmune disorder SLE, including anti-nuclear antibodies with dsDNA specificities, focal proliferative glomerulonephritis with IgG-containing immune complex deposition, anaemia and autoimmune thrombocytopenia. Interestingly this murine model also has aberrant expression of ICOS on all T cells, a cell-autonomous overrepresentation of Tfh and spontaneous formation of germinal centres. These characteristics are the result of homozygosity for a hypomorphic ‘san’ allele where a point mutation in the gene Roquin (Rc3h1) causes the methionine at position 199 to be substituted for Arginine. One of the key functions of Roquin is to restrict the expression of ICOS to effector T cells that have been legitimately licensed for activation.

ICOS is structurally and functionally related to CD28. Unlike CD28, which is constitutively expressed, ICOS expression is only upregulated on T cells after priming. Due to lack of ICOS on naïve T cells, priming of naïve T cells is controlled by the expression kinetics of the ligands for CD28, B7.1 and B7.2, which are limited to activated antigen presenting cells. This trans requirement ensures that only T cells responding to antigen presented by licensed dendritic cells are activated. After activation the expression of ICOS on T cells allows the primed T cell to proliferate independent of licensed dendritic cells, as the ICOS ligand is constitutively expressed on many different cell types. The repression of ICOS in naïve T cells therefore represents a cis-acting tolerance mechanism essential for the maintenance of tolerance, in particular entry into the Tfh lineage required for efficient germinal centre reactions. This intrinsic repression of ICOS is mediated by Roquin. Homozygosity of the san allele of Roquin causes naïve T cells to express ICOS and proliferate independent of
licensing by dendritic cells, allowing the spontaneous formation of germinal centres. The lupus-like phenotype in the sanroque mouse strain can be partially corrected by loss of one allele of ICOS, loss of CD28 or loss of Shd1a, genes encoding three key molecules for T\textsubscript{FH} formation and function (ML and C. Vinuesa unpublished data), indicating that the cis-acting tolerance system is composed of a number of molecules that contribute to a common pathway.

It is likely that defects in the same process occur in SLE patients. SLE is mediated by the production of anti-nuclear antibodies that deposit in immune complexes. The self-reactive immunoglobulins produced are of high affinity and have undergone class switching, indicating that they derive from within the germinal centre. As self-reactive B cells are normally excluded from the germinal centre, their participation in germinal centres in SLE patients represents a tolerance failure. Within germinal centres T\textsubscript{FH} cell help is essential for the maintenance of the reaction and selection of high affinity somatically mutated centrocytes prior to class switching. As ICOS over-expression has been linked to the pathogenesis of SLE, it appears that an unknown genetic defect in the Roquin-ICOS pathway allows the inappropriate commitment of naïve autoreactive T cells to the pathogenic T\textsubscript{FH} lineage. As autoantibodies also contribute to other autoimmune diseases, once the genetic defects in this pathway have been determined they are likely to be found to contribute to multiple autoimmune diseases.

In addition to restricting entry into the effector lineages, another tolerance mechanism intrinsic to effector T cells is the limitation of the effector phase. The apoptosis of effector T cells at the end of the immune response is coordinated by Fas and Bim. These two apoptotic pathways are partially redundant, as demonstrated by the relative health of Bim and Fas knockouts on a pure B6 background. Double deficiency, however, results in increased survival of T cells following an immune response causing severe autoimmunity. Even the loss of a single Bim allele on the lpr (Fas mutant) background results in autoimmunity. The relevance of this tolerance mechanism for human autoimmunity is demonstrated by the monogenic autoimmune disease ALPS. ALPS is a severe autoimmune disease caused by dysfunctions in FAS, FASL or the downstream mediators of apoptosis Caspase 8 and Caspase 10. ALPS patients characteristically develop lymphadenopathy and splenomegaly due to the failure of TCR-mediated apoptosis of mature T cells following activation. There is strong evidence that this pathway is impaired in the common autoimmune diseases. Wu et al identified an SLE patient with mutations in FASL. While this particular case may be a variant of typical ALPS, expression of FLIP, the inhibitor of the Fas pathway, is upregulated in T cells from SLE patients. Similarly, T cells from RA patients have been documented to express elevated levels of Bcl-2 and those from MS patients have increased Survivin expression, both anti-apoptotic proteins. Genetic abnormalities in the post-effector phase apoptotic process may therefore represent a mechanism of shared susceptibility to autoimmunity.

**Genetic defects contributing to organ-specific autoimmune disease**
Failures in organ-specific tolerance can occur in multiple ways. Factors outside the organ, such as the thymic presentation of organ-specific antigens, can modify the immune response altering negative selection and increasing self-reactive T cells. Alternatively, antigen expression or antigenicity within the target organ can be altered, increasing immune priming or otherwise bringing about attack by self-reactive T cells. Additionally, the organ itself can change in its structural and metabolic resilience to damage. It is likely that these and other pathways contribute to various human autoimmune diseases (Table 5).

**Organ-specific genetic defects in immune tolerance**

The generalised resistance to negative selection in the NOD mouse described above demonstrates that genetic defects in the negative selection process can increase susceptibility to autoimmune disease. The study of Autoimmune Polyendocrinopathy Syndrome type 1 (APS-1) has revealed that the expression of self-antigens in the thymic epithelium is a complex and exquisitely sensitive process, and represents a key fracture point in immune tolerance.

APS-1 is a monogenic autoimmune disease caused by homozygous mutations in the gene AIRE\(^{147,148}\). Clinical manifestations of APS-1 include a variety of organ-specific autoimmune diseases, usually including hypoparathyroidism and primary adrenocortical failure, accompanied by chronic mucocutaneous candidiasis\(^{149}\). Aire deficient mice were developed as a model of APS-1, and also present with multi-organ autoimmunity\(^{150,151}\). Expression of Aire is limited to epithelial cells in the thymic medulla and rare cells in secondary lymphoid organs\(^{151-153}\), and the role of Aire in suppressing autoimmunity is mediated by the thymic stroma\(^{150}\). In the absence of Aire, medullary thymic epithelial cells lose the trace expression of ~500 organ-specific antigens such as insulin\(^{150,154}\). While these transcripts had been previously dismissed as non-functional, in the absence of Aire-mediated activation of the insulin promoter a dramatic reduction was observed in the efficiency of the negative selection of autoreactive T cells\(^{155,156}\). This defect directly contributes to an increase in the number of autoreactive T cells in the periphery and the incidence of autoimmune disease\(^{156,157}\).

The mechanism by which Aire regulates transcription of organ-specific genes remains an open question. The Aire protein has biochemical properties suggestive of transcription factor activity\(^{158-162}\), and has been proposed to act directly upon target genes\(^{163}\). Alternatively, the quantity of Aire-dependent genes\(^{150,154}\) and the erratic expression patterns at the level of individual cells\(^{164}\) suggest that Aire may function via intermediates, such as functional interaction with additional cofactors\(^{165}\) or binding chromatin structures and recruiting transcriptional components\(^{166,167}\). Aire also appears to have functions in thymic epithelial differentiation\(^{164,168}\), which may be integral or unrelated to its activity to activate transcription of peripheral antigens. It does, however, suggest an explanation for the previously orphan data that impaired negative selection is observed against target antigens with unchanged thymic expression profiles\(^{169,170}\). With subtle alterations in thymic structure\(^{164,168}\) and late thymocyte development\(^{171}\).
thymic crosstalk between thymocytes and thymic epithelial cells is likely to be impaired \(^{51,52}\) and hence the generalised efficiency of negative selection reduced \(^{53}\).

Of interest to the genetics of common polygenic autoimmunity, Aire deficiency has been shown to interact with the loci involved in common autoimmune diseases, with susceptibility loci altering the disease progression in APS-1 patients \(^{172,173}\) and Aire-deficient mice \(^{169,174}\). Furthermore, several studies have demonstrated that the Aire pathway is sensitive to even small reductions in activity, with reduced expression of Aire causing a reduction in the expression of Aire-dependent antigens \(^{157,175}\) and hence negative selection towards those antigens \(^{157}\). This result alludes to the possibility that small changes in the thymic expression or presentation of individual antigens may contribute to autoimmune susceptibility in a disease-specific manner. Mouse model examples of this include the proteolipid protein splice variant found in SJL mice, which is expressed in the thymus in a version lacking the region PLP\(^{116-151}\). SJL mice show an increased frequency of peripheral T cells autoreactive to PLP\(^{139-151}\) and have an enhanced susceptibility to PLP-induced EAE \(^{176}\). Likewise, artificial heterozygous loss of the Myelin P0 protein is associated with increasing T cell autoimmunity towards this autoantigen \(^{177}\).

Of the gene associations unique to particular autoimmune diseases (Table 4), a number are likely to contribute to autoimmune susceptibility via altered thymic expression. For example polymorphisms in the VNTR microsatellite of the insulin promoter are associated with T1D \(^{178,179}\). The susceptibility alleles of the INS locus cause a 2-3 fold decrease in AIRE-dependent thymic expression of the insulin gene \(^ {178,180}\) (Table 5). Another example is the gene \(CHRNA1\), another organ-specific gene expressed in the thymus in an AIRE-dependent manner. Similar to INS, \(CHRNA1\) has allelic variants that reduce thymic expression of the antigen and are associated with autoimmunity directed against the self-antigen, in this case resulting in the autoimmune disease myasthenia gravis \(^ {181}\). In both of these cases it is expected that the reduced thymic expression allows the escape of autoreactive T cell clones which can participate in autoimmune reactions, but only towards specific tissues (Table 5). Other putative gene variants in this category are myelin basic protein (\(MBP\), associated with MS), thyroid stimulating hormone receptor (\(TSHR\), associated with AITD) and thyroglobulin (\(TG\), associated with AITD).

In each case the protein product is a major target antigen of the autoimmune disease, thus reduced thymic expression would predispose the individual to developing that specific autoimmune disease. Alternatively, the genes may be associated with heightened expression in the periphery, creating an imbalance between thymic and peripheral expression with the same functional outcome. A variant of this theme may be behind the association of the \(PADI4\) locus with RA \(^{182}\) and the \(TREX1\) and \(DNASE1\) loci with SLE \(^{183,184}\). While the protein products are not major target antigens of the disease, they are involved in the production of non-protein target antigens, with \(PADI4\) producing peptidyl citrulline and \(TREX1\) and \(DNASE1\) producing DNA fragments (Table 5). Another example which illustrates the synergy between genetic and environmental factors is the association of the \(PDS\) locus with AITD \(^{185}\). The protein
product of PDS, pendrin, is required for sulfation of thyroglobulin, which serves a role in thyroglobulin function and likely influences iodination of the protein (Table 5). Iodination of thyroglobulin, in turn, generates new epitopes and increases its antigenicity, as the primary autoantibodies and autoreactive T cells in the NOD.H2h4 AITD mouse model recognise highly iodinated thyroglobulin with a higher affinity than weakly iodinated thyroglobulin. An interesting explanation for this observation is the possibility that thymic production of thyroglobulin is limited to the uniodinated form, allowing T cells reactive to the iodinated form to bypass negative selection. Increased activity of PDS may therefore act in a similar manner to increased dietary iodine intake, which increases the risk of AITD in both NOD.H2h4 mice and human populations.

In addition to the tolerogenic necessity of antigen expression, efficient antigen presentation also needs to take place. This requirement is the basis for the strong association of the HLA locus, especially the MHC class II genes within the locus, with autoimmune diseases. The HLA locus encodes, among other proteins, the HLA class I and class II molecules that present peptides to CD8 and CD4 T cells, respectively. For many autoimmune diseases HLA is the greatest genetic contributor, and variants of the class II HLA-DR and -DQ genes have been associated with a plethora of autoimmune diseases. However generally different alleles of HLA are associated with different autoimmune diseases, and DQB1, DQA1, and DRB1 allelic variants have been identified which act as resistance alleles for one disease and susceptibility alleles for another. For example, the HLA-DR2 haplotype is protective against T1D, yet predisposes towards MS and SLE. Similarly in NOD mice the replacement of the H2g7 allele with H2h4 blocks the development of T1D but promotes AITD. This indicates that the tolerance defect that HLA variants represent is antigen-specific in nature, representing altered presentation of peptide subsets rather than generalised presentation issues (Table 5).

The main HLA allelic variations appear to alter the binding pocket of the MHC molecules and thus change the range of peptides that the protein is capable of presenting to T cells. Variants also act along a continuum to also alter the strength of the peptide-MHC interaction and the interaction between the peptide-MHC and TCR. Susceptibility-associated HLA variants may allow certain autoreactive T cell clones to escape tolerance mechanisms, while protection may occur by certain MHC molecules sequestering potentially autoimmunogenic peptides away from more dangerous MHC molecules. Two alternative mechanisms exist for the association of altered peptide presentation to autoimmunity – reduced thymic presentation of major target autoantigens for tolerogenic purposes and enhanced peripheral presentation of major target autoantigens.

A well studied variation associated with type 1 diabetes is the absence of an aspartic residue at position 57 of the HLA-DQ β protein (HLA-DQ8). When this amino acid is substituted with a serine, alanine or valine immunogenic insulin peptides have enhanced binding to HLA-DQ and may elicit an autoimmune response. The NOD mouse also has a MHC Class II allele, I-Ag7, that contains a non-aspartic acid at
position β57. In the NOD mouse this allele permits preferential binding to an alternative and larger set of peptides than MHC molecules with a β57 aspartic residue. Mouse transgenic studies have shown that the HLA-DQ8 can directly substitute for the diabetogenic role of I-A\textsuperscript{87}, with an absence of negative selection of pancreas-specific T cell clones and an enhanced level of peripheral activation. Another example is the association of \textit{HLA-DR2} alleles with MS. The associated variants have an increased ability to display a dominant epitope of myelin basic protein (MBP) to CD4 T cells. Structural studies have indicated that there is a very weak interaction between the DR2-MBP peptide complex and the cognate TCR, which indicates that the mechanism of susceptibility is enhanced peripheral presentation of antigen to weakly-binding and promiscuous autoreactive T cells that escaped thymic negative selection.

A particular case for genetic synergy can be made for the association of altered presentation of peptide and altered TCR signalling capacity. For example, in rheumatoid arthritis, some variants of class II HLA-DRB1 are biased towards recognising a cartilage-specific protein CII. When this allele is combined with the \textit{PTPN22} allele that reduces the strength of TCR signalling there is a greatly compounded risk of developing disease. These two mutations may combine to reduce the strength of TCR signalling during negative selection to allow the escape of autoreactive T cells from central tolerance and then have enhanced peripheral presentation to compensate for the reduced TCR signal strength and precipitate autoimmunity.

While most of the effects of the \textit{HLA} locus are likely to be antigen-specific in nature, the \textit{HLA} region also contains the \textit{HLA-Cw} locus, encoding molecules that are recognised by NK cells. NK cells express both inhibitory and activating NIK receptors. The inhibitory receptors bind to HLA-Cw epitopes that are often absent on infected or cancerous cells. An imbalance between signals through the inhibitory and activating receptors of NK cells has been associated with autoimmune disease. Two of the activating receptors on NK cells, KIR2DS1 and KIR2DS2, are found in approximately 35% and 55% of European Americans, respectively. The presence of an activating KIR is most detrimental when the patient also lacks ligands for an inhibitory KIR receptor that could otherwise dampen the NK response. For example, subjects were found to be most at risk for psoriatic arthritis if they carried the activating receptors KIR2DS1 and/or KIR2DS2 and also lacked the HLA-Cw group ligands for the inhibitory receptors KIR2DL1 or KIR2DL2/3. Furthermore, subjects that have NK cells expressing the inhibitory KIR2DL3 receptor along with target gut epithelial cells expressing the ligand HLA-Cw class 1 show a mild protective effect against ulcerative colitis, possibly due to the increased inhibition of NK cells in the gut. The HLA locus may therefore also alter susceptibility to autoimmunity by generalised effects on the activation of an effector cell population.

\textit{The contribution of genetic defects intrinsic to the target organ on autoimmunity}
In the above scenarios the genetic predisposition to autoimmunity was modified by changes extrinsic to the target organ, reducing immune tolerance in a generalised or antigen-specific manner. However an additional mechanism is also likely to synergise with these immune tolerance modifying genetic components, that of genetic variations that act intrinsic to the target organ itself. Target organ-intrinsic genetic defects could increase susceptibility to autoimmunity in a number of ways. For example, the expression or presentation of key target antigens within the organ and draining lymph nodes could be altered, promoting autoimmune attack. Alternatively, changes to the target organ could increase immune trafficking, raising the chances that the ignorance of autoreactive T cell clones will be broken. Another putative mechanism is developmental alterations in the functionality of the target organ altering the resistance of the constituting cells to apoptosis under low-grade apoptotic pressure. This area of research is still nascent; however there are a number of gene associations suggestive of these functions in Crohn’s disease, diabetes, AITD, and rheumatoid arthritis.

Multiple gene associations unique to Crohn’s disease are suggestive of increased leukocyte trafficking through the organ increasing the risk of precipitating an autoimmune reaction, including ATG16L1, IRGM, MDR1, MST1, NCF4 and NXX-2.3 (Table 4). Both ATG16L1 and IRGM are involved in the elimination of bacterial infections from the gut. MST1 influences the movement and phagocytosis of resident peritoneal macrophages and NCF4 assists in the generation of antimicrobial reactive oxygen species. MDR1 encodes Pgp-1, a protein pump that transports lipophilic compounds out of intestinal epithelial cells and is thought that this protein has a protective role against potentially harmful microbial products. NKX-2.3 is a transcriptional regulator that is required for proper architecture of the small intestine, a change which likely weakens defences against infection. Changes in these genes which reduce the capacity of innate and structural defences may increase the reliance on adaptive immune defences, with the corresponding risk of autoimmunity (Table 5).

A number of defects in the target organ may also be operating during T1D. In the NOD mouse in addition to the known immune defects genes linked to pancreas-intrinsic defects have also been discovered. Lymphocyte infiltration of the pancreas appears to be assuaged by TRPV1, a sensory channel expressed by sensory neurons in beta-islets that is less active in NOD mice and is encoded by a polygenic gene within a known diabetogenic locus. Another polymorphic gene within a diabetogenic locus is TNFR2. After infiltration occurs, the NOD islet cells display an intrinsic increase in susceptibility to destruction, possibly due to prolonged signalling through TNFR2 on beta islets. We have also observed increased susceptibility of NOD β islets to non-autoimmune destruction due to metabolic stress (AL, unpublished observations). In human T1D there are not the gene association studies to clearly demonstrate a similar contribution of organ-intrinsic function. There are, however, epidemiologic studies which link T1D with the non-autoimmune type 2 diabetes (T2D). Fourteen percent of Finnish families with a T2D proband also have at least one member with T1D. Ten percent of T2D patients later develop an autoimmune component to this disease. Relatives of women who develop gestational diabetes, another syndrome due to metabolic defects of the pancreas, have an increased chance of developing both T1D
Furthermore, progression of T1D children from subclinical to clinical disease is more rapid in individuals who are obese, and thus have a greater metabolic stress on their pancreas. These data suggest that there is a genetic component to the metabolic fitness of the pancreas, and that genetic reductions in this fitness can enhance susceptibility to autoimmune diabetes (Table 5).

Other complicated gene associations with autoimmunity are TG and TSHR withAITD. As discussed above, since TG and TSHR are key target autoantigens in AITD, altered thymic expression may predispose an individual to anti-thyroid autoimmunity. However other possible explanations of the association exist with organ-intrinsic mechanisms. One possibility is that polymorphisms may result in increased antigen shedding from the organ, seeding higher levels of presentation in the draining lymph node. Another putative mechanism is altered cellular stress due to reduced functionality. Loss-of-function allelic variants of TG have been associated with non-autoimmune hypothyroidism, raising the possibility that partial reduction in activity alleles exist which are sufficient for thyroid function but place the producing cells under increased metabolic stress. This functional stress may then result in failure under conditions of autoimmunity which would otherwise be subclinical, resulting in Hashimoto’s disease. In the case of TSHR and Graves disease, pathology results from autoantibodies to TSHR constitutively activating the receptor. Since polymorphisms exist which are known to result in non-autoimmune hyperthyroidism via increased activity, it is possible that partial gain-of-function alleles exist that are not sufficient to cause non-autoimmune hyperthyroidism but can trigger pathogenesis at lower levels of autoantibodies.

Another possible mechanism that could underlie organ-intrinsic defects is an inability for the organ to recover after immunological insult. A polymorphism in KAZALDI has been linked to rheumatoid arthritis. As this gene is involved in tissue regeneration, it may be modifying the ability of the joints to heal after autoimmune attack, resulting in pathogenic damage being caused under lower levels of autoimmune pressure (Table 5).

**Concluding remarks**

Autoimmune diseases constitute a diverse range of conditions caused by dysregulation of the adaptive immune system and the generation of T and B cell responses against the target organ. The genetic component of predisposition to autoimmune diseases is strong but complex, with most individual autoimmune diseases controlled in a polygenic manner with a high degree of genetic heterogeneity. Despite the complexity of autoimmune genetics, the common aetiology of the syndromes allows genetic lesions in immune tolerance pathways to contribute to multiple disorders. The few rare monogenic autoimmune conditions are enlightening as to the immune tolerance pathways that constitute the genetic weak points – defects in the negative selection of autoreactive T cells in the thymus, defects in trans-acting tolerance mechanisms in the periphery and defects in the cis-acting mechanisms restraining effector T cells (Table 6). Numerous genetic associations in the common autoimmune diseases (Table 4)
indicate that while complete failure in a given mechanism is limited to the multi-organ monogenic syndromes, partial defects in these same mechanisms are likely to underlie polygenic autoimmunity. Layered on top of this complex interplay of defects in generalised immune tolerance are genetic defects that impair organ-specific immune tolerance pathways and the innate capacity of the target organ to withstand pathogenic onslaught (Table 5). The development of autoimmune disease is therefore a cumulative effect of partial and synergistic defects in multiple immune tolerance mechanisms being directed towards a specific target organ by additional organ-specific defects, heavily modified by environmental influences. The relatively limited number of pathways involved, as opposed to the large number of individual genes, increases the likelihood that targeted intervention to reinforce these pathways will result in effective blockade of autoimmunity.

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<table>
<thead>
<tr>
<th>Disease risk for twin of proband</th>
<th>Population</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monozygotic</td>
<td>Dizygotic</td>
<td></td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>27.3%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>15.4%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>24%</td>
<td>3%</td>
</tr>
<tr>
<td>Systemic Lupus erythematosus</td>
<td>24%</td>
<td>2%</td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Grave’s disease</td>
<td>22%</td>
<td>0%</td>
</tr>
<tr>
<td>- Hashimoto’s disease</td>
<td>37.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>50%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 1. Examples of disease incidence in autoimmune proband twins.
Table 2. Examples of increased incidence of additional autoimmunity in patients with one autoimmune disease.

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>Incidence of additional autoimmunity (vs control population)</th>
<th>Population</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Diabetes</td>
<td>AITD (25% vs 8%)</td>
<td>Korean</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Sjogren’s syndrome (18-55% vs 3-14%)</td>
<td>English</td>
<td>2</td>
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<tr>
<td></td>
<td>Coeliac disease (1.6%)</td>
<td>French</td>
<td>3</td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
<td>T1D (6.7%)</td>
<td>Brazilian</td>
<td>225</td>
</tr>
<tr>
<td></td>
<td>Coeliac disease (3.3%)</td>
<td>Italian</td>
<td>226</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>AITD (20.5% vs 11.2%)</td>
<td>Italian</td>
<td>226</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>AITD (21.7%)</td>
<td>Dutch</td>
<td>227</td>
</tr>
<tr>
<td></td>
<td>Vitiligo (9.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sjogren’s syndrome (2.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1D (1.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coeliac disease (1.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>AITR (9.4% vs 1.9% in males)</td>
<td>Austrian</td>
<td>228</td>
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<tr>
<td>Juvenile arthritis</td>
<td>AITR (44%)</td>
<td>Bulgarian</td>
<td>229</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>AITD (58%)</td>
<td>Bulgarian</td>
<td>229</td>
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</table>
Table 3. Examples of increased incidences of autoimmunity in families of autoimmune probands.

<table>
<thead>
<tr>
<th>Autoimmune risk of family members (vs control population)</th>
<th>Population</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Diabetes</td>
<td>Columbian</td>
<td>4</td>
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<tr>
<td>Sjogren’s syndrome</td>
<td>Columbian</td>
<td>230</td>
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<tr>
<td>Celiac disease</td>
<td>Italian</td>
<td>231</td>
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<tr>
<td>Multiple Sclerosis</td>
<td>British</td>
<td>232</td>
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<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>American</td>
<td>233</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>American</td>
<td>234</td>
</tr>
<tr>
<td>Idiopathic inflammatory myopathies</td>
<td>American</td>
<td>235</td>
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</table>
Table 4. Examples of gene associations in common autoimmune diseases.

<table>
<thead>
<tr>
<th>OMIM</th>
<th>Unique locus associations</th>
<th>Unique locus associations in pathways shared with multiple autoimmune diseases</th>
<th>Locus associations shared with multiple autoimmune diseases</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>222100</td>
<td>CLEC16A, ERBB3, INS</td>
<td>CD226</td>
<td>CTLA4, HLA, IFIH1, IL2RA, IL2RB, IL7RA, KIAA1109/TFENR/IL2/IL21, PTPN2, PTPN22, SH2B3, SUMO4, VDR</td>
<td>5, 8, 9, 58, 236-238</td>
</tr>
<tr>
<td>180300</td>
<td>KAZALD1, PADI4</td>
<td>GC, NFkBIL1, RUNX1</td>
<td>CTLA4, FCRL3, HLA, IL1B, IL2RA, IL2RB, IL18, IRF5, KIAA1109/TFENR/IL2/IL21, MHC2TA, PTPN22, SH2D2A, SLC22A4, STAT4, SUMO4, TNFA</td>
<td>8, 12, 56, 236, 237, 239-248</td>
</tr>
<tr>
<td>126200</td>
<td>MBP</td>
<td>CD58, LAG3, PRKCA, TCRβ</td>
<td>CD24, CD45, CTLA4, IL2RA, IL7RA, HLA, ICAM1, IRF5, MHC2TA, SH2D2A</td>
<td>7, 57, 244, 249-259</td>
</tr>
<tr>
<td>152700</td>
<td>DNASE1, FCGR2A, FCGR3A, TREX1</td>
<td>FASL</td>
<td>CD24, CTLA4, FCRL3, HLA, IL18, IRF5, PTPN22, STAT4, TNFA</td>
<td>11, 143, 183, 184, 239, 240, 260-266</td>
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<tr>
<td>127500</td>
<td>PDS, TG, TSHR</td>
<td>CD40</td>
<td>CTLA4, FCRL3, HLA, IFIH1, IL2RA, PTPN22, SUMO4, VDR</td>
<td>6, 10, 58, 132, 185, 237, 239, 267, 268</td>
</tr>
<tr>
<td>266600</td>
<td>ABCB1, ATG16L1, CARD15, DGL5, IRGM, NCF4, NKX2-3, MST1, PHOX2B</td>
<td></td>
<td>HLA, IL10, IL12B, IL23R, IRF5, PTPN2, PTPN22, SLC22A4, TNFA</td>
<td>8, 133, 269-276</td>
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</table>
Table 5. Potential mechanisms of organ-specific autoimmune disease susceptibility

<table>
<thead>
<tr>
<th>Potential mechanism of organ-specific effect</th>
<th>Disease</th>
<th>Putative examples</th>
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</thead>
<tbody>
<tr>
<td>Poor presentation of target antigen in the thymus</td>
<td>T1D</td>
<td>INS&lt;sup&gt;178, 179&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Myasthenia gravis</td>
<td>CHRNA1&lt;sup&gt;181&lt;/sup&gt;</td>
</tr>
<tr>
<td>Altered production of non-protein target antigen</td>
<td>RA</td>
<td>PADI4&lt;sup&gt;182&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>SLE</td>
<td>TREX1, DNASE1&lt;sup&gt;183, 184&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alteration of antigenicity of target antigen</td>
<td>AITD</td>
<td>PDS&lt;sup&gt;185&lt;/sup&gt;</td>
</tr>
<tr>
<td>Altered thymic/peripheral presentation of target antigen</td>
<td>T1D</td>
<td>HLA&lt;sup&gt;191&lt;/sup&gt;</td>
</tr>
<tr>
<td>Altered lymphocyte trafficking through the organ</td>
<td>Crohn’s disease</td>
<td>ATG16L1, IRGM&lt;sup&gt;200, 201&lt;/sup&gt;</td>
</tr>
<tr>
<td>Impairment of the metabolic integrity of the organ</td>
<td>T1D</td>
<td>unknown</td>
</tr>
<tr>
<td>Decreased ability to regenerate after insult</td>
<td>RA</td>
<td>KAZALD1&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Disease</td>
<td>OMIM</td>
<td>Causative gene(s)</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>-------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Autoimmune Lymphoproliferative Syndrome (ALPS)</td>
<td>601859</td>
<td><em>CASP8, CASP10, FAS, FASL</em></td>
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<tr>
<td>Autoimmune Polyendocrinopathy Syndrome Type 1 (APS1)</td>
<td>240300</td>
<td><em>AIRE</em></td>
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<tr>
<td>Immunodysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX)</td>
<td>304790</td>
<td><em>FOXP3</em></td>
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<tr>
<td>Omenn Syndrome (OS) and related syndromes</td>
<td>603554 602700 606593 176947</td>
<td><em>ADA, DCLRE1C, IL3RG, IL7RA, LIG4, RAG1, RAG2, RMRP, ZAP70</em></td>
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References


106. Rubtsov, Y.P. et al. IL-10 produced by regulatory T cells contributes to their suppressor function by limiting inflammation at environmental interfaces. *Immunity In Press* (2008).


