

Unravelling the association of partial T-cell immunodeficiency and immune dysregulation

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Abstract | Partial T-cell immunodeficiencies constitute a heterogeneous cluster of disorders characterized by an incomplete reduction in T-cell number or activity. The immune deficiency component of these diseases is less severe than that of the severe T-cell immunodeficiencies and therefore some ability to respond to infectious organisms is retained. Unlike severe T-cell immunodeficiencies, however, partial immunodeficiencies are commonly associated with hyper-immune dysregulation, including autoimmunity, inflammatory diseases and elevated IgE production. This causative association is counter-intuitive — immune deficiencies are caused by loss-of-function changes to the T-cell component, whereas the coincident autoimmune symptoms are the consequence of gain-of-function changes. This Review details the genetic basis of partial T-cell immunodeficiencies and draws on recent advances in mouse models to propose mechanisms by which a reduction in T-cell numbers or function may disturb the population-dependent balance between activation and tolerance.

Immunodeficiency

A state in which the capacity of the immune system to respond to infectious disease is compromised or completely absent.

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Congenital T-cell immunodeficiencies are rare diseases caused by mutations in genes that are essential for T-cell differentiation and which result in a severe deficiency in peripheral T cells. A more complex and poorly understood class of diseases is that which comprises the partial T-cell immunodeficiency diseases, in which effector T cells are present but in reduced numbers or with reduced function. These diseases are genetically heterogeneous with a largely undetermined aetiology, but they include associations with alternative mutations in the same genes that can cause severe T-cell immunodeficiency. Although many diseases in this class are relatively rare, together they are probably more common than the severe T-cell deficiencies. The most striking clinical manifestation of the partial T-cell immunodeficiencies is the frequent association of these diseases with immune dysregulation, such as autoimmune disease and elevated IgE production, both of which are consequences of effector T-cell hyperactivity. The association of effector T-cell hyperactivity symptoms with an effector T-cell hypoactive disease is counter-intuitive. However, recent studies in mouse models have shown that hyperactivation of immune system components can be a direct outcome of a partial decrease in T-cell number or activity.

In this Review, we describe the insights gained from mouse models into immune dysregulation during partial numerical or functional immunodeficiency and propose a model of 'population-dependent' immune tolerance mechanisms to explain the coincident presentation of both partial T-cell immunodeficiency and immune dysregulation. This model is based on the assumption that tolerance mechanisms evolved in the context of a complete peripheral T-cell niche, and that these mechanisms start to break down when they are forced to operate in the suboptimal context of a reduction in the functional T-cell population size. Partial reduction in the number or function of T cells therefore disturbs the tolerogenic balance, generating the unfortunate combination of immunodeficiency and immune dysregulation.

Genetic basis of T-cell immunodeficiency

Nearly 40 different genes have been identified that can cause monogenic severe T-cell immunodeficiencies in humans. These genes can be grouped into five main categories based on the cellular function of the proteins that they encode. Four of these categories include genes that encode proteins involved in functional processes that are essential for the differentiation of T cells

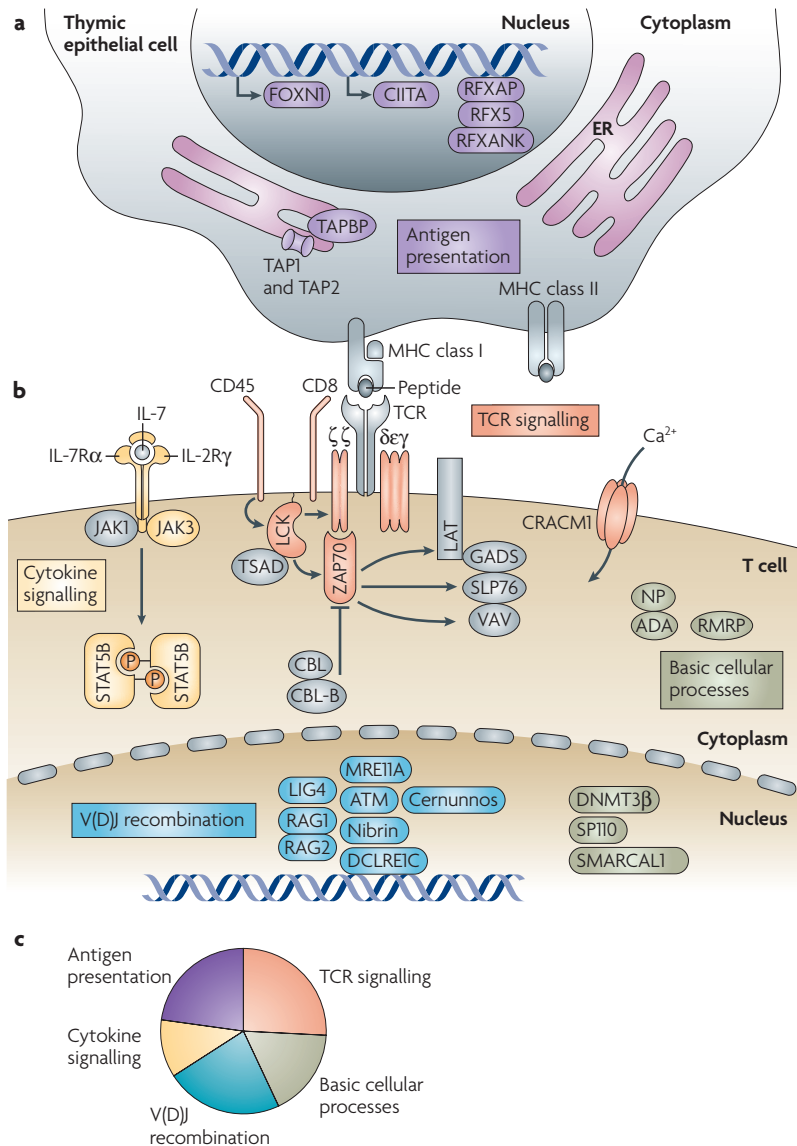


Figure 1 | Human gene defects responsible for severe T-cell deficiency. Genes with mutations that cause monogenic severe T-cell immunodeficiency in humans can be intrinsic to the thymic epithelium or to T cells. **a** | Genetic defects that are intrinsic to thymic epithelial cells ultimately affect the antigen-presentation pathway. **b** | Genetic defects that are intrinsic to T cells include those that affect T-cell receptor (TCR) signalling, cytokine signalling, somatic recombination or basic cellular processes. Other genes that are important to these pathways or processes but have not been linked to severe T-cell deficiency in humans are shown in grey. **c** | The pie chart shows the proportion of defective genes that affect each of these categories. ADA, adenosine deaminase; ATM, ataxia-telangiectasia mutated; CBL, Casitas B-lineage lymphoma; CIITA, class II transactivator; DCLRE1C, DNA crosslink repair 1C; DNMT3β, DNA cytosine-5 methyltransferase 3β; ER, endoplasmic reticulum; FOXN1, forkhead box N1; GADS, GRB2-related adaptor protein; IL-2Rγ, IL-2 receptor γ-chain; IL-7, interleukin-7; IL-7Rα, IL-7 receptor α-chain; JAK, Janus kinase; LAT, linker for activation of T cells; LIG4, ligase IV; MRE11A, meiotic recombination 11 homologue A; Nibrin, Nijmegen breakage syndrome 1; NP, nucleoside phosphorylase; CRACM1, calcium release-activated calcium modulator 1; RAG, recombination-activating gene; RFX5, regulatory factor X5; RFXANK, RFX-associated ankyrin-containing protein; RFXAP, RFX-associated protein; RMRP, RNA component of mitochondrial RNA-processing endoribonuclease; SLP76, SRC-homology-2-domain-containing leukocyte protein of 76 kDa; SMARCA1, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin a-like 1; SP110, SP110 nuclear body protein; STAT5B, signal transducer and activator of transcription 5B; TAP, transporter associated with antigen processing; TAPBP, TAP-binding protein; TSAD, T-cell-specific adaptor protein; ZAP70, ζ-chain-associated protein kinase of 70 kDa.

(FIG. 1) (see [Supplementary information S1 \(table\)](#)). The first of these four categories comprises those genes of which the protein products are involved in cytokine signalling. The cytokine interleukin-7 (IL-7) is necessary for the differentiation and peripheral maintenance of T cells and therefore mutations in genes encoding molecules for IL-7-induced signalling can cause T-cell immunodeficiencies. The three other functional categories that include proteins essential for T-cell differentiation are antigen presentation, somatic recombination of the T-cell receptor (TCR) and TCR signalling. These three categories represent the requirement of T cells for positive selection signalling through the TCR during thymic development and peripheral activation. Proteins encoded by genes in the antigen presentation category function in the thymic epithelium, whereas proteins encoded by genes in the TCR V(D)J recombination or TCR signalling categories are T-cell intrinsic. As B cells and T cells share common components of the V(D)J recombination machinery, defects in the genes belonging to this category also result in B-cell immunodeficiency, albeit to a varying degree depending on the component that is mutated. Part of this variation may be explained by the additional roles of several components in DNA repair. It is clear why defects in the described functions of the proteins encoded by all of the genes in these four categories would lead to T-cell immunodeficiency, as they are necessary for the function of essential pathways during T-cell differentiation.

The fifth category of gene defects that can cause moderate to severe T-cell immunodeficiency comprises several apparently unrelated pathways. The proteins produced by these genes are all known to have a role in basic cellular processes that are common to multiple cell types. For example, ADA (adenosine deaminase) and NP (nucleoside phosphorylase; also known as PNP) are both involved in basic cellular metabolism; DNMT3β (DNA cytosine-5 methyltransferase 3β) and SP110 (SP110 nuclear body protein) have broad functions in gene regulation; SMARCA1 (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin subfamily a-like 1) is a chromatin remodelling protein; and RMRP (RNA component of mitochondrial RNA-processing endoribonuclease) is part of the mitochondrial RNA-processing endoribonuclease complex (see [Supplementary information S1 \(table\)](#)). Because each of these genes is expressed by multiple cell types, defects in these genes would not be predicted to give T-cell-specific phenotypes. It is possible that these genes might have currently unknown T-cell-specific functions; however, it is more likely that T cells are uniquely susceptible to mild defects in these basic cellular processes. This possibility is highlighted by the T-cell-specific defects observed in mice with a point mutation in *Ncapd2* (non-SMC condensin II complex subunit H2; which encodes kleisin-β)¹ and in mice lacking *Rpl22* (ribosomal protein L22)². Kleisin-β is a component of the ubiquitous chromosome condensin II subunit that is involved in cellular proliferation. The point mutation causes no obvious defects in the mice apart from reduced T-cell numbers, a phenotype that is independent of somatic recombination or TCR signalling¹. RPL22

Positive selection

One step in the process of T-cell differentiation in the thymus. T cells that express T-cell receptors with moderate to high affinity for self antigens receive a survival signal and continue to develop towards becoming double positive (CD4⁺ CD8⁺) T cells. Positive selection occurs through antigens presented by resident stromal cells and dendritic cells in the thymic cortex and is followed by negative selection.

is a component of the ubiquitous 60S large ribosomal subunit. Unlike other ribosomal subunits, it is not essential for the function of the large subunit, and loss of the homologue protein in yeast only results in mild growth retardation^{3,4}. In *Rpl22*^{-/-} mice, the global cellular defect is compensated for in all cell types except in early thymocytes, which die in a p53-dependent manner². The functional underpinning of such unique susceptibility may lie in the extremely rapid proliferation cycle of early thymocytes, allowing defects that would otherwise be redundant at slow proliferation rates to reach pathological status in thymocytes.

Clinical association with immune dysregulation

Although the most severe forms of T-cell immunodeficiency completely disable the adaptive immune system, a more common clinical manifestation is partial immunodeficiency, in which adaptive immune responses are

impaired but retain some function (TABLE 1). In most of these diseases additional leukocyte subsets are affected, either directly or indirectly, and have an effect on the clinical presentation of these patients (in this Review however we focus exclusively on the T-cell effects). Intuitively, decreased T-cell function owing to partial immunodeficiency would be predicted to lower the incidence of conditions associated with hyperactivity of the adaptive immune system, such as autoimmunity, elevated IgE or inflammatory disease, in these patients. Yet, contrary to these theoretical speculations, up to half of all patients with partial T-cell deficiencies develop autoimmune disease⁵. This does not include diseases in which primary autoimmunity is likely to be the driving force behind secondary partial immunodeficiency, such as *APECED* (autoimmune polyendocrinopathy-candidiasis-ectodermal-dystrophy syndrome) and *IPEX* (immunodysregulation, polyendocrinopathy and enteropathy,

Table 1 | Clinical conditions with T-cell immunodeficiency and immune dysregulation

Disease	Gene	T-cell deficiency and B-cell involvement	Immune dysregulation	Refs	OMIM
Monogenic conditions with a shared genetic basis to severe immunodeficiency					
Omenn syndrome	<i>RAG1, RAG2, DCLRE1C, IL7RA, RMRP, IL2RG*</i>	Oligoclonal T-cell repertoire with reduced proliferative response; B cells affected	Elevated production of IgE and eosinophilia, lymphadenopathy, hepatosplenomegaly, erythrodermia	9–11, 129,130	603554
ADA deficiency	<i>ADA</i>	Varying levels of T-cell deficiency and onset age; B cells affected	Autoimmunity (ITP), elevated production of IgE, asthma	32–34	102700
Ligase IV deficiency	<i>LIG4</i>	Reduced T-cell numbers with reduced proliferative response; B cells affected	Autoimmunity (ITP)	18	606593
ZAP70 deficiency	<i>ZAP70</i>	Absence of CD8 ⁺ T cells, reduced proliferative response of CD4 ⁺ T cells; B cells unaffected	Elevated production of IgE	35	176947
Growth-hormone insensitivity with immunodeficiency (type II Laron syndrome)	<i>STAT5B</i>	Reduced T-cell numbers with reduced proliferative response; B cells affected	Autoimmunity (JRA)	26	245590
Monogenic conditions with a unique genetic basis					
Wiskott–Aldrich syndrome	<i>WAS</i>	Reduced CD8 ⁺ T-cell numbers, reduced proliferative response of T cells; B cells affected	Elevated production of IgE and eosinophilia, eczema, autoimmunity (~30–72%) (AHA, JRA, ITP)	36,38, 131,132	301000
IL-2R α deficiency	<i>IL2RA</i>	Reduced CD4 ⁺ T-cell numbers and reduced proliferative response	Extensive lymphocytic infiltrate	43,44	606367
Clinical conditions of uncertain genetic basis					
Hyper-IgE syndrome (autosomal recessive form)	Largely unknown	Reduced T-cell proliferative response; B cells affected	Elevated production of IgE and eosinophilia eczema, autoimmunity (AHA, ANA)	133,134	147060
Common variable immunodeficiency	Heterogeneous disorder, largely undetermined	Reduced T-cell numbers (~20%) and reduced proliferative response (~40%); B cells affected	Allergy, autoimmunity (AHA, ITP, RA)	135	240500
22q11 syndrome (DiGeorge syndrome or velocardiofacial syndrome)	~90% due to deletion of 22q11	Reduced T-cell numbers; B cells unaffected	Elevated production of IgE (~30%), autoimmunity (~10%) (JRA, ITP)	136–138	188400/192430
Combined immunodeficiency with autoimmunity and spondylometaphyseal dysplasia	Unknown	Reduced T-cell numbers with reduced proliferative response	Autoimmunity (ITP, JRA, Crohn's disease)	139	607944

*Including other cases related to Omenn syndrome. ADA, adenosine deaminase; AHA, autoimmune haemolytic anaemia; ANA, antinuclear antibodies; *DCLRE1C*, DNA crosslink repair 1C; *IL2RA*, interleukin-2 receptor α -chain; *IL7RA*, IL-7 receptor α -chain; *IL2RG*, IL-2 receptor γ -chain; ITP, idiopathic thrombocytopenia purpura; JRA, juvenile rheumatoid arthritis; *LIG4*, ligase IV; RA, rheumatoid arthritis; RAG, recombination-activating gene; RMRP, mRNA component of mitochondrial RNA-processing endonuclease; *STAT5B*, signal transducer and activator of transcription 5B; WAS, Wiskott–Aldrich syndrome; *ZAP70*, ζ -chain-associated protein kinase of 70 kDa.

V(D)J recombination

Somatic rearrangement of variable (V), diversity (D) and joining (J) regions of the genes that encode antigen receptors, leading to repertoire diversity of both T-cell and B-cell receptors.

APECED

(Autoimmune polyendocrinopathy-candidiasis-ectodermal-dystrophy syndrome). A rare human autoimmune disorder that is inherited in an autosomal recessive manner and is characterized by various endocrine deficiencies, chronic mucocutaneous candidiasis and ectodermal dystrophies. It is caused by several different mutations in the gene that encodes autoimmune regulator (AIRE).

IPEX

(Immunodysregulation, polyendocrinopathy and enteropathy, X-linked syndrome). A disease caused by mutations in FOXP3 (forkhead box P3) and characterized by refractory enteritis and, in some patients, autoimmune endocrinopathies, autoimmune diabetes and thyroiditis.

Graft-versus-host disease

Tissue damage in a recipient of allogeneic tissue (usually a bone-marrow transplant) that results from the activity of donor cytotoxic T cells recognizing the tissues of the recipient as foreign. This disease varies markedly in extent, but it can be life threatening in severe cases. Damage to the liver, skin and gut mucosa are common clinical manifestations.

Autoimmune thrombocytopaenia

A reduced number of circulating platelets, owing to increased immune-mediated clearance from the blood, predominantly in the spleen.

X-linked syndrome). APECED and IPEX, together with the more common autoimmune diseases, are caused by primary defects in T-cell tolerance mechanisms. The associated increase in susceptibility to infections in these diseases is likely to be due to secondary effects caused by autoimmunity rather than due to a direct reduction in the capacity of effector T cells to combat infection. The clinical presentation of immune dysregulation in patients with partial T-cell immunodeficiencies can be so striking that the first of these conditions identified was recognized much earlier than the severe T-cell immunodeficiencies.

Monogenic partial immunodeficiencies with a shared genetic basis to severe immunodeficiency. In several cases, mutations in the same genes are known to result in either severe immunodeficiency without further immunological complications or in partial immunodeficiency with autoimmune or allergic manifestations. One example of this is *Omenn syndrome*, which is characterized by a combination of immunodeficiency and graft-versus-host-disease-like autoimmunity and immune dysregulation with elevated IgE production. Partial loss-of-function variants of the genes *RAG1* (recombination-activating gene 1), *RAG2*, *DCLRE1C* (DNA crosslink repair 1C; also known as *ARTEMIS*), *IL2RG* (IL-2 receptor γ -chain), *IL7RA* and *RMRP* are known to cause Omenn syndrome^{6–11}. Other related conditions arise from defects in the genes *ADA* (ADA deficiency), *LIG4* (ligase IV deficiency), *ZAP70* (ζ -chain-associated protein kinase of 70 kDa; ZAP70 deficiency) and *STAT5B* (signal transducer and activator of transcription 5B; growth-hormone insensitivity with immunodeficiency). These 10 genes are also linked to severe immunodeficiency without autoimmune complications.

The *RAG1*, *RAG2* and *DCLRE1C* mutations associated with Omenn syndrome cause impaired V(D)J recombination and the emergence of an oligoclonal T-cell repertoire, which indicates that thymic selection in individuals with these mutations is restricted to those few T cells in which recombinase activity was sufficient to generate a functional TCR. Despite the limited number of functional T cells produced, the absolute peripheral number of T cells is often normalized by niche-filling mechanisms that expand the clones that have a successfully rearranged TCR¹². Although in most cases different sets of mutations are responsible for the complete immunodeficiency phenotype, there does seem to be some overlap, as siblings of patients with Omenn syndrome have been observed to have severe T-cell immunodeficiency¹³, and identical *RAG1* or *RAG2* mutations have been identified in patients with severe T-cell immunodeficiency or Omenn syndrome¹⁴. The reason why identical *RAG1* or *RAG2* mutations can result in either the severe or partial form of immunodeficiency is currently unknown; it might be due to the stochastic effects of recombinase activity in individual thymocytes on the composition of the oligoclonal TCR repertoire, an alteration of recombinase activity by additional genetic factors or the influence of environmental factors (such

as viral infections) on the T-cell clones that manage to expand^{15,16}. Ligase IV is also required for V(D)J recombination and *LIG4* mutations can manifest as complete immunodeficiency¹⁷; however, the majority of individuals with *LIG4* mutations have partial immunodeficiency and include autoimmune components such as autoimmune thrombocytopaenia^{18,19}.

IL2RG and *IL7RA* have essential roles in IL-7-dependent thymocyte survival, and mutations in these genes have been associated with both Omenn-like syndrome^{10,11} and severe T-cell deficiency^{20–23}. In the case of *IL2RG*, identical alleles have been identified in both diseases^{11,24}. A similar effect may be responsible for the variations in the clinical manifestation of deficiency of *STAT5B*, a component of the receptor signalling pathway for growth hormones and key haematopoietic-cell cytokines (including IL-7). *STAT5B* deficiency can manifest as either classical immunodeficiency with growth retardation²⁵ or a complex of conditions including partial immunodeficiency with recurring infections, growth retardation, and the autoimmune conditions of thyroiditis and juvenile arthritis²⁶.

Mutations in *RMRP* have been observed in two patients with Omenn syndrome⁹. *RMRP* encodes the RNA component of the ribonuclease mitochondrial RNA-processing complex, which is required for mitochondrial DNA replication. Although it is not known how defects in *RMRP* lead to T-cell oligoclonality and partial immunodeficiency, other mutations in *RMRP* cause cartilage-hair hypoplasia, a disorder that is commonly associated with partial lymphopaenia²⁷ and, in rare cases, with severe T-cell immunodeficiency^{28–30}. Complete loss-of-function mutations in *RMRP* have not been observed.

Likewise, severe mutagenic defects in *ADA* are associated with severe T-cell immunodeficiency, and patients with partial defects and less severe delayed-onset immunodeficiency have been seen to develop autoimmunity or have elevated levels of IgE^{31–33}. An interesting case is that of a family in which one sibling suffered from classical severe T-cell immunodeficiency symptoms, whereas the other sibling showed spontaneous reversion of the *ADA* mutation in a subset of lymphocytes, and had less severe immunodeficiency and elevated IgE production³⁴. In a similar manner, rare cases of ZAP70 deficiency result in a combination of partial immunodeficiency and production of allergen-specific IgE³⁵.

Monogenic partial immunodeficiencies without genetic association to severe immunodeficiency. Mutations in other genes are also associated with partial T-cell immunodeficiency and immune dysregulation, but these have not been associated with complete T-cell immunodeficiency. These genes include *WAS* (mutation of which can cause Wiskott–Aldrich syndrome), and *IL2RA*, (mutation of which causes IL-2R α deficiency).

Wiskott–Aldrich syndrome is characterized by eczema, thrombocytopaenia and bloody diarrhoea, combined with an increased susceptibility to infection. Around 40–70% of all patients with Wiskott–Aldrich

syndrome also develop autoimmunity, most frequently haemolytic anaemia, neutropaenia and arthritis^{36,37}. Shortly after the causative gene, WAS, was identified³⁸, mutations in the same gene were revealed to cause a distinct clinical condition known as X-linked thrombocytopaenia, which is also associated with autoimmunity^{39,40}.

Common allelic variants in *IL2RA* have been linked to the autoimmune diseases type 1 diabetes and Graves' disease^{41,42}, but not to T-cell immunodeficiency. However, mutations in *IL2RA* have been identified in two patients, one with partial immunodeficiency (with frequent infections and an inability to reject allogeneic skin grafts) and extensive multi-tissue lymphocytic infiltration⁴³, and another with frequent infections and autoimmunity but no T-cell lymphopaenia⁴⁴.

Clinical conditions of uncertain genetic basis. Several other conditions combine partial immunodeficiency with immune dysregulation, but have no definitive genetic basis. In particular, three syndromes — hyper-IgE syndrome (the autosomal recessive form, rather than the classical autosomal dominant form that is not associated with autoimmunity), common variable immunodeficiency, and combined immunodeficiency with autoimmunity and spondylometaphyseal dysplasia — have a largely undefined genetic aetiology. These disorders have distinct immunological phenotypes and only a subset of patients exhibit partial T-cell lymphopaenia (which is of relevance to this Review), whereas others have normal T-cell counts. An additional disorder combining immunodeficiency with autoimmunity is 22q11 deletion syndrome (also known as velocardiofacial syndrome and DiGeorge syndrome). The genetic basis of this disorder is a deletion of chromosomal region 22q11, with multiple genes affected. As no mouse models that reproduce the immunological phenotype of these diseases are available, they are not discussed further in this Review. The possibility should be noted, however, that these diseases may result from a failure of immunological tolerance similar to the diseases listed above.

Despite the ambiguities of a common causality in several of the conditions described, it is clear that partial T-cell immunodeficiencies are associated with autoimmune disorders at a more frequent rate than the incidence of either disease alone would predict. Furthermore, the association of multiple genes with both severe immunodeficiency and partial T-cell immunodeficiency with immune dysregulation indicates that the association is not the property of select genes with differential effects, but rather an underlying consequence of partial T-cell immunodeficiency.

Although the clinical combination of partial immunodeficiency and immune dysregulation is relatively common, there are few mouse models available to dissect the association of partial immunodeficiency with autoimmunity. The key reasons for this deficit are likely to be the reliance on gene knockout mouse models and the incomplete understanding of the genetic basis of several diseases.

Mouse models of shared monogenic disorders

Nine of the ten human genes that have been identified both in patients with complete T-cell deficiency and in patients with partial T-cell deficiency have been well studied in mouse models. Mice that lack *Rag1* (REFS 45,46), *Rag2* (REFS 47,48), *Zap70* (REFS 49–53), *Il7ra*⁵⁴ or *Dclre1c*^{55,56} show a severe defect in the production of T cells. These knockout mouse models accurately represent the alleles associated with severe disease in humans, but do not reflect the complex clinical presentation associated with alternative alleles. Mice lacking *Ada*^{57,58} and *Lig4* (REF. 59) have also been developed, but they have a more severe phenotype than that in human patients and die *in utero*^{57,59}. This may reflect the retention of hypomorphic rather than null alleles in the human population. Mice deficient in *Il2rg* or *Stat5* develop the same severe T-cell immunodeficiency phenotype as seen in humans and also show signs of immune dysregulation^{60–63}. *Rmrp*-knockout mice have not been generated for comparison to the human phenotypes.

Using more sophisticated methods of genetic manipulation, including targeted gene alterations and missense mutations, mice with partial loss-of-function alleles of some of these genes have been generated. So far, 19 mouse strains have been generated that show some combination of partial T-cell immunodeficiency and immune dysregulation (TABLE 2). Of these strains, three have *N*-ethyl-*N*-nitrosourea (ENU)-induced mutations, three have spontaneous mutations, three have designed alleles, one is mediated by *Cre-LoxP* technology and nine have the genes knocked out.

Partial loss-of-function in somatic recombination genes.

Whereas knockout mouse strains of *Rag1*, *Rag2*, *Dclre1c* and *Lig4* do not reproduce the dual phenotype observed in some human patients, mouse strains with hypomorphic alleles of *Rag1*, *Rag2* and *Lig4* do. A fourth strain, the *Tcra*^{-/-} mouse strain, may also fit into this category, as loss of TCR α results in a less severe T-cell immunodeficiency than loss of TCR β or RAG proteins and is also accompanied by autoimmune symptoms⁶⁴.

An ENU-induced hypomorphic allele of *Lig4* that generates an amino-acid substitution at position 288 (LIG4^{Y288C}) does not affect viability of mice but results in severely reduced numbers of T cells and B cells⁶⁵. LIG4^{Y288C} mice spontaneously develop antinuclear antibodies at a high incidence (R. Cornall, personal communication), indicating that these mice also develop immune dysregulation, analogous to the autoimmune symptoms of patients with partial ligase IV deficiency. As yet, the mechanisms underlying this immune dysregulation are not clear.

Recently, two mouse models of Omenn syndrome have been developed with hypomorphic RAG alleles. The first used a knock-in allele of *Rag2* that results in the RAG2^{R229Q} variant, a mutation that is found in human patients with 'leaky' severe T-cell immunodeficiency and Omenn syndrome and that confers a 150-fold reduction in activity by this recombinase¹⁴. RAG2^{R229Q} mice show a severe defect in T-cell

Graves' disease

A type of autoimmune disease in which autoantibodies produced by the immune system overstimulate the thyroid gland, causing hyperthyroidism.

N-ethyl-*N*-nitrosourea

(ENU). An ethylating chemical that produces a high rate of genome-wide point mutations at random in the germline.

Cre-LoxP technology

A site-specific recombination system. Two short DNA sequences (LoxP sites) are engineered to flank the target DNA. Expression of Cre recombinase leads to excision of the intervening sequence. Depending on the type of promoter, Cre can be expressed at specific times during development or in specific sets of cells.

Antinuclear antibodies

Autoantibodies generated against antigens within the nucleus, including DNA. They are indicative of systemic lupus erythematosus, but are also common in patients with rheumatoid arthritis, Sjogren's syndrome and other autoimmune diseases, and are rarely found in healthy individuals.

Table 2 | Mouse strains showing partial T-cell immunodeficiency and immune dysregulation

Variant	Method	Immune dysregulation	Refs
<i>Il2rg</i> ^{-/-}	Knockout	Colitis	60–62
<i>Stat5a</i> ^{-/-} <i>Stat5b</i> ^{-/-}	Knockout	Multi-organ infiltration	63
<i>Lig4</i> ^{Y288C}	ENU mutant	Autoantibodies	*
<i>Rag1</i> ^{R972Q}	Spontaneous mutant	Elevated production of IgE, IgM, IgG2b and IgG2a, eosinophilia	67
<i>Rag2</i> ^{R229Q}	Designed allele	Elevated production of IgE, eosinophilia, inflammatory diarrhoea, alopecia	66
<i>Lat</i> ^{Y136F}	Designed allele	Multi-organ infiltration, autoantibodies, elevated production of IgE and IgG1	80,81
<i>Lat</i> ^{Y77/8/9F}	Designed allele	Elevated production of IgE and IgG1	82
<i>Lcp2</i> ^{-/-} <i>Cbl</i> ^{-/-}	Knockout	Multi-organ infiltration, elevated production of IgE and IgG1	76
<i>Lcp2</i> ^{twp}	ENU mutant	IgG autoantibodies, elevated production of IgE and IgG1	†
<i>Rasgrp1</i> ^{-/-}	Knockout	Elevated production of immunoglobulin	78
<i>Rasgrp1</i> ^{lag}	Spontaneous mutant	Elevated production of IgG and IgM, autoantibodies	78
<i>Sh2d2a</i> ^{-/-}	Knockout	Elevated production of IgG and IgM, autoantibodies, kidney disease and lung infiltration	79
<i>Stim1</i> ^{-/-} <i>Stim2</i> ^{-/-}	CD4–Cre crossed to floxed alleles	Multi-organ infiltration, lymphoproliferation	83
<i>Tcra</i> ^{-/-}	Knockout	Colitis, autoantibodies, elevated production of IgE and IgG1	64
<i>Vav1</i> ^{-/-} <i>Cblb</i> ^{-/-}	Knockout	Multi-organ infiltration, autoantibodies	77
<i>Was</i> ^{-/-}	Knockout	Inflammation of the colon	89,90
<i>Wip</i> ^{-/-}	Knockout	Elevated production of IgE and IgM	97
<i>Zap70</i> ^{okg}	Spontaneous mutant	Rheumatoid-like arthritis, elevated production of IgG	84
<i>Zap70</i> ^{mrd/mrt}	ENU mutant	Elevated production of IgE, IgG autoantibodies	87

*R. Cornall, personal communication. †C. Goodnow, personal communication. *Cbl*, Casitas B-lineage lymphoma; ENU, N-ethyl-N-nitrosourea; *Il2rg*, interleukin-2 receptor γ -chain; *Lat*, linker for activation of T cells; *Lcp2*, lymphocyte cytosolic protein 2; *Lig4*, ligase IV; *Rasgrp1*, RAS guanyl-releasing protein 1; *Sh2d2a*, SRC-homology-2-domain protein 2A; *Stat*, signal transducer and activator of transcription; *Stim*, stromal interaction molecule; *Tcra*, T-cell receptor α -chain; *Was*, Wiskott–Aldrich syndrome; *Wip*, WASP-interacting protein; *Zap70*, ζ -chain-associated protein kinase of 70 kDa.

Negative selection

The deletion of self-reactive thymocytes in the thymus. Thymocytes expressing T-cell receptors that strongly recognize self peptide bound to self MHC molecules undergo apoptosis in response to the signalling generated by high-affinity binding.

FOXP3⁺ regulatory T cells

A rare population of CD4⁺ T cells that naturally express high levels of CD25 (the interleukin-2 receptor α -chain) and the transcription factor forkhead box P3 (FOXP3), and that have suppressive regulatory activity towards effector T cells and other immune cells. Absence or dysfunction of these cells is associated with severe autoimmunity.

development at the double negative 3 (DN3) stage and develop elevated levels of IgE and inflammatory disease⁶⁶. The second model uses a spontaneous mutant of *Rag1* that results in the RAG1^{R972Q} protein variant that has only 12% of wild-type activity⁶⁷. The corresponding human mutation, RAG1^{R975Q}, has been observed in patients with Omenn syndrome⁶⁸. Similar to RAG2^{R229Q} mice, the RAG1^{R972Q} mice are lymphopaenic and develop T-cell-dependent increased IgE production and inflammatory disease⁶⁷.

The mechanism by which hypomorphic *Rag* alleles precipitate immune dysregulation is unclear, although there have been several interesting experimental results generated from studying these mice. In mice expressing the RAG1^{R972Q} mutant, the activation of CD4⁺ T cells depends on the lymphopaenic environment, as wild-type CD4⁺ T cells transferred into RAG1^{R972Q} mice exhibit the same activated phenotype⁶⁷. In mice expressing the RAG2^{R229Q} mutant, thymic expression of autoimmune regulator (AIRE) is reduced⁶⁶, as is the case in patients with Omenn syndrome⁶⁹, leading to the possibility that negative selection of developing thymocytes is dysfunctional⁷⁰. RAG2^{R229Q}-expressing mice also have a reduced percentage of forkhead box P3 (FOXP3)⁺ regulatory T cells in the thymus and spleen, and this could precipitate autoimmunity by allowing FOXP3⁻ T cells to proliferate⁷¹. Which of these defects are causative of the immune dysregulation is as yet unknown.

Mouse models with cytokine signalling defects. Mouse models of *Il7ra*, *Il2rg* or *Stat5b* deficiency are all available. Although *Il7ra*- or *Il7*-knockout mice have severe T-cell immunodeficiency^{54,72} and *Stat5b*-knockout mice have T-cell defects without autoimmunity^{73,74}, *Il2rg*-knockout mice and mice deficient in both STAT5A and STAT5B reproduce both immunodeficiency and immune dysregulation.

Stat5b-knockout mice show growth retardation, minor T-cell lymphopaenia and defects in T-cell function, but they have not been documented to develop autoimmunity^{73,74}. However, mice lacking both *Stat5a* and *Stat5b* have a more severe phenotype⁷⁵. They develop similar symptoms to human patients, with growth-hormone insensitivity, stunted growth and immunodeficiency. The mice also have a severe deficiency in total T-cell numbers and CD4⁺CD25⁺ regulatory T-cell numbers, and develop T-cell-dependent autoimmunity affecting the colon, liver and kidney⁶³. As the transfer of wild-type CD4⁺ T cells prevents disease, the pathogenicity of *Stat5a*^{-/-}*Stat5b*^{-/-} T cells is not intrinsic to the effector T cells and is probably either a direct result of lymphopaenia or a defect in regulatory T-cell capacity⁶³.

Mouse models with TCR signalling defects. ZAP70 deficiency blocks signalling through the TCR and typically results in severe T-cell immunodeficiency^{49–51}. However, a case has been observed in which expression

of the homologous kinase SYK (spleen tyrosine kinase) apparently compensated for the loss of ZAP70 and partially restored TCR signalling activity, resulting in the patient developing elevated levels of IgE³⁵. A comprehensive range of mouse models are available for partial TCR signalling blockades, many of which combine partial immunodeficiency with elevated levels of IgE or autoimmunity. Double-knockout models can lead to intermediate effects by simultaneously removing a positive and negative modulator of TCR signalling, such as *Lcp2* (lymphocyte cytosolic protein 2; also known as *Slp76*) and *Cbl* (Casitas B-lineage lymphoma)⁷⁶ or *Vav1* and *Cblb*⁷⁷. Loss of a TCR signalling mediator, such as SH2D2A (SRC-homology-2-domain protein 2A; also known as TSAD) or RASGRP1 (RAS guanyl-releasing protein 1), also partially impairs TCR signalling^{78,79}, as do designed mutations of the TCR adaptor protein LAT (linker for activation of T cells)^{80–82}. The block in T-cell differentiation that occurs in mice expressing the LAT mutant (LAT^{Y136F}) is accompanied by elevated IgE and IgG1 production and multi-organ infiltration of lymphocytes^{80,81}. By contrast, mice expressing LAT^{Y7/8/9F} (where tyrosines seven, eight and nine were mutated to phenylalanine) have a partial repertoire of $\gamma\delta$ T cells with CD4⁺ $\alpha\beta$ T-cell properties that drive elevated production of IgG1 and IgE⁸². Mice lacking both the calcium sensors *Stim1* (stromal interaction molecule 1) and *Stim2* have a severe impairment in generating sustained calcium flux⁸³. Despite the resulting defect in NFAT (nuclear factor of activated T cells) translocation, these mice develop a lymphoproliferative syndrome⁸³. Another example of autoimmunity in mice with partial defects in TCR signalling is the *Zap70*^{skg} mouse strain, which has a spontaneous hypomorphic W163C mutation in ZAP70 and suffers from a partial T-cell differentiation block together with T-cell-dependent autoimmune arthritis⁸⁴. So, there are multiple mouse models in which partial defects in TCR signalling recapitulate the human syndrome of both immunodeficiency and immune dysregulation.

The proposed mechanisms for the development of immune dysregulation in these TCR-signalling mutant mice include impaired negative selection, and thereby disrupted central tolerance, in the *Zap70*^{skg} and LAT^{Y136F} strains^{84,85}, and a defect in FOXP3⁺ regulatory T-cell commitment or peripheral activation, and therefore defective peripheral tolerance, in the LAT^{Y136F} strain⁸⁶ and in strains deficient in both STIM1 and STIM2 (REF. 83). Peripheral T cells in all of these mouse strains show a profound reduction in activation capacity^{83–85}, yet this raises the question of why the decreased immunogenic signalling (the ability of effector T cells to become activated) does not cancel out the tolerogenic signalling defect (FIG. 2). If immunogenic signalling processes (such as stimulatory TCR signalling to activate effector T cells or inhibitory signalling in regulatory T cells) were controlled in the same way as tolerogenic signalling processes (stimulatory TCR signalling in regulatory T cells, or inhibitory TCR signalling resulting in anergy or deletion of effector T cells), any defect in TCR signalling should be neutral in terms of

the immunogenic–tolerogenic balance. If the effects are not equal, there are two distinct mechanisms that could explain the phenomenon. The first is that tolerogenic and immunogenic TCR signalling have differential signalling requirements (such as their reliance on signalling subpathways), and the specific alleles that cause autoimmunity are separation-of-function alleles that impair tolerogenic signalling to a greater extent than immunogenic signalling, for example by slightly reducing effector T-cell activation but greatly impeding negative selection. The second is that the alleles are simple reduction-of-function alleles, but the balance between tolerance and immunity is based on complex interactions rather than on proportional interactions. In this scenario, even equal reductions in tolerogenic and immunogenic signalling can result in autoimmunity, if, for example, stimulatory TCR signalling was equally reduced in effector and regulatory T cells, but regulatory T cells lost function more rapidly than effector T cells.

In the case of the LAT^{Y136F} mouse strain, the lack of FOXP3⁺ regulatory T cells is due to a separation-of-function change, probably because the Y136F mutation in LAT eliminates its ability to recruit phospholipase C γ 1 (PLC γ 1)⁸¹. This causes a selective defect in the NFAT and Ca²⁺ signalling pathways but leaves the extracellular-signal-regulated kinase (ERK) signalling pathway intact⁸¹. The tolerogenic process of FOXP3 induction seems to be more reliant on the NFAT and Ca²⁺ signalling pathways than the immunogenic processes, as the observed defect in FOXP3⁺ regulatory T cells is greater in LAT^{Y136F} mice than in ZAP70 hypomorphic mice, whereas both the LAT^{Y136F} and ZAP70 hypomorphic mice have a similar reduction in positive selection⁸⁷. It also seems that the separation-of-function change can act in an intrinsic manner to unbalance immunogenic and tolerogenic signalling in effector T cells, as LAT^{Y136F} effector T cells still show immune dysregulation in the presence of wild-type FOXP3⁺ regulatory T cells and the absence of MHC class II interaction⁸⁸. This mouse strain shows that, in principle, separation-of-function TCR signalling alleles can result in both immunodeficiency and immune dysregulation.

Two other mouse strains, *Lcp2*^{twp} and *Zap70*^{mrd/mrt}, demonstrate that pure reduction-of-function alleles are also able to promote autoimmunity. In the *Lcp2*^{twp} strain, an ENU-induced mutation in a splice donor site reduces the amount of full-length mRNA encoding SLP76 (SH2-domain-containing leukocyte protein of 76 kDa) that can be produced (C. Goodnow and L. Miosge, personal communication). An intermediate level of T-cell immunodeficiency occurs and the mice develop enhanced IgE levels without any coding change in the TCR signalling machinery. In the *Zap70*^{mrd/mrt} strain, two hypomorphic ENU-induced mutations are combined. The *Zap70*^{mrd} mutation encodes an I367F amino-acid substitution and causes a minor reduction in ZAP70 activity, whereas the *Zap70*^{mrt} mutation encodes a W504R amino-acid substitution that leaves only marginal ZAP70 activity. Neither parental strain develops hyper-production of IgE or autoantibodies (negating specific allele effects),

$\gamma\delta$ T cells

T cells that express a T-cell receptor consisting of a γ -chain and a δ -chain.

Immunogenic signalling

Signalling that results in immunity by enhancing the immune response. Immunogenic T-cell receptor signalling can be defined as signalling that increases the activation of effector T cells or reduces the activity of regulatory T cells.

Tolerogenic signalling

Signalling that results in the suppression of immunity or the induction of immune tolerance. Tolerogenic T-cell receptor signalling can be defined as signalling that reduces the activation of effector T cells or increases the activity of regulatory T cells.

Immunological synapse
A region that can form between two cells of the immune system in close contact. The immunological synapse originally referred to the interaction between a T cell and an antigen-presenting cell. It involves adhesion molecules, as well as antigen receptors and cytokine receptors.

yet the compound heterozygous mice have a level of immunodeficiency that is intermediate between that of the two homozygous strains and spontaneously produce autoantibodies⁸⁷. These results indicate that it is the degree of immunodeficiency that is responsible for spontaneous autoimmunity.

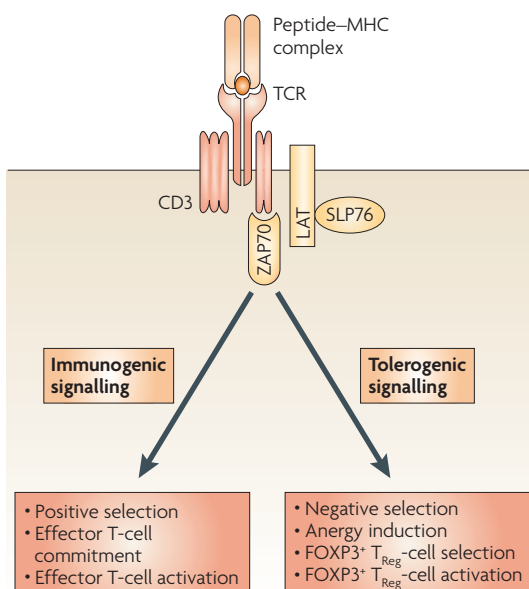
Mouse models of unique monogenic disorders

As detailed in TABLE 1, two monogenic partial T-cell immunodeficiencies have been identified in which the causative gene has not been associated with a classical severe T-cell immunodeficiency phenotype — IL-2R α

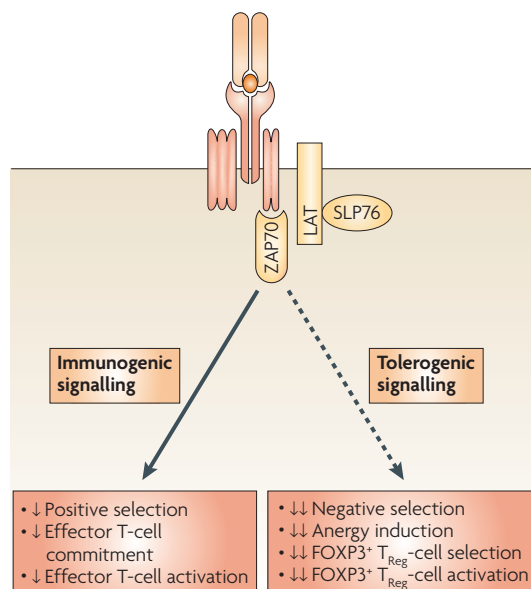
deficiency and Wiskott–Aldrich syndrome. Knockout mice have been generated for both genes, but only *Was*^{-/-} mice mimic the immunological aspects of the human condition.

Was-knockout mice develop both partial immunodeficiency and autoimmunity, including severe inflammation of the colon^{89,90}. The loss of WAS protein (WASP) leads to severe defects in T-cell signalling due to the function of WASP in actin organization during the formation of the immunological synapse^{90–92}. The reduction in TCR signalling capacity is linked to defects in the production⁹³, homeostasis⁹⁴ and function^{93,95,96} of FOXP3⁺ regulatory

a Normal signal strength



b Separation-of-function signalling defect



c Partial loss-of-function signalling defect

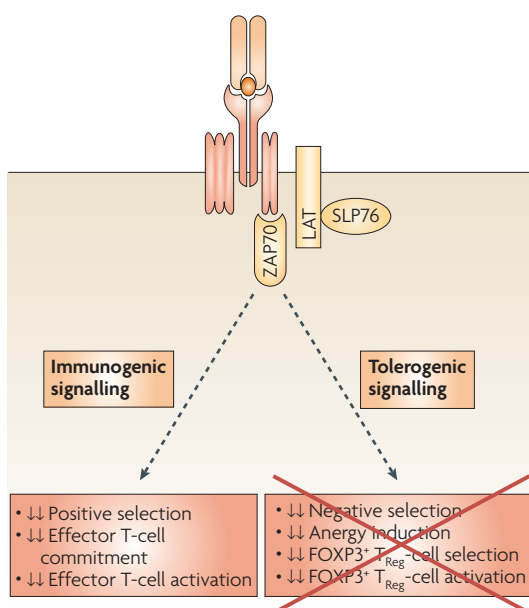


Figure 2 | Immunogenic and tolerogenic T-cell receptor (TCR) signalling. The TCR signalling pathway leads to both immunogenic and tolerogenic outcomes. **a** | TCR signalling is required for thymocyte positive selection, effector T-cell lineage commitment and effector T-cell proliferation or activation. However, TCR signalling is also crucial for tolerogenic processes, such as the negative selection and anergy induction of autoreactive T cells and the selection and activation of regulatory T cells. The balance between these two processes results in immunological tolerance while still allowing immunogenic responses when necessary. **b** | Separation-of-function defects in TCR signalling may induce simultaneous immunodeficiency and autoimmunity by reducing immunogenic signalling pathways but having a greater impact on tolerogenic signalling pathways. **c** | Partial loss-of-function defects in TCR signalling may also induce simultaneous immunodeficiency and autoimmunity. In this case, signalling to immunogenic and tolerogenic pathways is equally reduced, but the outcome to each branch is nonlinear and tolerogenic mechanisms fail under a loss of signalling that still allows immunogenic mechanisms to operate at a reduced level. FOXP3, forkhead box P3; LAT, linker for activation of T cells; SLP76, SRC-homology-2-domain-containing leukocyte protein of 76 kDa; T_{Reg} cell, regulatory T cell; ZAP70, ζ -chain-associated protein kinase of 70 kDa.

T cells, and this may contribute to the observed autoimmunity in patients with Wiskott–Aldrich syndrome. It is also probable that loss of WASP causes a B-cell-intrinsic defect, as *Was*^{-/-} mice have reduced responses to T-cell-independent antigens and B-cell lines from patients with Wiskott–Aldrich syndrome show reduced chemotaxis towards CXC-chemokine ligand 13 (CXCL13). As the most frequently observed autoimmune diseases in WAS are autoantibody mediated, these B-cell defects may contribute to disease; however, autoantibody production may instead be secondary to the T-cell phenotype. Mice that lack WASP-interacting partner (*Wip*) develop a similar phenotype, with loss of T-cell proliferation and the generation of immune dysregulation^{97,98}. For defects in both *Was* and *Wip*, a model for how the regulatory T-cell defect overcomes the defect in effector T cells has not yet been proposed.

IL-2R α deficiency has only been observed in two patients, one with numerical T-cell-deficiency and extensive lymphocytic infiltrates⁴³ and one with normal T-cell counts but frequent infections and IPEX-like

autoimmunity⁴⁴. Mice that lack *Il2ra*, *Il2rb* and *Il2* have been generated, but although they all exhibit immunopathology, the mice are not immunodeficient^{99–101}. The primary effect of loss of IL-2 responsiveness is a reduction in the thymic production and peripheral maintenance of FOXP3⁺ T cells, resulting in a loss of suppression of low-affinity, self-reactive T-cell clones^{102,103}. Although IL-2 is a potent immune stimulator, *Il2*-knockout mice do not develop immunodeficiency. As yet, there are insufficient patients with *IL2RA* deficiency to determine whether loss of IL-2R signalling in humans generates primary immunodeficiency due to differences in the relative role of IL-2 in humans and mice, or whether the immunodeficiency observed in these patients is secondary, akin to IPEX.

Mechanistic models

Mouse models that result in intermediate TCR signalling or somatic recombination capacity indicate that the degree of T-cell immunodeficiency sets the conditions for uncontrolled T-cell activation and immune dysregulation. Mild or very severe immunodeficiency does not trigger immune dysregulation, whereas intermediate levels do. If both immunogenic and tolerogenic activities were equally impaired owing to immunodeficiency, this outcome would be paradoxical (FIG. 3a). However, these opposing activities do not need to respond equally, as tolerogenic mechanisms evolved in the context of homeostatic T-cell numbers with no evolutionary pressure for them to operate correctly at sub-homeostatic T-cell levels. The occurrence of hyperimmune activity only during an intermediate range of immunodeficiency can then be explained by distinct patterns of the response to various degrees of immunodeficiency. If the tolerogenic and immunogenic mechanisms respond with different kinetics, the balance that occurs during homeostasis can be lost only during partial immunodeficiency, resulting in the observed opposing clinical outcomes (FIG. 3b).

Multiple and not mutually contradictory disconnections may be responsible for these effects. Immune dysregulation in *Lcp2*^{trwp} mice depends on the poor function of their FOXP3⁺ regulatory T cells, as immune dysregulation is suppressed on transfer of wild-type but not *Foxp3*^{-/-} T cells (C. Goodnow and L. Miosge, personal communication), whereas immune dysregulation in *Zap70*^{mrd/mrd} mice is intrinsic to effector T cells, suggesting that the immune defect is due to impaired negative selection⁸⁷. There are several mechanisms by which these processes may require homeostatic conditions for attaining sufficient tolerogenic function. For TCR signalling mutants, both FOXP3⁺ regulatory T-cell commitment and negative selection have altered signalling requirements compared with effector T-cell activation^{86,104–106}. This could allow a partial defect in TCR signalling capacity that causes a more potent impairment of both negative selection and induction of FOXP3 expression than will occur for positive selection and peripheral activation. These differential signalling requirements potentially give loss-of-function TCR signalling mutations a disproportionate effect on tolerogenic processes over immunogenic processes (FIG. 2).

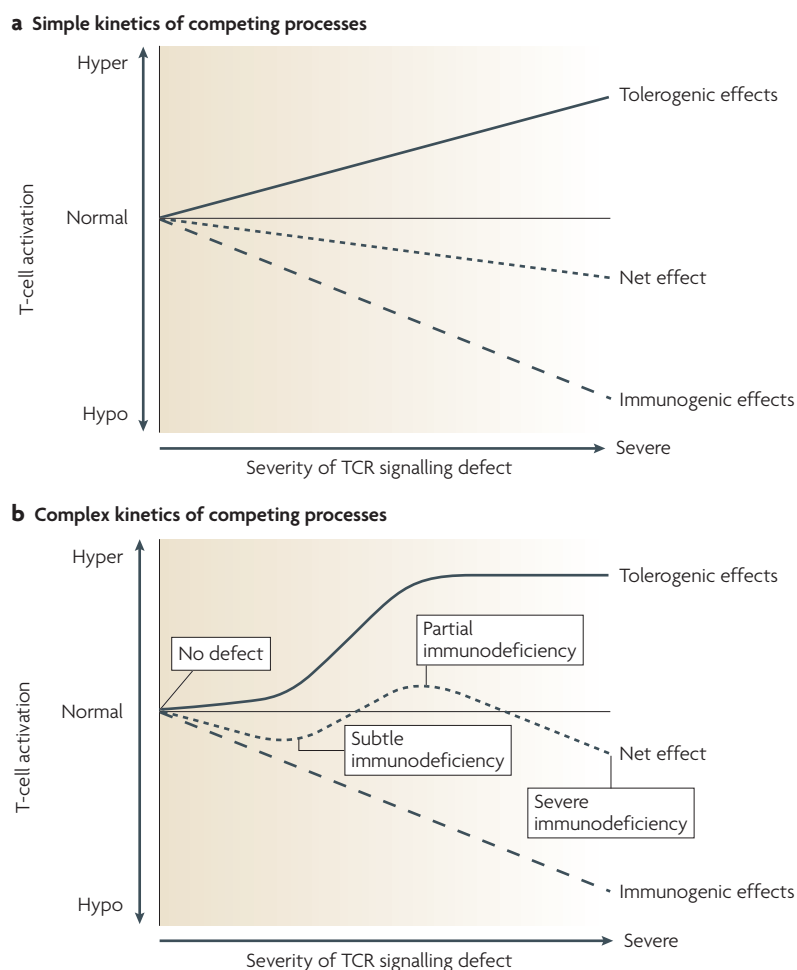


Figure 3 | Complex kinetics of competing processes explain paradoxical outcomes of gene variants. Competing immunogenic and tolerogenic processes alter the net ability of T cells to be activated (y axis). **a** | When both processes are proportionally modified by a reduction in T-cell receptor (TCR) signalling ability (x axis), an intuitive net effect occurs. **b** | When immunogenic and tolerogenic processes respond to TCR-signalling variants with unique kinetics, counter-intuitive net effects can occur.

Other complex interactions do not need to cause changes in signalling capacity and may be directly affected by the size of the T-cell population. For these population-dependent mechanisms, any mutation that reduces T-cell differentiation will impair the effectiveness of tolerogenic processes, whether the mutation affects TCR signalling, cytokine signalling or V(D)J recombination. For example, the effectiveness of regulatory T cells in carrying out their suppressive function may be disproportionately reduced by restrictions in the T-cell repertoire. FOXP3⁺ T cells require antigen for activation of their suppressor function^{107,108}, so a broad repertoire of TCRs expressed by the FOXP3⁺ T-cell population is probably required for effective suppression of potential autoimmune effector T cells (FIG. 4a). Restriction of both the effector and regulatory T-cell populations to an oligoclonal repertoire would reduce the overlap between regulatory and effector T-cell specificities, facilitating the escape of autoreactive oligoclonal effector T cells (FIG. 4b). This principle has been demonstrated by the reconstitution of a lymphopaenic recipient mouse with different numbers of CD4⁺CD25⁺ regulatory T cells. Whereas the transfer of either low or high numbers of precursors resulted in the same absolute number of CD4⁺CD25⁺ regulatory T cells after lymphopaenic expansion, mice that received a low number of T-cell precursors were subsequently unable to control introduced naive CD4⁺ T cells and developed autoimmunity, allergy and elevated levels of serum IgE^{109,110}. So, although the regulatory T-cell populations that arise in the recipient mice are genetically and numerically identical, when they originate from a diverse TCR repertoire pool they are protective, but when they arise from a limited TCR repertoire pool immune dysregulation can ensue.

Another process that may depend on T-cell population size is the efficiency of negative selection in the thymus. In the analogous process of B-cell negative selection, the population size modulates the efficiency of apoptosis in response to antigen stimulation¹¹¹. A similar interaction may occur during T-cell negative selection. Microarchitecture in the thymic medulla depends on the crosstalk between mature thymocytes and the medullary epithelium through the lymphotoxin pathway^{112,113}. Lymphotoxin is also required for the expression of chemokines to guide thymocyte migration, and the ability of epithelial cells to respond to lymphotoxin increases the efficiency of negative selection¹¹⁴ (FIG. 4c). Early studies suggested that lymphotoxin promotes AIRE expression¹¹⁵, however recent analyses have suggested that this effect is secondary to the role of lymphotoxin in the development of thymic epithelial cells¹¹² and that the key inducer for AIRE expression is RANKL (receptor activator of nuclear factor- κ B ligand)¹¹⁶. RANKL is expressed by lymphoid-tissue inducer cells rather than thymocytes, making it a population-insensitive pathway¹¹⁶. Under conditions in which the number of mature thymocytes is restricted (such as during partial T-cell immunodeficiency), lower amounts of lymphotoxin are available to epithelial cells, reducing the effectiveness of thymocyte–epithelial-cell communication, and the thymic microarchitecture becomes disordered¹¹³. This is likely to make efficiency of negative selection a

population-sensitive process, as the quantity of T cells, above and beyond the properties of the individual cells, alters the efficiency of negative selection (FIG. 4d). Previous studies have shown that even slight changes to the thymic expression of peripheral antigens can reduce the effectiveness of negative selection¹¹⁷, which demonstrates that even subtle defects in negative selection can have pathogenic consequences.

Both of the mechanisms above are sensitive to numerical T-cell defects in the thymus, regardless of whether the size of the T-cell pool is normalized in the periphery. Other mechanisms are likely to be sensitive to the size of the peripheral T-cell pool. The activation of effector T cells, for example, has been shown to occur with greater ease and towards lower affinity antigens under conditions of lymphopaenia^{118,119}. Several different factors may contribute to this reduced threshold for activation. One is an increased availability of serum IL-7, with fewer T cells competing for a constant resource¹²⁰. Another factor is the expression of co-stimulatory factors by dendritic cells, which respond to T-cell lymphopaenia by increasing their expression of CD80 and CD86, among other factors, and this lowers the activation threshold and potentially allows autoreactive T cells to proliferate¹²¹. Peripheral lymphopaenia not only increases the capacity of T cells to expand in response to low-affinity ligands (such as positively selecting self ligands), but it also reduces the efficiency of peripheral deletion mechanisms in response to self antigens¹²². All of these mechanisms, and probably additional ones, act in a population-dependent manner, in that the efficacy is reduced simply by virtue of the reduced population size, rather than by changes at the cellular level.

Concluding remarks

A survey of the published clinical literature of the partial T-cell immunodeficiencies highlights the surprising frequency with which these conditions are accompanied by immune dysregulation in the form of elevated production of IgE, inflammatory disease or autoimmunity. For at least a subset of these conditions, it is likely that the immune dysregulation component is a direct consequence of the partial nature of the immunodeficiency.

The growing number of ‘designer’ alleles and point mutations has allowed the generation of multiple mouse strains with immunodeficiency in the intermediate range. These mice develop a range of immune dysregulation symptoms due to defects in negative selection and regulatory T-cell function under conditions of partial immunodeficiency. The use of a titration of *Zap70* hypomorphic alleles indicates that immune dysregulation can be a spontaneous condition that is dependent on the level of immunodeficiency rather than on the consequences of particular alleles. The degree to which heterozygous polymorphisms in different genes can synergistically produce a similar effect remains an open question. Taken together, the mouse models indicate that a single common mechanism — reduced efficiency of tolerance mechanisms at suboptimal functional T-cell population sizes — can be used to explain the development of immune dysregulation as a consequence of partial T-cell immunodeficiency.



Figure 4 | Putative population-dependent tolerance mechanisms. Regulatory T-cell repertoire diversity, thymic negative selection and peripheral T-cell activation have the potential to act in population-dependent manners. **a** | Under homeostatic conditions, regulatory T cells control autoreactive T cells, through the expression of complementary T-cell receptor (TCR) repertoires specific for antigen sets. **b** | Under conditions of partial thymic immunodeficiency, a reduced number of successful thymocytes mature and enter the periphery. This results in oligoclonal expansion and hence 'holes' in the TCR repertoire for both regulatory T cells and autoreactive T cells, which by chance can create gaps in antigen-specific tolerance as indicated by asterisks (*), whereby the regulatory T-cell repertoire is limited but the autoreactive T-cell repertoire is present. **c** | Thymic crosstalk between single-positive (SP) thymocytes and medullary thymic epithelial cells (mTECs) via lymphotoxin, supports a well-structured thymic microarchitecture and efficient elimination of autoreactive T cells. **d** | Restriction of positive selection results in decreased production of SP thymocytes, reduced lymphotoxin levels and a disordered thymic microarchitecture. This may result in an increased number of autoreactive T cells escaping negative selection in the thymus. **e** | Under conditions of homeostasis, the limiting levels of interleukin-7 (IL-7) and co-stimulation signals from dendritic cells (through CD80 and CD86) increase the activation threshold for naive T cells, preventing naive autoreactive T cells from becoming activated. **f** | Under conditions of peripheral lymphopaenia, the reduced numbers of T cells allows each T cell increased access to the constant level of IL-7. Under lymphopaenic conditions, dendritic cells increase surface levels of CD80 and CD86. The combined effect of these two factors lowers the activation threshold for naive T cells. This may allow naive autoreactive T cells that would otherwise remain quiescent to become activated and pathogenic.

This opens up the study of which tolerance mechanisms depend on the size of the functional population, and to what degree they are sensitive to changes in functional T-cell population density. An understanding of the population sensors involved may allow manipulation of the effectiveness of these tolerance mechanisms, and hence susceptibility to immune dysregulation.

The translation of observations made in the mouse model to human disease presents a major challenge for the future. However, if replicated, these findings open up several interesting possibilities. First, they suggest a mechanism for this close clinical association of apparently opposite conditions. Second, they suggest that non-familial cases of partial immunodeficiency and immune dysregulation may result from the inheritance of particular combinations of hypomorphic alleles that act synergistically to lower T-cell numbers or function to the point at which immune dysregulation occurs spontaneously. In this regard, the increase in large-scale sequencing will soon allow us to sequence all or most of the genes involved in T-cell development and signalling in humans. Third, these findings suggest potential new avenues for investigation of common autoimmune and allergic diseases. Can minor defects in the T-cell population act in a synergistic manner with disease-specific polymorphisms to increase susceptibility to disease? The contribution of peripheral lymphopaenia to autoimmune diabetes that occurs spontaneously in the BB rat model indicates that it is at least plausible¹²³. The association of polymorphisms in *PTPN22* (protein tyrosine phosphatase, non-receptor type 22)^{124,125} and *SH2D2A*¹²⁶, which are known to lower TCR signalling capacity, with common autoimmune diseases extends the potential for this contribution to human patients. Whether these alleles function by inducing a mild degree of T-cell deficiency awaits direct testing. The direct measurement of minor degrees of T-cell deficiency in autoimmunity is made difficult, as thymic tissue is generally unavailable for direct detection of defects in T-cell differentiation, and peripheral inflammation and

compensation mechanisms can mask the initiating defect. A sensitive and reliable surrogate measure to test for mild immunodeficiency in common autoimmune diseases could be the measurement of TCR repertoire diversity in the peripheral blood.

An even more striking example of translation to the polygenic scenario in humans is the association of *IL7RA* polymorphisms with multiple sclerosis and type 1 diabetes^{127,128}. As described above, severe loss-of-function alleles of *IL7RA* cause severe T-cell deficiency^{20,21}, whereas moderate loss-of-function alleles can cause Omenn syndrome¹⁰. The *IL7RA* allele associated with common autoimmunity alters the splicing efficiency of the mRNA and results in a twofold upregulation of *IL7RA* transcripts lacking exon 6 (REF. 127). This exon encodes the transmembrane domain, so the *IL7RA* polymorphism results in an increase in a soluble form of IL-7R α , which probably reduces the availability of serum IL-7. As this allele is insufficient to induce autoimmunity alone, but acts as a susceptibility allele for several common autoimmune diseases, it provides a direct connection between the rare monogenic conditions discussed in this Review and more prevalent polygenic autoimmune diseases.

Note added in proof

In a recent publication by Vignali and colleagues, the effect of intermediate levels of TCR signalling capacity was tested by generating mice with different numbers of immunoreceptor tyrosine-based activation motifs (ITAMs) in the TCR-CD3 complex, ranging from the normal complement of 10 to the null signal level of 0 (REF. 140). Conforming to the models described in this Review, they found that minor loss of signalling capacity (9–7 ITAMs) was compensated for, extreme loss of signalling (0–1 ITAMs) resulted in profound immunodeficiency, and an intermediate level of signalling capacity (6–2 ITAMs) resulted in the dual presentation of partial immunodeficiency and autoimmunity¹⁴⁰.

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DATABASES

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