

Immunological and genetic bases of new primary immunodeficiencies

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Abstract | Since 1952, when congenital agammaglobulinaemia was described by Bruton, the characterization of genetically defined immunodeficiencies in humans has been crucial for a better understanding of the biology of the innate and adaptive immune responses. This Review focuses on the characterization of new primary immunodeficiencies and disease-related genes. A series of primary defects of innate immunity have recently been discovered and are discussed here. Moreover, new defects in pre-B-cell and B-cell differentiation and antibody maturation are summarized and recently discovered monogenic immunodeficiencies that disturb the homeostasis of both the innate and the adaptive immune systems are discussed.

Toll-like receptor (TLR). A type of pattern-recognition receptor that recognizes unique structures derived from microorganisms. Signalling through TLRs promotes inflammatory immune responses, cytokine production and cell activation in response to microorganisms.

Immunological and molecular genetic approaches to determine susceptibility to infectious diseases have led to the discovery of more than 200 primary immunodeficiency diseases (PIDs) and more than 100 disease-related genes^{1,2}. In most cases, PIDs are inherited as monogenic disorders, and once the clinical and immunological phenotype is established in any given patient, existing technologies allow for the identification of the underlying genetic defect^{3,4}. PIDs are challenging for both scientists and clinicians because they represent natural models of immunopathology, which usually can be studied effectively only in animal models, and may manifest with a wide range of clinical symptoms including susceptibility to infections, allergy, autoimmune and inflammatory diseases, lymphoproliferation and cancer. Over the past decade, advances in research on PIDs have shed unexpected light on the basic mechanisms of the development and function of the immune system. The genetic defects that cause PIDs can affect the expression and function of proteins that are involved in a range of biological processes, such as immune development, effector-cell functions, signalling cascades and maintenance of immune homeostasis. In this Review, we focus on recent advances in the recognition of novel forms of PIDs and in the characterization of their molecular basis.

New primary defects of innate immunity

Innate immunity comprises a range of evolutionarily ancient mechanisms of host defence^{5,6}. The innate immune system includes phagocytic cells, dendritic cells (DCs), natural killer (NK) cells, complement proteins and many cytokines and chemokines that direct

the interaction between cells of the innate and adaptive immune systems^{5,7}. Innate recognition of pathogenic microorganisms occurs rapidly during pathogen invasion and is mediated by Fc and complement receptors, lectin receptors (such as the mannose receptor and dectin-1 receptor), Toll-like receptors (TLRs) and non-TLR receptors⁸. Innate immune receptors such as TLRs can recognize conserved pathogen-associated molecules that are shared by different microorganisms, and following engagement can trigger the production of inflammatory cytokines and chemokines through the nuclear factor- κ B (NF- κ B)-dependent and interferon (IFN)-regulatory factor (IRF)-dependent signalling pathways⁶. Along with several known PIDs with defects in innate immunity (BOX 1)^{4,9}, a series of new defects have recently been discovered.

TLR3-mediated signalling defects in HSV encephalitis.

Herpes simplex virus 1 (HSV1) is a ubiquitous pathogen that causes acute, self-limiting infections in children. Primary exposure to HSV1 infection usually results in herpetic gingivostomatitis. More rarely, patients with primary HSV1 infection can develop HSV encephalitis (HSE). Individuals who are affected by HSE are otherwise healthy and are not more susceptible to other infections. It has recently been discovered that in some patients the unique susceptibility to HSE might be inherited as a monogenic, autosomal recessive trait^{10,11}. Some of these patients carry mutations in *UNC93B1*, which encodes an endoplasmic reticulum (ER)-expressed protein that is involved in signalling through *TLR3*, *TLR7*, *TLR8* and *TLR9*, which reside in the ER and

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Box 1 | Other primary immunodeficiencies in the innate immune system

Inherited defects in myeloid cells are characterized by recurrent infections with pyogenic bacteria and fungi^{9,88,89}. Patients with severe congenital neutropaenia or cyclic neutropaenia typically suffer from pyogenic infections of the skin, mouth and rectum. Chronic granulomatous disease (CGD) is characterized by impaired activation of the NADPH oxidase activity in phagocytic cells, resulting in the inability of these cells to generate toxic oxygen radicals and hence to kill catalase-positive bacteria⁹⁰. Patients with CGD suffer from recurrent abscesses in the lymph nodes, liver, bones and joints⁸⁸. As phagocytic cells are able to move and ingest but not kill viable microorganisms in these patients, granuloma formation is common and can cause obstruction in the gastrointestinal and urinary tracts, and rectal fistulas similar to those found in Crohn's disease⁹¹.

Genetic deficiencies of nearly all the components of the complement pathway have been described⁹². The clinical expression of complement deficiencies include hereditary angioedema in patients with complement component 1 (C1) esterase deficiency, increased susceptibility to infections, and immunocomplex diseases in the case of early complement-pathway-component deficiencies. Recurrent invasive meningococcal infections can result from deficiencies of the terminal complement component (C5–C9)⁹³.

Some defects of innate immunity lead to selective susceptibility to specific pathogens, such as in epidermodysplasia verruciformis caused by mutation in the *TMC6* or *TMC8* genes (previously known as *EVER1* and *EVER2*, respectively). Patients with epidermodysplasia verruciformis have persistent infection with human papilloma viruses⁹⁴. An IL-1 receptor-associated kinase 4 (*IRAK4*) deficiency predisposes affected patients to invasive pneumococcal disease⁹, whereas defects of the interleukin-12 (IL-12)–IL-23–interferon- γ axis are associated with non-tuberculous mycobacterial infections^{21–23,95–97}.

endosomal compartments. The apparent redundancy of UNC93B for protective immunity to other viruses might reflect activation of the interleukin-1 receptor (IL-1R)-associated kinase 4 (*IRAK4*)-dependent signalling pathway by intracellular TLRs in response to other viruses (but not HSV1), resulting in the release of IFN α , IFN β and IFN λ ¹⁰.

Recently, heterozygous, dominant negative mutations in the gene that encodes TLR3 have been identified in otherwise healthy children with HSE¹¹. TLR3 is expressed in the central nervous system, where it controls the IFN response to double-stranded RNA (dsRNA) intermediates of HSV1. TLR3 is expressed by DCs and epithelial cells as well, which also use TLR3-independent pathways to produce IFNs in response to viral dsRNA, thereby justifying the resistance to other viruses in TLR3-deficient patients. The identification of *TLR3* and *UNC93B1* mutations in patients with HSE shows the essential role of TLR3-triggered, UNC93B-dependent induction of type I IFNs in response to HSV1.

Cytokine-induced JAK–STAT pathway defects in hyper-IgE syndrome. Hyper-IgE syndrome (HIES) is a severe PID that is characterized by eczema, typical facial and teeth abnormalities, elevated serum levels of IgE and recurrent pyogenic and candidal infections of the skin, lungs, lymph nodes and bones¹². Impaired IFN γ production by mononuclear cells has been reported in patients with HIES¹³. Whereas most cases of HIES are inherited as an autosomal dominant trait (AD-HIES) or represent sporadic presentations, an autosomal recessive variant (or variants) of the syndrome (AR-HIES) has also been described¹⁴, although its phenotype does not entirely overlap with

that of AD-HIES. Recently, important discoveries have shed light on the pathophysiology of HIES. Minegishi *et al.* have identified a homozygous nonsense mutation in tyrosine kinase 2 (*TYK2*), which encodes the Janus kinase (JAK) protein TYK2, in a family with AR-HIES¹⁵. TYK2 is involved in the JAK–STAT (signal transducer and activator of transcription) signalling pathway that is triggered by IFN α and IL-12. The affected patient presented with high levels of IgE, atopic-dermatitis-like skin lesions and recurrent infections with bacteria, HSV, Bacille Calmette–Guérin (BCG) and fungi. Stimulation of peripheral-blood mononuclear cells (PBMCs) from this patient with type I IFNs and IL-12 failed to induce STAT1, STAT2, STAT3 and STAT4 phosphorylation. In addition, these PBMCs did not respond to IL-6 and IL-10. The impaired T helper 1 (T_H1)-cell response that was observed correlated with the T_H2-cell phenotype that was detected *in vivo*. Although screening of other patients with AR-HIES has failed to identify other individuals who have TYK2 mutations, which indicates that there is genetic heterogeneity in patients with AR-HIES¹⁶, identification of this TYK2 deficiency has paved the way to the characterization of the molecular basis of AD-HIES.

In particular, Minegishi *et al.* were the first to describe heterozygous mutations in *STAT3* in patients with classical, multisystem HIES¹⁷. Shortly thereafter, similar findings were reported by Holland *et al.*¹⁸ The heterozygous *STAT3* mutations were permissive for protein expression and affected the DNA-binding domain^{17,18} or the SRC homology 2 (SH2) domain¹⁸ of *STAT3*, and the mutants exerted a dominant negative effect. In particular, the mutants in the DNA-binding domain did not alter the dimerization of mutant *STAT3* with wild-type *STAT3*, but severely interfered with the binding of the dimer to DNA in response to IFN α and impaired the cellular response to IL-6 and IL-10 (REF. 17). This reduced responsiveness to IL-10 might have a role in determining the hyper-IgE phenotype. In addition, *STAT3* is involved in the development of T_H17 cells¹⁹ and in IL-22 signalling, which results in the secretion of β -defensins in the skin and lungs²⁰. Defects in these pathways might cause the increased susceptibility to infections in patients with HIES.

X-linked susceptibility to mycobacterial disease. Mendelian susceptibility to mycobacterial diseases (MSMD) is characterized by recurrent and severe infections that are sustained by weakly virulent bacterial species, such as nontuberculous environmental mycobacteria and BCG, and is associated with impaired IL-12–IL-23–IFN γ -dependent innate immunity^{21–23} (FIG. 1). Germline mutations in five autosomal genes of the IL-12–IL-23–IFN γ axis were reported to cause MSMD (FIG. 1). Recently an X-linked variant of MSMD was described in three kindreds²⁴. The affected patients carried hemizygous mutations in *IKBK* (inhibitor of κ -light polypeptide gene enhancer in B cells, kinase- γ), which encodes the γ -subunit of the I κ B (inhibitor of NF- κ B) kinase (IKK) complex (also known as IKK γ and NEMO) that regulates the activation of the NF- κ B

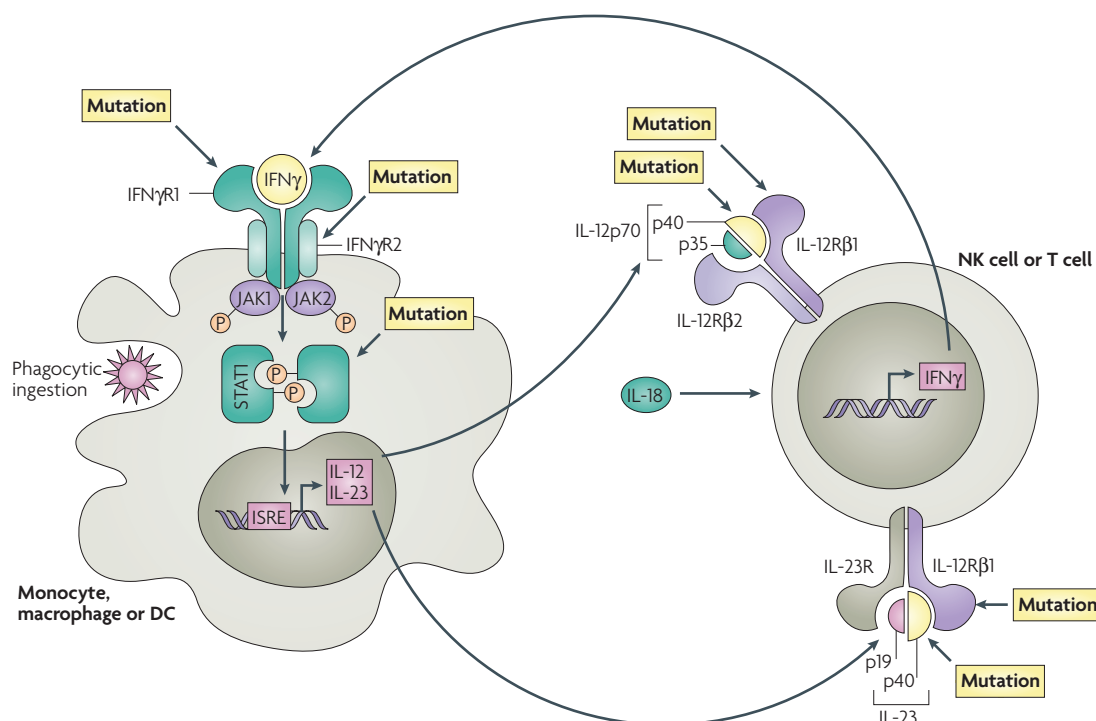


Figure 1 | The JAK–STAT pathway and its role in the regulation of innate immunity. Immune defence mechanisms against mycobacteria, salmonella and other intracellular pathogens involve monocytes and macrophages, dendritic cells (DCs), natural killer (NK) cells and T cells. Following infection with these pathogens, mononuclear phagocytes and DCs produce interleukin-12 (IL-12) and IL-23. These cytokines will then induce the production of interferon- γ (IFN γ) by NK cells, which occurs during the first 24 hours of infection, and constitute the most effective form of innate immunity against these pathogens. Next, naive T cells will preferentially develop into T helper 1 cells in the presence of IFN γ . IL-18 also induces the release of IFN γ by NK cells and T cells. IFN γ binds to its cell-surface receptor, which consists of the two heterodimeric subunits IFN γ R1 (IFN γ receptor 1) and IFN γ R2, which are coupled with Janus kinase 1 (JAK1) and JAK2. IFN γ binding results in dimerization of the two receptor subunits and phosphorylation of JAK1 and JAK2. Activated JAKs phosphorylate IFN γ R1, leading to recruitment and activation of signal transducer and activator of transcription 1 (STAT1) proteins that translocate to the nucleus and bind to responsive elements (such as IFN-stimulated response element (ISRE)) of IFN γ -inducible genes, which are then transcribed. In a large number of patients with Mendelian susceptibility to mycobacterial diseases (MSMD) the IL-12–IL-23–IFN γ axis is functionally deficient^{22,23}. Mutations in *IFNGR1*, which encodes IFN γ R1, *IFNGR2*, which encodes IFN γ R2, *IL12RB1*, which encodes the IL-12 receptor β 1-chain (IL-12R β 1), *IL12B*, which encodes the p40 subunits of IL-12 and IL-23, *STAT1*, or *IKBK*G, which encodes IKK γ (inhibitor of nuclear factor- κ B kinase- γ ; also known as NEMO; not shown) have been previously reported to cause MSMD^{22,23}. Partial forms of IFN γ R1 and IFN γ R2 deficiencies resulting from allelic heterogeneity have also been reported^{95,96}. In addition, complete forms of IFN γ R1, IFN γ R2 and IL-12R β 1 deficiencies have been found in which surface-expressed receptors failed to bind specific ligands^{97,100,101}.

signalling pathway. These mutations affect residues that are likely to form a salt bridge in the leucine-zipper domain of IKK γ . *In vitro* studies unveiled an intrinsic defect in T-cell-dependent IL-12 production by monocytes from these patients. Importantly, none of the patients displayed anhydrotic ectodermal dysplasia with immunodeficiency, which is the clinical phenotype that is most commonly associated with hypomorphic mutations in *IKBK*G in males. These studies clearly indicate a crucial role of IKK γ in protective immunity against mycobacteria in humans and demonstrate the importance of T-cell-triggered, IKK γ –NF- κ B-mediated induction of IL-12 by mononuclear phagocytes in protection against mycobacterial infection. Further research by the same group revealed that other X-linked recessive forms of MSMD may exist²¹. Linkage analysis in one large family

that includes four affected males who are maternally related identified two potential candidate regions at Xp11.4–Xp21.2 and at Xq25–Xq26.3 (REF. 25).

Severe congenital neutropaenia. Severe congenital neutropaenia (SCN) includes a heterogeneous group of PIDs that are characterized by a remarkable reduction in the number of neutrophils in the bone marrow and peripheral blood that causes recurrent and severe bacterial and fungal infections²⁶. Autosomal recessive SCN (*AR-SCN*) was first described by Rolf Kostmann more than 50 years ago in a large family from northern Sweden²⁷. An arrest in the maturation of the myeloid-cell lineage at the promyelocyte–myelocyte stage of differentiation and an increase in apoptosis of myeloid cells were found to be responsible for the low

Hypomorphic mutation

A mutation in a gene that results in reduced expression or activity of the gene without complete loss of function.

Linkage analysis

A method for tracking the transmission of genetic information across generations to identify the map location of genetic loci on the basis of co-inheritance of genetic markers and discernable phenotypes in families.

number of circulating mature neutrophils. Genetic studies have revealed that more than 50% of patients with SCN and almost all of those with cyclic neutropaenia have a dominant heterozygous mutation in *ELA2*, which encodes the neutrophil granule serine protease elastase ELA2 (REF. 28). An X-linked form of chronic neutropaenia results from activating mutations in *WASP* (Wiskott–Aldrich syndrome protein)²⁹, which causes increased actin polymerization, defective cytokinesis and mitosis, and cytogenetic abnormalities³⁰.

Recently, genome-wide linkage analysis was performed in three large Kurdish families with SCN. All the affected patients had recurrent pyogenic infections and a promyelocyte–myelocyte maturation arrest in bone-marrow cells. In all of these patients, mutational analysis unveiled a homozygous single nucleotide insertion in *HAX1*, resulting in its premature termination and a complete lack of HAX1 expression in Epstein–Barr virus (EBV)-transformed B cells was observed³¹. In addition to the four patients in the index families, 19 additional patients with SCN, including those belonging to the original pedigree described by Kostmann, were found to carry homozygous *HAX1* mutations³¹.

HAX1 is a mitochondrial protein that is involved in B-cell receptor (BCR)-mediated signalling and cytoskeletal organization^{32,33}. In addition, HAX1 has a crucial role in maintaining the inner-mitochondrial-membrane potential and protects against apoptosis³¹. Neutrophils from HAX1-deficient patients showed accelerated spontaneous and tumour-necrosis factor (TNF)-induced apoptosis compared with cells from healthy individuals. In addition, neutrophils from these patients showed a rapid dissipation of the inner-mitochondrial-membrane potential. This observation points to the involvement of mitochondrial control of apoptosis as a regulator of myeloid-cell homeostasis in humans. As HAX1 is ubiquitously expressed, it remains elusive why primary HAX1 deficiency does not appear to lead to disease manifestations in tissues, other than neutrophils.

In contrast to HAX1 deficiency, neutrophil maturation in the bone marrow is intact in patients with a hereditary deficiency in p14, an endosomal adaptor protein that is encoded by *MAPBPIP* (mitogen-activated protein (MAP)-binding protein-interacting protein)³⁴. The phenotype of primary p14 deficiency has been reported recently in four siblings from a large caucasian Mennonite family³⁴, and manifests as SCN, short stature, coarse facial features, partial albinism and recurrent respiratory-tract infections. In eukaryotic cells, p14 has been shown to be involved in MAP kinase signalling to late endosomes, and to be crucial for the normal functioning of B cells, cytotoxic T cells, neutrophils and melanocytes³⁵. Mice with a targeted deletion of *Mapbpip* are not viable, suggesting an essential role of this protein in embryonic development³⁵.

Linkage analysis and mutational studies in the family with p14 deficiency unveiled a homozygous point mutation in the 3' untranslated region of *MAPBPIP* that

accounted for decreased RNA stability and reduced protein levels, as well as for the abnormal lysosomal function in the affected individuals³⁴. Cytotoxic activity of T cells from these patients against CD95 (also known as FAS)-insensitive target cell lines was decreased, suggesting that p14 may be required for the coordinated release of the pre-stored content of cytotoxic granules. Although the phagosome–lysosome fusion, which is necessary for efficient killing of ingested microorganisms, appeared to be normal in affected individuals, cytotoxic T-cell activity was markedly reduced. Moreover, whereas neutrophils from these patients could phagocytose bacteria, a severe defect of bactericidal activity was observed. Also, the proportion of both memory and class-switched B cells was reduced, and serum IgM levels were very low in all of the patients. Importantly, the introduction of normal p14 into cultured precursors of myeloid cells isolated from these patients restored cellular morphology and bactericidal activity.

So, characterization of this subgroup of individuals with SCN has revealed a previously unrecognized role for p14 in regulating the subcellular localization of late endosomes and lysosomes. Combined defects of pigmentation and immune function (which are features of primary p14 deficiency) have also been previously described in patients with Chediak–Higashi syndrome³⁶, Griscelli syndrome type 2 (REF. 37) and Hermansky–Pudlak syndrome type 2 (REF. 38). These PIDs are caused by defects in proteins that are involved in regulating intracellular protein trafficking and cytoplasmic organelle movement.

Altogether, these studies have illustrated the complexity of biological mechanisms that are involved in myeloid-cell homeostasis, from the regulation of apoptosis to correct intracellular protein trafficking and sorting to granules, to the regulation of cytokinesis.

Leukocyte adhesion deficiency type III. The inflammatory response is highly dependent on the appropriate recruitment of leukocytes to specific target sites. This process requires extravasation of circulating white blood cells, in particular, neutrophils. Several different proteins mediate the interaction between circulating leukocytes and endothelial cells. For example, the interaction between sialyl-Lewis X (a fucose-containing protein that is expressed by leukocytes) and selectins (expressed by endothelial cells) mediates leukocyte rolling, whereas firm adhesion involves the binding of β_2 -integrins (expressed on the surface of leukocytes) to intracellular adhesion molecule 1 (ICAM1) and ICAM2 expressed by endothelial cells at sites of inflammation. In addition, the interaction of chemokines with appropriate chemokine receptors on the surface of leukocytes results in the activation and conformational modification of β_2 -integrins that can then bind their ligands with higher affinity.

Defects in the expression of β_2 -integrins and fucose-containing proteins account for leukocyte adhesion deficiency type I (LAD-I) and LAD-II, respectively. More recently, a third form of LAD (LAD-III) has been reported³⁹, in which integrin expression by leukocytes

Chediak–Higashi syndrome

An autosomal recessive disorder characterized by oculocutaneous albinism, recurrent infections, neurological abnormalities, neutrophil chemotactic defects and giant cytoplasmic granules. The lysosomal trafficking regulator (*LYST*) gene of as yet poorly defined function, is mutated in this syndrome.

Griscelli syndrome type 2

An autosomal recessive disorder characterized by partial albinism, silvery grey hair, variable cellular immunodeficiency, recurrent infections and an accelerated phase.

Hermansky–Pudlak syndrome type 2

An autosomal recessive disorder characterized by oculocutaneous albinism, platelet dysfunction and bleeding tendency, neutropaenia and impaired cytotoxic activity.

is normal, but the integrins fail to generate high avidity for their cognate endothelial-cell ligands. In addition, patients with LAD-III also suffer from severe and recurrent bleeding, indicating a defect in the function of platelet $\alpha_{IIb}\beta_3$ -integrin, the main fibrinogen receptor.

Integrin activation in response to a range of stimuli is known to involve the small GTPase RAP1 (RAS-related protein 1). Activation of RAP1 is defective in patients with LAD-III. Through the analysis of two patients of Turkish origin, both born to consanguineous parents, it has recently been shown that LAD-III results from mutations in RAS guanyl-releasing protein 2 (*RASGRP2*, also known as *CALDAG-GEF1*). *RASGRP2* is a key RAP1 and RAP2 guanine-nucleotide-exchange factor⁴⁰. Both patients shared the same homozygous splice-site mutation that resulted in aberrant splicing and lack of protein expression. As a result of *RASGRP2* mutations, functional abnormalities have been detected in the ability of neutrophils and T cells from these patients to bind ICAM1 expressed by endothelial cells and therefore to arrest in response to chemokines. The analysis of this unique group of patients, therefore, has disclosed a crucial role for *RASGRP2* in the regulation of integrin activation by inside-out signalling in human haematopoietic cells.

Primary defects in B-cell development

B-cell deficiencies represent the most common type of PIDs in humans (BOX 2). Starting from 4–6 months of life, in parallel with the decrease of maternally acquired IgG, patients suffer from recurrent bacterial infections unless they receive regular immunoglobulin-replacement therapy. Several genetic defects have been shown to compromise the antigen-independent or antigen-dependent stages of B-cell development in humans (FIG. 2).

Primary immunoglobulin deficiency. Two reports have recently described mutations in *B29*, which encodes Ig β (also known as CD79b, and is a component of the pre-BCR signalling complex) in patients with congenital agammaglobulinaemia^{41,42}. In one case, a homozygous nucleotide substitution in *B29* results in a stop codon in the extracellular immunoglobulin domain, preventing the expression of the functional protein and interfering with the assembly of the pre-BCR complex on the cell surface⁴¹. Accordingly, transfection studies to reconstruct the BCR complex in *Drosophila melanogaster* Schneider-2 (S2) cells showed that, in contrast to the wild-type protein, mutant Ig β failed to promote expression of the BCR complex on the cell surface⁴¹. Examination of B-cell development in the bone marrow of the Ig β -deficient patient showed an arrest at the pro- to pre-B-cell stage, as has been observed in other known forms of agammaglobulinaemia⁴¹. In the other patient, a homozygous glycine-to-serine substitution at codon 137 resulted in inefficient formation of the disulphide bond between Ig α and Ig β , and in markedly reduced export of the μ heavy (μ H) chain to the cell surface⁴². Immunological leakiness in this patient was associated with a low, but detectable, number of CD19⁺ B cells in the circulation⁴².

Primary CD19 deficiency. During mammalian B-cell development CD19 expression begins at the pro-B-cell stage⁴³ and is maintained on the surface of B cells until they differentiate into plasma cells. CD19 is expressed in a molecular complex with CD21, CD81 and CD225. This group of surface molecules, which is also referred to as the CD19 complex, signals in conjunction with the BCR and may lower the threshold for antigen stimulation of B cells through the BCR⁴⁴. Further insight into the biology of the CD19 complex was provided by the characterization of four patients from two unrelated families who had homozygous mutations in the *CD19* gene⁴⁵, and shared increased susceptibility to infections, hypogammaglobulinaemia and poor antibody responses, but had a normal number of circulating CD20⁺ mature B cells. Surface expression of CD19 was either undetectable or barely detectable in these patients, and the levels of CD21 were decreased. By contrast, CD81 and CD225 were normally expressed. Calcium flux and proliferation in response to BCR crosslinking were also defective, and the number of both unswitched and switched memory B cells (CD27⁺IgD⁺ and CD27⁺IgD⁻ cells, respectively) was decreased. These data indicate that CD19 is dispensable for B-cell development, but is required for differentiation into memory and plasma cells, and for normal antibody responses to antigens and immunoglobulin production.

Class-switch recombination and antibody-maturation defects. Terminal B-cell differentiation and antibody maturation take place in the germinal centres of secondary lymphoid organs. Maturation of the antibody response of B cells includes class-switch recombination (CSR) and somatic hypermutation (SHM) that ultimately allows for positive selection of B cells that express high-affinity antibody to the antigen. Defects in CSR is the hallmark of the hyper-IgM (HIGM) syndrome phenotype that is characterized by normal or elevated levels of serum IgM and decreased or undetectable levels of serum IgG, IgA and IgE^{46,47}. In a subgroup of patients with HIGM syndrome, defective CSR is associated with impaired SHM⁴⁷.

Interaction between CD40 ligand (CD40L; also known as CD154), which is expressed on the surface of activated CD4⁺ T cells, and CD40, which is constitutively expressed by B cells, is a crucial event in the induction of CSR and SHM during the antibody response to T-cell-dependent antigens⁴⁸. Mutations in *CD40L* and *CD40* cause X-linked and autosomal recessive forms of HIGM, respectively^{49,50}.

CD40 crosslinking leads to activation of the NF- κ B signalling pathway. Another form of X-linked HIGM that is associated with anhydrotic ectodermal dysplasia is caused by hypomorphic mutations in the gene that encodes IKK γ ⁵¹. Null mutations in this gene are lethal in human males and cause incontinentia pigmenti in heterozygous females⁵². Patients with CD40L, CD40 or IKK γ deficiency suffer not only from bacterial infections but also from opportunistic infections, reflecting a defect in T-cell priming owing to the impaired CD40L–CD40 crosstalk between activated T cells and CD40-expressing DCs and macrophages.

Inside-out signalling

The process by which intracellular signalling mechanisms result in the activation of a cell-surface receptor, such as integrins. By contrast, outside-in signalling is the process by which ligation of a cell-surface receptor activates signalling pathways inside the cell.

Class-switch recombination

(CSR). This process alters the immunoglobulin heavy chain (H) constant (C)-region gene that is expressed by B cells from C μ to one of the other C μ genes. This results in a switch of immunoglobulin isotype from IgM/IgD to IgG, IgA or IgE, without altering antigen specificity.

Somatic hypermutation

(SHM). A unique mutation mechanism that is targeted to the variable regions of rearranged immunoglobulin gene segments. Combined with selection for B cells that produce high-affinity antibody, SHM leads to affinity maturation of B cells in germinal centres.

Box 2 | Other primary immunodeficiencies associated with lymphocytes

Primary immunodeficiencies that are associated with inherited defects in B or T cells can result in deficiencies in antibody production, cellular immunity, or both⁹⁸. Patients with B-cell deficiencies either lack B cells or have deficiencies in B-cell function (humoral or antibody deficiencies), and usually develop infections with encapsulated pyogenic bacteria that require opsonization for phagocytic ingestion, such as *Haemophilus influenzae* type b and *Streptococcus pneumoniae*. These patients may also acquire infections with *Staphylococcus aureus*, Gram-negative bacteria and the parasite *Giardia lamblia*⁹⁹.

Severe viral infections are rare, but patients with X-linked agammaglobulinaemia (XLA) have a unique susceptibility to meningoencephalitis or dermatomyositis-like syndrome owing to infection with enteroviruses. In patients with XLA, which is the prototype of B-cell deficiencies, lymph nodes are very small. In addition, the concentration of all immunoglobulin isotypes are very low, and circulating B cells are either absent or present in negligible numbers in such patients. By contrast, lymphoid tissues are often enlarged in autosomal recessive hyper-IgM (HIGM) syndrome owing to activation-induced cytidine deaminase (AID) deficiency^{47,54}. Growth and development are normal in most children with B-cell deficiencies, provided that they receive regular immunoglobulin-replacement therapy.

Patients with T-cell immunodeficiencies are highly susceptible to infections with opportunistic pathogens, such as *Pseudomonas jiroveci*, *Candida albicans*, herpesviruses, adenovirus, parainfluenzae virus type 3 and non-virulent mycobacteria³. Haematopoietic stem-cell transplantation is the mainstay of treatment for most patients with severe T-cell defects.

Microhomology

The presence of short stretches of homologous nucleotides that flank DNA double-strand breaks (DSBs). The presence of such sequences favours the alignment of DNA ends and DNA repair through microhomology-mediated end-joining (MMEJ), a mechanism that is less dependent on Ku proteins than non-homologous end-joining (NHEJ). MMEJ might function as a salvage pathway for DNA DSBs that cannot be repaired by NHEJ.

Non-homologous end-joining

(NHEJ). A pathway that rejoins DNA strand breaks without relying on significant homology. The main known pathway uses the Ku-end binding complex and is regulated by DNA protein kinase. The pathway is often used in mammalian cells to repair strand breaks caused by DNA-damaging agents, and some of the same enzymes are used during the strand-joining steps of V(D)J recombination.

Holliday junction

A point at which the strands of two double-strand DNA molecules exchange partners, which occurs as an intermediate during genetic recombination.

Activation-induced cytidine deaminase (AID), which is encoded by *AICDA*, is a protein that is selectively expressed by germinal-centre B cells. AID has a unique functional activity: it initiates both CSR and SHM by deaminating DNA cytosine residues to uracil within the switch (S) and the variable (V) regions of immunoglobulin genes⁵³. The resulting mismatch that is generated between the two opposite DNA strands is resolved by uracil-DNA glycosylase (UNG), an enzyme that removes uracil from DNA. Subsequently, the abasic site is cleaved by a DNA endonuclease. This results in the generation of DNA double-strand breaks at the S and V regions that are eventually resolved by the integrated activity of several DNA repair proteins⁴⁶.

Mutations in *AICDA* result in severe defects in both CSR and SHM⁵⁴. Accordingly, these patients suffer from recurrent bacterial infections. In addition, they show prominent lymphoid hyperplasia. UNG deficiency also results in impaired CSR. In these patients, SHM is preserved, but is characterized by a large excess of transitions versus transversions at G–C residues⁵⁵.

A severe CSR defect was also identified in a group of patients who do not have mutations in *AICDA* and UNG or impaired CD40L–CD40 coupling⁵⁶. In this new form of HIGM syndrome, a block in CSR downstream from the DNA double-strand breaks in the S regions was identified, suggesting a defect in DNA repair⁵⁶. It has been shown that this condition is characterized by increased cellular radiosensitivity and abnormal formation of S junctions, with increased use of microhomology⁵⁷. No defects have been identified in any of the known genes that are involved in non-homologous end-joining (NHEJ) DNA repair, suggesting that the disease is caused by a defect (or defects) of an as yet unknown gene (or genes) of the DNA-repair pathway.

Defective DNA repair might also have a role in common variable immunodeficiency (CVID) and in IgA deficiency (IgAD), the most common forms of humoral antibody deficiencies in humans. In particular, genetic variations in *MSH5*, which encodes the mismatch repair protein MSH5, have recently been shown to be associated with CVID and IgAD in a large cohort of patients⁵⁸. Interestingly, *MSH5* maps to the HLA class III region and linkage to this region has been shown in families with CVID and IgAD. MSH5 is known to form heterodimers with MSH4, and has a crucial role in resolving Holliday junctions that are formed between homologous DNA strands during meiosis⁵⁹. It has been hypothesized that the MSH4–MSH5 heterodimer may have a similar role during the intrachromosomal synapsis of S_{μ} to downstream target S_x sequences, and facilitates the recruitment of proteins required for NHEJ DNA repair⁵⁸. In keeping with this observation, a high proportion of congenic MRL–*lpr* mice carrying a hypomorphic *MSH5* allele showed reduced levels of serum IgG3, and increased use of long stretches of microhomology at immunoglobulin S junctions⁵⁸. Interestingly, increased microhomology and lower mutation rates were also observed in CVID patients carrying disease-associated *MSH5* alleles⁵⁸. This might account for the low-affinity antibody responses in CVID.

SCID due to impaired calcium flux

Severe combined immunodeficiency (SCID) comprises a heterogeneous group of monogenic disorders that result in early-onset severe infections by a range of pathogens (such as bacteria, viruses and fungi). Over 20 different genetic defects have been identified that account for SCID in humans^{3,4}. Typically, patients with SCID have a severe defect in T-cell differentiation, along with direct or indirect impairment of B-cell development and function. However, a few patients with SCID have been described in whom T-cell development is apparently unaffected, but whose peripheral T cells fail to proliferate in response to activation stimuli and show defective nuclear translocation of nuclear factor of activated T cells (NFAT) as a result of defective Ca^{2+} signalling⁶⁰. One of the earliest events following T-cell receptor (TCR) crosslinking is the activation of phospholipase C γ (PLC γ), which generates inositol-1,4,5-trisphosphate that releases Ca^{2+} that is stored in the ER. This triggers Ca^{2+} influx by opening the calcium-regulated activated calcium (CRAC) channels on the cell membrane⁶¹. However, the molecular identity of CRAC channels has remained obscure until recently. Feske *et al.* studied a family with SCID caused by defective Ca^{2+} flux and identified the disease-causing locus at chromosome 12q24 using an elegant approach⁶². This involved unequivocal identification of heterozygous family members (who showed intermediate Ca^{2+} -flux responses), followed by whole-genome linkage analysis. In parallel, a genome-wide RNA interference screen for NFAT regulators was conducted in *D. melanogaster*, taking into account that the pathways that regulate the shuttling of NFAT are highly conserved in

different species. Two potential candidates were identified by this method that interfered with the activation of store-operated Ca^{2+} entry and NFAT translocation: *D. melanogaster* stromal interaction molecule (*Stim*) (*dStim*) and *D. melanogaster* *Orai* (*dOrai*). A human homologue for *dOrai* (*ORAI1*) that mapped at

chromosome 12q24 was found. Homozygosity for a non-conservative amino-acid change in the first of four potential transmembrane domains of *ORAI1* was identified in the affected patients with SCID. Subsequently, the same group identified *ORAI1* as an essential component of the CRAC channel⁶³.

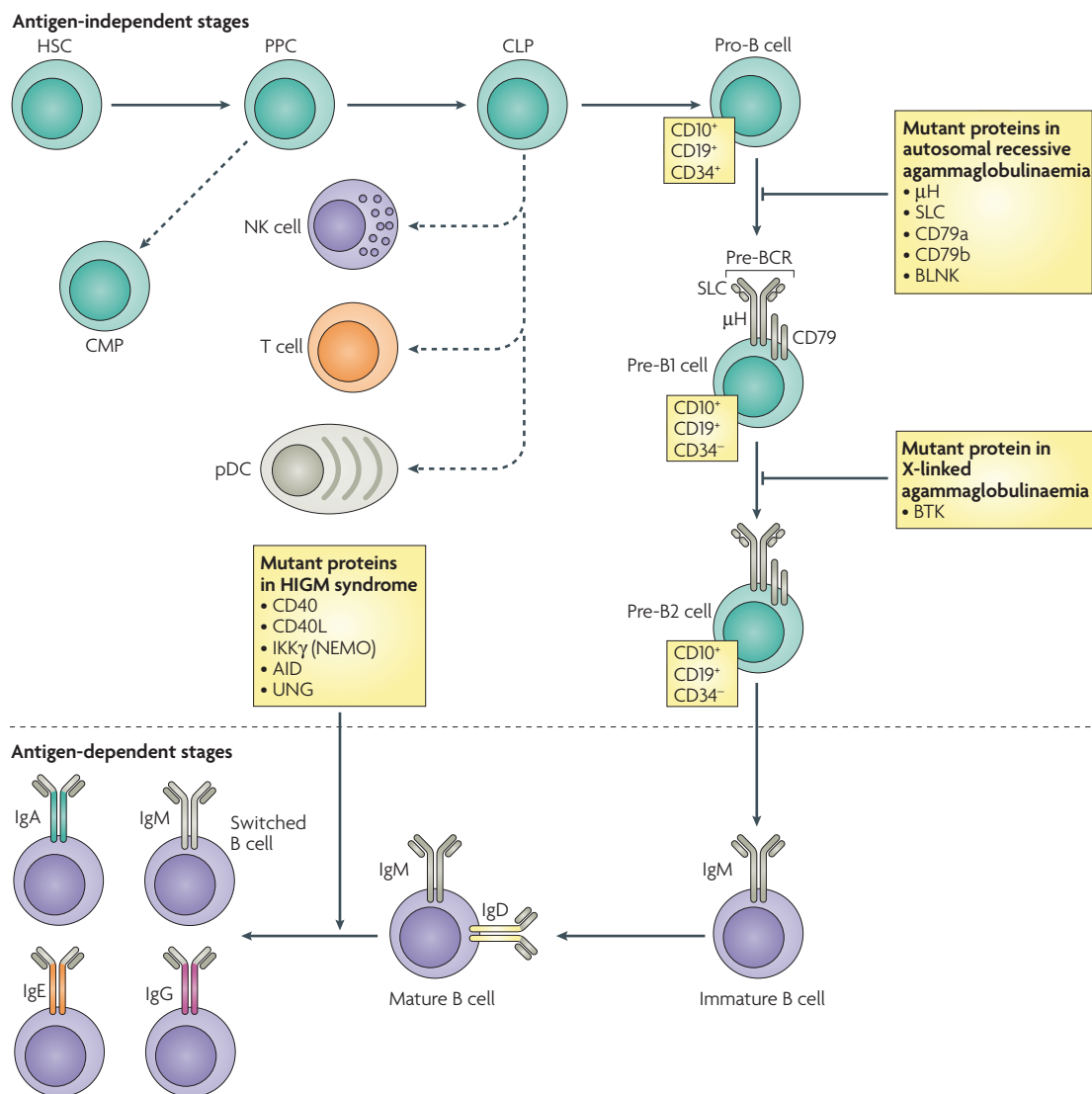


Figure 2 | Human B-cell development and primary antibody deficiencies. Haematopoietic stem cells (HSCs) with self-renewing capacity give rise to pluripotent progenitor cells (PPCs) that can differentiate into common myeloid progenitors (CMPs) or common lymphoid progenitors (CLPs). CLPs progress to B-cell-restricted precursors, in addition to giving rise to T cells, natural killer (NK) cells and plasmacytoid dendritic cells (pDCs). B-cell-lineage-restricted cells then pass through a CD10⁺CD19⁺CD34⁺ pro-B-cell developmental stage. Pro-B cells differentiate into CD10⁺CD19⁺CD34⁻ pre-B cells that express the membrane μ H chain associated with the λ 5/14.1 surrogate light chain (SLC) and the CD79a (Ig α) and CD79b (Ig β) signalling molecules to form the pre-B-cell receptor (pre-BCR). Mutations in components of the pre-BCR and in B-cell linker (BLNK) results in autosomal recessive agammaglobulinaemia with no mature B cells in the periphery. Defects in the B-cell signalling pathway mediated by Bruton's tyrosine kinase (BTK) lead to X-linked agammaglobulinaemia. In peripheral lymphoid tissues, mature naive B cells bearing both IgM and IgD undergo class-switch recombination and somatic hypermutation following stimulation by activated T cells, and give rise to memory B cells and plasma cells (switched B cells). Failure of T cells to deliver appropriate signals to B cells (through CD40 and CD40 ligand (CD40L)), or intrinsic B-cell deficiencies can affect maturation of the antibody response and result in hyper-IgM (HIGM) syndrome^{41–47,99}. IKK γ , inhibitor of nuclear factor- κ B kinase- γ ; AID, activation-induced cytidine deaminase; UNG, uracil-DNA glycosylase.

Intrachromosomal synapsis

The pairing of homologous chromosomes along their length. Synapsis usually occurs during prophase I of meiosis, but it can also occur in somatic cells of some organisms.

MRL-*lpr* mouse

A mouse strain that spontaneously develops glomerulonephritis and other symptoms of systemic lupus erythematosus (SLE). The *lpr* mutation causes a defect in CD95 (also known as FAS), preventing apoptosis of activated lymphocytes. The MRL strain contributes disease-associated mutations that have yet to be identified.

Primary defects in immunoregulation

In the last few years, an increasing number of monogenic diseases have been identified that disturb the homeostasis of both the innate and adaptive immune systems^{4,64}.

X-linked lymphoproliferative syndromes. A group of genetically determined PIDs can lead to defective regulation of the immune response resulting in susceptibility to particular infections, autoimmunity, haemophagocytic lymphohistiocytosis and lymphomas^{64–68}. X-linked lymphoproliferative syndrome 1 (XLP1) is characterized by a unique vulnerability to infection by EBV^{65,67} (FIG. 3). Patients with XLP1 have subtle defects in T-cell- and NK-cell-mediated cytotoxicity, a depletion of NKT cells, impaired IgG class switching, and they are unable to generate EBV-specific IgG antibodies. Mutations in *SH2D1A* (SH2 domain protein 1A), which is located at Xq25 and encodes the adaptor protein signalling lymphocyte activation molecule (SLAM)-associated protein (SAP), were identified as being responsible for XLP1 (REF. 67). However, as many as 20–40% of patients with XLP1 show normal expression of SAP, and have no mutations in *SH2D1A*.

A new form of XLP, designated XLP2, has been recently reported to be caused by mutations in *BIRC4*, which encodes the X-linked inhibitor of apoptosis protein (XIAP)⁶⁸. Apoptosis of lymphocytes from patients with XIAP deficiency was enhanced in response to various stimuli, including crosslinking of CD3, CD95 and TNF-associated apoptosis-inducing ligand receptor (TRAILR). Similar to patients with XLP1, patients with XIAP deficiency have severely reduced numbers of NKT cells, indicating that both SAP and XIAP are required for normal differentiation and function of these cells⁶⁸.

In spite of this, the pathophysiology of XLP2 remains largely obscure. In particular, it is difficult to explain how the increased apoptotic phenotype of patients with XLP2 could account for the lymphoproliferation observed *in vivo*. It has been speculated that deficiency of XIAP might also affect other signalling pathways that are unrelated to apoptosis, such as transforming growth factor- β (TGF β), NF- κ B, JUN N-terminal kinase (JNK), protein kinase B (also known as AKT) and copper-metabolism pathways⁶⁸.

Autoimmune lymphoproliferative syndrome. Autoimmune lymphoproliferative syndrome (ALPS) is characterized by chronic non-malignant lymphadenopathy and hepatosplenomegaly resulting from impaired lymphocyte apoptosis that leads to the gradual accumulation of non-malignant lymphocytes^{69–72}. Autoimmune manifestations, including Coombs-positive haemolytic anaemia, immune thrombocytopaenic purpura, neutropaenia, vasculitis and glomerulonephritis, are common. In addition, patients with ALPS have hypergammaglobulinaemia and an expansion of circulating polyclonal CD4⁺CD8[−] (double negative) TCR $\alpha\beta$ ⁺ T cells. Mutations in several genes that are involved in programmed cell death and CD95-mediated apoptosis may cause ALPS. According to the genotype, ALPS can be classified as type Ia, type Ib or type II, based on germline mutations in the genes

encoding *CD95* (*TNFRSF6*), *CD95L* (*TNFSF6*) or *cas-pase-10* (*CASP10*), respectively⁶⁹. In some patients with ALPS, somatic mutations in the gene encoding CD95 were detected, accounting for a variant disease designated type Im (mosaic)⁷⁰. A large number of patients with ALPS have no detectable mutation in the CD95-mediated apoptosis pathway, which is classified as the type III form of the disease.

Whereas mutations in CD95 are a relatively common cause of ALPS, until recently, mutations in the gene encoding CD95L had only been identified in a patient with systemic lupus erythematosus. In 2006, the first patient with ALPS caused by a homozygous mutation in the gene encoding CD95L was reported⁷³. T-cell blasts from this patient failed to induce apoptosis in a CD95-transfected mouse target-cell line; furthermore, CD95-dependent cytotoxicity was markedly reduced in Chinese hamster ovary cells transfected with the mutant CD95L. The mutation resulted in a single amino-acid change in the extracellular domain of CD95L, but did not affect protein expression. However, the homozygous CD95L mutation interfered with the induction of BCL2-interacting mediator of cell death (BIM) by CD95 (REF. 74).

The genes that encode RAS proteins are a subfamily of oncogenes and proto-oncogenes that have a role in the transduction of growth signals, cell proliferation and apoptosis^{75,76}. Somatic mutation in the genes encoding RAS proteins are frequent in patients with cancer, and germline mutations in the RAS-encoding genes *HRAS* and *KRAS* cause Noonan syndrome and Costello syndrome, respectively^{77,78}. In a search for new disease-related genes in patients with type III ALPS, an activating *NRAS* mutation was found in association with a unique defect in IL-2-withdrawal-induced apoptosis in an adult patient who had typical manifestations of ALPS since childhood, and who had been treated for leukaemia and lymphoma⁷⁹. A selective decrease of the levels of pro-apoptotic BIM activation was proposed to contribute to the defect in apoptosis in this form of ALPS. This study suggests that gain-of-function mutations in the *NRAS* oncogene may not impair CD95-mediated apoptosis under physiological conditions. Furthermore, it suggests that, in contrast to *HRAS* and *KRAS* mutations, a germline-activating mutation in *NRAS* may result in chronic benign lymphoproliferation, similar to that which occurs in type III ALPS. Defective IL-2-withdrawal-induced apoptosis of peripheral-blood mononuclear cells appears to be a unique immune abnormality in type III ALPS, which helps to differentiate it from other known forms of the disease.

Autosomal recessive IPEX-like syndrome. CD25 (also known as the α -chain of IL-2R) deficiency was first described in an infant with massive lymphocyte infiltration in the lungs, liver, spleen, lymph nodes and bone marrow, and poor T-cell responses to stimulation by CD3-specific antibodies, phytohaemagglutinin and IL-2 (REF. 80); a second case of CD25 deficiency has recently been reported⁸¹. The affected patient in the first description of the syndrome was a compound heterozygote for a nonsense mutation and a single-base insertion, and his

Immune thrombocytopaenic purpura

An acute-onset thrombocytopaenia caused by autoantibodies directed against unknown antigens on the platelet surface. Antibody-coated platelets are recognized and eliminated from the circulation by splenic macrophages. Immune thrombocytopaenic purpura usually develops 2–4 weeks after exposure to common viral pathogens, including Epstein–Barr virus and HIV.

Noonan syndrome

A developmental disorder characterized by short stature, facial dysmorphisms, congenital heart defects and skeletal anomalies.

Costello syndrome

An autosomal dominant disorder comprising growth deficiency, mental retardation, curly hair, coarse facial features, nasal papillomata, low-set ears with large lobes, cardiac anomalies, redundant skin on palms and soles with prominent creases, dark skin and propensity to certain solid tumours. *HRAS* mutations have been implicated in approximately 85% of the affected cases.

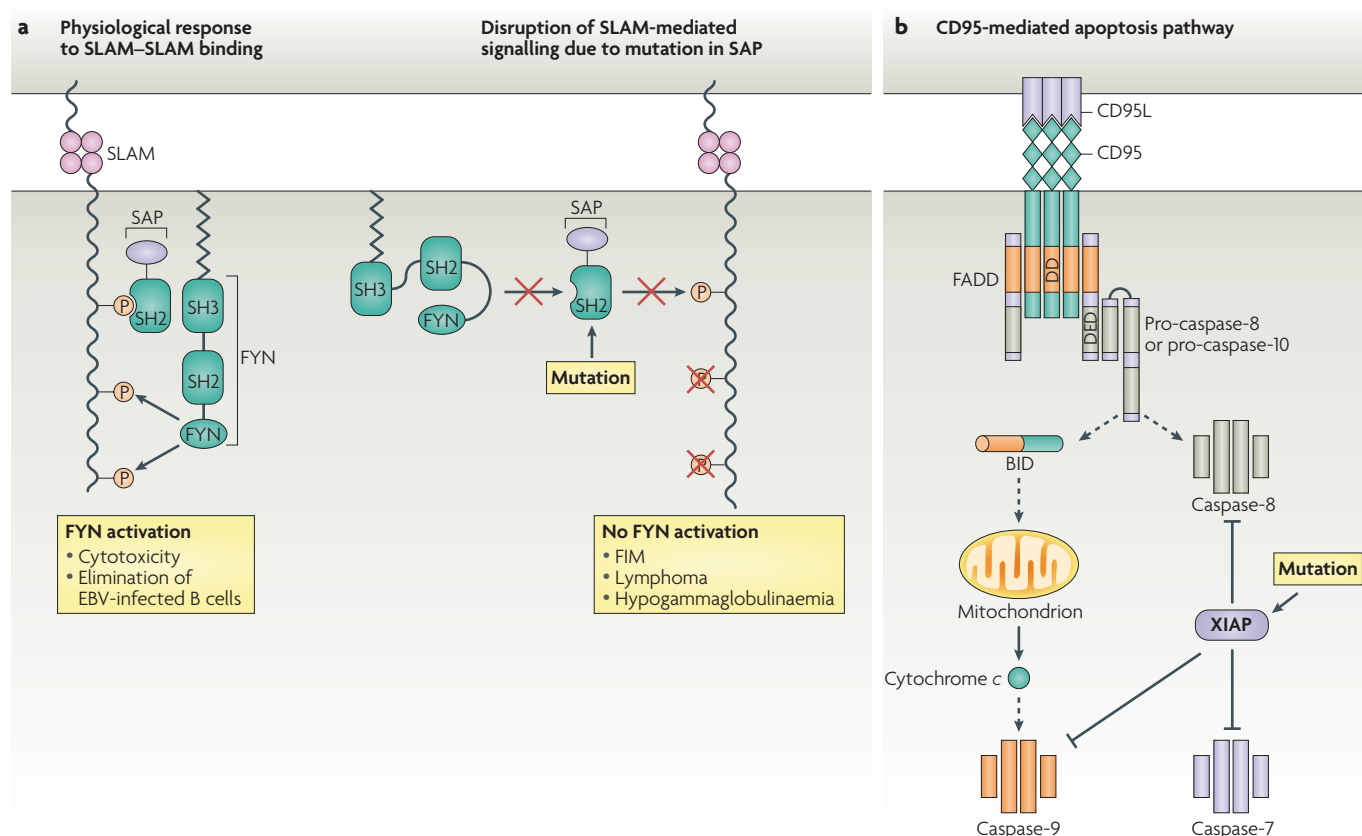


Figure 3 | Models for the pathophysiology of X-linked lymphoproliferative disease 1 (XLP1) and XLP2. Mutations in signalling lymphocyte activation molecule (SLAM)-associated protein (SAP) and X-linked inhibitor of apoptosis (XIAP) cause XLP1 and XLP2, respectively. **a** | SLAM, which is expressed by T cells, natural killer (NK) cells, B cells, dendritic cells and macrophages, is a homotypic immune receptor that interacts with SLAM expressed by other cell types¹⁰². Following a SLAM-SLAM interaction, SAP couples the cytoplasmic tail of SLAM (or other SLAM-like receptors) to the SRC-related FYN tyrosine kinase (panel **a**, left). SAP is composed almost exclusively of an SRC homology 2 (SH2) domain that preferentially recognizes tyrosine-based motifs of SLAM¹⁰³. SAP-binding initiates the activation of FYN and phosphorylation of additional tyrosine residues of SLAM. A germline mutation in SAP will disrupt the activation of FYN and signalling through SLAM and other SLAM family members (panel **a**, right). SAP is involved in T- and NK-cell cytotoxicity; in addition, signalling through SLAM induces inducible T-cell co-stimulator (ICOS) expression in follicular T helper cells. This contributes to the complex clinical phenotype observed in XLP1, which includes fatal infectious mononucleosis (FIM), high susceptibility to lymphoma, and hypogammaglobulinaemia. **b** | Apoptosis is mediated, in part, by the binding of CD95 ligand (CD95L) to CD95 (also known as FAS), which in turn recruits the adaptor protein FAS-associated death domain (FADD) through its death domain (DD). FADD then recruits pro-caspase-8 and pro-caspase-10 through its death effector domain (DED) to form the death-inducing signalling complex⁹⁹. Release of highly active caspase-8 causes the death of the cell, which is augmented by caspase-8 processing of BH3-interacting-domain death agonist (BID). The active form of BID induces cytochrome c release from the mitochondrion. XIAP can suppress apoptosis by interacting with caspases through its baculoviral inhibitory repeat (BIR) domain^{68,102,103}. EBV, Epstein-Barr virus.

peripheral lymphocytes failed to express CD25 following activation *in vitro*. The clinical phenotype was remarkable for its similarity to that observed in immunodysregulation, polyendocrinopathy and enteropathy, X-linked (IPEX) syndrome, which is caused by mutations in forkhead box P3 (FOXP3; a regulatory T-lineage specification factor)⁸². When activated *in vitro* with CD3- and CD46-specific antibodies, the CD4⁺ T cells from the patient failed to produce IL-10, a cytokine with important immunosuppressive properties. Another similar case of IPEX-like syndrome owing to nonsense mutations in CD25 has been recently identified (A. H. Filipovich and J. Sümegi, personal communication). In both cases, CD4⁺FOXP3⁺ T cells were present in normal numbers, indicating that

CD25 expression is not required for the development of FOXP3⁺ regulatory T cells. These data are in agreement with previous observations in gene-targeted mice⁸³. These intriguing cases suggest that much remains to be learned about the pathophysiology of PIDs that present with lymphoproliferation and autoimmunity, and are caused by an imbalance of positive and negative signals of immune activation owing to mutations in genes that encode regulatory components of the immune system⁸⁴.

Hepatic veno-occlusive disease with immunodeficiency. Hepatic veno-occlusive disease (VOD) is characterized by hepatic vascular occlusion and fibrosis. Most often, VOD follows haematopoietic-cell transplantation and

results from toxic damage to the endothelium in hepatic sinusoids, with clinical symptoms of hepatomegaly, ascites and jaundice⁸⁵. Hepatic VOD with immunodeficiency (VODI) is a rare condition in which VOD is associated with lymphopaenia, severe hypogammaglobulinaemia, increased occurrence of opportunistic infections and a reduced number of memory T and B cells. It has been recently shown that VODI results from mutations in *SP110*, which encodes one of the PML nuclear-body proteins⁸⁶. SP110 is an immunoregulatory protein that is expressed by T and B cells in the lymph nodes, spleen and liver. Intracellular expression of various cytokines, including IFN γ , IL-2, IL-4 and IL-10, following *in vitro* stimulation of cells from patients with VODI with phorbol 12-myristate 13-acetate and ionomycin were reduced to a variable extent compared with cells from healthy individuals.

Conclusions

Identification of the genetic basis of PIDs has provided better diagnostic and therapeutic opportunities, and has also increased our knowledge of the molecular pathophysiology of the immune system. As compared with gene-targeted mice and other animal models, the study of humans with PIDs continues to offer unique opportunities. Different mutations within single genes can manifest with different phenotypes. For example, mutations in *WASP* may cause Wiskott–Aldrich syndrome or X-linked neutropaenia. In the case of genes in which null mutations in mice are embryonically or perinatally lethal, hypomorphic

mutations detected in humans can lead to a distinct phenotype, as illustrated by neutropaenia owing to p14 deficiency. Dominant negative mutations may interfere with the function of the protein and lead to abnormal intracellular signalling, as in HIES owing to *STAT3* mutations. Finally, the spectrum of microorganisms that can colonize or infect the human body (and the conditions under which such interactions occur) vary from what is observed in mice. Not surprisingly, several forms of PID have been shown to result in unique and ‘narrow’ susceptibility to pathogens, as illustrated by familial HSE and MSMD.

Ultimately, unveiling the genetic basis of an inherited monogenic immunodeficiency disorder not only allows physicians to identify the disease-related mutation in the proband, but provides the opportunity for family screening and prenatal diagnosis. Furthermore, identification of disease-causing genes might provide a solid basis for immunotherapy of PIDs. This is exemplified by the recognition that *UNC93B1* mutations may be associated with an impaired secretion of type 1 IFN in patients with HSE, suggesting that administration of IFN α and/or IFN β might be effective in treating patients with this encephalitis. Yet, in spite of this progress, many patients with PIDs remain undiagnosed owing to inadequate recognition or lack of appropriate diagnostic tools. Awareness campaigns in the professional and lay community should therefore continue for the benefit of patients with PIDs, in particular in countries with lower socio-economic conditions, including those in eastern Europe⁸⁷.

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DATABASES

Entrez Gene: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene>
 AICDA1|B29|caspase-10|CD19|CD40|CD40L|CD95|CD95L|EL2|HAX1|IFNA|IFNB|IFNG|IKBKKG|FOX P3|IRAK4|MSH5|RASGRP2|SH2D1A|SP110|STAT3|TLR3|TLR7|TLR8|TLR9|TYK2|UNC93B1|WASP
OMIM: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>
 AD-HIES|AID|ALPS|AR-HIES|AR-SCN|CVID|HIGM|HSE|IgAD|IPEX|VOD|XLP1

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