Immunodeficiency, Primary: Affecting the Adaptive Immune System

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Primary immunodeficiency (PID) is an intrinsic defect of the immune system. Patients with PID have increased susceptibility to recurrent and persistent infections, but other symptoms are also common.

Introduction

Adaptive immune mechanisms recognize and neutralize foreign molecules or microorganisms in a specific manner. Lymphocytes, B and T cells, can respond specifically to thousands of nonself materials. Adaptation is further acquired with memory of previous infections. Immunodeficiencies impair the functioning of the immune system. Deficiencies are highly variable with regard to symptoms, phenotype, genotype, severity, etc. because many cells and molecules are required for both natural and adaptive immunity. However, increased susceptibility to infection is common to all immunodeficiencies. See also: Cells of the immune system; Immunodeficiency; Immune system

Close to 150 primary immune deficiencies (PIDs) are now known, and have been grouped according to the components of the immune system affected (International Union of Immunological Societies, 1999; Buckley, 2000; Bonilla and Geha, 2003; ImmunoDeficiency Resource). Most PIDs are relatively rare disorders. Antibody deficiency disorders are defects in immunoglobulin-producing B cells (Table 1). T cells, which are responsible for killing infected cells or helping other immune cells, can also be targets for immunodeficiency disorders. These disorders usually result in combined immune deficiencies (CIDs), where both T cells and antibody production are defective. Other immunodeficiencies affect the complement system or phagocytic cells, impairing antimicrobial immunity. Secondary immunodeficiencies may allow similar infections to PIDs, but are associated with some other factors such as malnutrition, age, drugs, tumours or infections, including human immunodeficiency virus (HIV). See also: B lymphocytes; Immunodeficiency disorders due to antibody deficiency (B lymphocyte disorders); Immunodeficiency: secondary; T lymphocytes: helpers

The incidence of PIDs varies greatly from about 1:500 births with selective IgA deficiency to only a few known cases of the rarest disorders. Patients with antibody deficiencies are particularly susceptible to encapsulated bacteria, such as Haemophilus influenzae, Staphylococcus aureus and Streptococcus pneumoniae, which cause pyogenic infections. T-cell immunodeficiencies and severe CIDs (SCIDs) are marked by opportunistic infections caused by common environmental microorganisms. Patients with PIDs have recurrent serious infections starting soon after birth. Life-threatening symptoms can arise within the first few days of life in SCID. However, in immunoglobulin (Ig) deficiencies, children are protected for 6–12 months by the maternal IgG. See also: Immunodeficiency: severe combined immunodeficiency; Infections in the immunocompromised host

The infections in PID patients require prolonged treatment with antibiotics at high doses. Antibody deficiencies are treated with intravenous immunoglobulin substitution therapy. Gammaglobulins are extracted from human blood from donor pools. Leucocytes (B and T cells) are produced from stem cells in bone marrow. In SCIDs bone...
marrow transplantation from histocompatibility leucocyte antigen (HLA)-identical or haploidentical donors is the most effective treatment. In certain metabolic disorders (adenosine deaminase deficiency and purine nucleoside phosphorylase deficiency) enzyme substitution therapy can be applied.

**Genetic Basis**

The immune system consists of a large number of molecules and processes, and immunodeficiencies can therefore be caused by genetic alterations at many loci (Figure 1). A particular PID can potentially be caused by defects in any one of several molecules that are required for certain responses, because a defect in any of the sequential steps can impair the system. A large number of affected genes has been identified from all major PID groups (ImmunoDeficiencyResource). The inheritance of the majority of PIDs is autosomal-recessive, although the most studied cases are X-linked.

**Diversification of immunological recognition molecules**

Recognition of the enormous range of nonself substances is the basis of adaptive immunity and is achieved by mechanisms that produce largely heterogeneous receptors, namely antibodies, T-cell receptors (TCRs) and the components of the major histocompatibility complex (MHC). These molecules owe their high variability to a large number of genetic segments, which can be joined in random fashion. See also: Major histocompatibility complex (MHC)

Antibodies or immunoglobulins are proteins that are free in serum, or one part of the B-cell receptor (BCR). The main role of antibodies is to recognize foreign substances and facilitate their destruction. Antibodies consist of two light and two heavy chains. The genes for each antibody are built from a number of regions by gene rearrangement. Both the heavy and light chains contain constant and variable regions. Antibodies are produced by plasma cells, which mature from pluripotent stem cells in multiple steps, including deoxyribonucleic acid (DNA) rearrangements.
For each part of the antibody gene there are a number (up to 100) of different segments, but only one is used in each cell. Antibody coding regions are clustered in chromosomes. First, one diversity region (D) segment is combined with a single joining (J) segment and then with one of the variable regions (V). This V(D)J rearrangement facilitates the enormous diversity of antibodies. In the last step, one of the constant regions (C) determining the class of the antibody is added to complete the full V(D)JC gene. Antibody diversification is further increased by somatic hypermutations, gene conversion and class switch conversion processes. Related mechanisms also produce a great diversity of antigen-specific TCRs by gene rearrangement.

See also: Antibodies; Antibody classes; Antibody function; Immunoglobulin gene rearrangements

MHC molecules are membrane-bound proteins that form a peptide-binding cleft on the surface of the cell. This cleft is coded by highly polymorphic gene segments and thereby facilitates recognition of different molecules. MHC class-I molecules bind to foreign peptides processed within infected cells, and present them to cytotoxic CD8+ T cells, which can kill the infected cells. Class-II molecules bind to peptides presented within specialized antigen-presenting cells, and present them to helper CD4+ T cells.

See also: Major histocompatibility complex: human; Major histocompatibility complex: interaction with peptides

Errors in the construction of the highly variable antibodies and receptors lead to immunodeficiencies. Immunoglobulin gene mutations are usually deletions of the constant heavy chain, although also some \( \lambda \) and \( \kappa \) light-chain gene mutations have been identified. In general, patients with these immunodeficiencies do not have a markedly increased risk of infection. See also: Signal transduction: overview

Signal transduction in lymphocytes

The cells producing adaptive immunity are regulated by complex networks of molecules and their interactions. Surface receptors transmit signals inside the cells, where further cascades of reactions are triggered. Defects in these signalling pathways can result in immunodeficiencies (Figure 1). See also: Lymphocyte activation signals: transduction

Bruton tyrosine kinase (Btk) is the defective molecule in X-linked agammaglobulinaemia (XLA). Mutations in the gene for \( BTK \) prevent B-cell maturation since Btk is a crucial signalling molecule regulating B-cell development into antibody-producing plasma cells. Btk protein consists of five domains, all of which can be affected by disease-causing alterations. Mutations causing several immunodeficiencies, including XLA, have been collected into databases (Väliaho et al., 2000; Vihinen et al., 2001). Nuclear factor (NF) \( \kappa B \) is a crucial regulator for the expression of a wide variety of immunity and inflammation-related genes. Its activity is controlled by the inhibitor of NF-\( \kappa B \) (IKB), which in its phosphorylated form is degraded leading to NF-\( \kappa B \) activation. IKB kinase (IKK) is responsible for the phosphorylation. Cells with mutated NF-\( \kappa B \) essential modulator (NEMO) lack NF-\( \kappa B \) activity and are susceptible to tumour necrosis factor (TNF)-\( \alpha \)-induced apoptosis. Btk and BLNK are involved in the formation of lipid rafts following B-cell receptor induction. Then activation of phospholipase C\( \gamma_2 \) induces calcium signalling and NF-\( \kappa B \) activation.

IgG, IgA and IgE levels are severely reduced in hyper-IgM (HIM) syndrome, but IgM levels are normal or increased, indicating that there is an immunoglobulin isotype-switching problem. The X-linked form of the disease is caused by mutations in the CD40 ligand (CD40L) in T cells and autosomal form by alterations in CD40 in B cells. CD40–CD40L interaction is fundamental for T-cell-dependent B-cell responses, including generation of memory B cells. Another X-linked form arises from mutations of B-cell NEMO protein, which is a regulator subunit of IKK signalome and NF-\( \kappa B \) modulator. See also: Immunological memory

In X-linked lymphoproliferative disease (XLP) or Duncan disease, patients are exceptionally susceptible to Epstein–Barr virus (EBV). SAP is a short Src homology 2 (SH2)-domain-containing molecule, which interacts with signalling lymphocyte activation molecule (SLAM), which appears on the surface of T cells. Phosphorylation of SLAM provides docking sites for SH2-domain-containing proteins including protein phosphatase SHP-2. SAP regulates by competing with SHP-2 for binding to SLAM. SAP regulates the activity of SLAM by recruiting Src family kinases leading to phosphorylation of SLAM. Mutations in SAP affect the interaction between T and B cells to uncontrolled B-cell proliferation in EBV infection. See also: Epstein-Barr virus

There are both autosomal recessive and X-linked forms of SCID. In the X-SCID, mutations appear in the common \( \gamma \) chain of the receptors for cytokines interleukin (IL)-2, -4, -7, -9, and -15, affecting the differentiation and growth of lymphocytes. IL-2 receptor (IL2R) \( \alpha \)-chain (CD25) and IL-7R \( \alpha \)-chain (CD127) deficiency has also been described. Binding to IL-2 causes dimerization of the receptors and leads to activation of Janus kinase 3 (JAK3) tyrosine kinase. Activated JAK family members phosphorylate multiple tyrosine residues in the receptors. Signal transducers and activators of transcription (STATs) are transcription factors that bind with their SH2 domains to the phosphotyrosines in the receptor. Activated, dimerized STATs then dissociate from the receptor and translocate to nucleus, where they bind to enhancer regions in DNA and thereby effect transcription of cytokine-responsive genes. Immunodeficiency-causing mutations are known in STAT1 and STAT5B.

Cytokines are essential mediators for intercellular signalling. T-cell functions can be impaired due to interferon \( \gamma \) (IFN\( \gamma \)) receptor or IL-12 receptor subunit mutations. In
these defects the T-cell response is compromised because the T-cell activation fails to occur appropriately.

In addition to protein kinases immunodeficiency can arise also from counteracting protein phosphatase mutations. CD45 is a receptor-type protein tyrosine phosphatase, which is required for T-cell activation through TCR. Zap-70 is required for TCR triggered signalling cascades. Immunodeficiencies can also be caused by deficiencies in the factors controlling lymphocyte activation and proliferation as indicated by Fas (CD95) and Fas ligand mutations.

**B-cell Immunodeficiency**

B-cell immunodeficiencies are antibody deficiency disorders that are restricted to antibody function (Ballow, 2002; Buckley, 2000, 2002) (Table 1). Either B-lymphocyte development is impaired, or B cells fail to respond to T-cell signals (Figure 1). All or selected subsets of immunoglobulins may be deficient. Such patients have recurrent pyogenic infections with encapsulated bacteria, requiring early and vigorous treatment with antibiotics and life-long immunoglobulin replacement therapy. See also: Immunodeficiency disorders due to antibody deficiency (B lymphocyte disorders)

XLA is a typical antibody deficiency in which production of antibodies is prevented due to a block in B-cell maturation (Smith et al., 2001). The prevalence is about 1:200,000. Serum concentrations of IgG, IgA and IgM are markedly reduced. Levels of circulating B lymphocytes are significantly decreased and plasma cells are absent from lymph nodes and bone marrow, whereas the number of T cells is normal or increased. The clinical phenotype may be variable, and even members of the same family can have different symptoms. XLA represents a block in the B-cell differentiation. Btk, the affected protein, is a tyrosine kinase that regulates activity of signalling pathways by phosphorylation. Adaptor protein BLNK has multiple tyrosine residues as phosphorylation targets. It recruits signalling molecules including Btk to membrane lipid rafts for Ca signalling.

IgA deficiency can be selective, affecting only IgA levels, or it may be combined with the lack of other isotopes (Hammarström et al., 2000). IgA deficiency is the most prevalent PID (1:500 Caucasians), but its mechanism remains unknown. Only about one-third of the patients are particularly prone to infection. The serum concentrations of the other immunoglobulins are usually normal.

Selective deficiencies of IgG subclasses, with or without IgA deficiency, are caused by defects in several genes. Also selective IgA and IgE class or subclass deficiencies have been reported. IgG subclass deficiency may be an isolated single subclass defect or simultaneous deficiency of two or more subclasses.

Common variable immune deficiency (CVID) includes a group of undifferentiated disorders, in all of which antibody formation is defective (Hammarström et al., 2000). Patients with CVID usually have normal numbers of circulating but defective B cells, but low serum levels of IgG and IgA. CVID affects females and males equally and it usually has a later age of onset than other antibody immunodeficiencies. CVID forms arise from several different genetic defects.

Other B-cell deficiencies have also been described, including, for example, μ heavy-chain deficiency, κ light-chain deficiency.

**Severe Combined Immune Deficiency**

In combined B- and T-cell immunodeficiencies, the most severe disorders, all adaptive immune functions are absent. The condition is fatal unless the immune system can be reconstituted, either by transplants of immunocompetent tissue or by enzyme replacement. The immunological, genetic and enzymatic characteristics of these diseases show great diversity (Table 1). SCIDs have an average frequency of approximately 1 in 75,000 births. See also: Immunodeficiency; severe combined immunodeficiency

X-linked SCID, which constitutes about 50–60% of SCID cases, is caused by IL-2 receptor γ chain mutations which lead to very low numbers of T and natural killer (NK) cells, whereas B cells are present in high numbers. However, the B cells are immature and defective. The γ chain of the receptor also forms part of the receptor for some other cytokines that are important for stimulating cell growth and differentiation. Patients with X-SCID have extreme susceptibility to infection. The autosomal-recessive form of SCID is caused by mutations in JAK3 tyrosine kinase. The γc–JAK3 pathway transmits the signal to the nucleus via STATs and effects the transcription of genes that respond to cytokines. See also: Natural killer (NK) cells

Purine nucleoside phosphorylase (PNP) deficiency is characterized by accumulation of toxic purine metabolites, primarily 2’-deoxyguanosine triphosphate (dGTP), in cells. PNP catalyses the phosphorolysis of the purine nucleosides, (deoxy)inosine and (deoxy)guanosine, to purine bases and ribose 1-phosphate. dGTP is particularly toxic to T cells by inhibition of ribonucleotide reductase and subsequently DNA synthesis and proliferation. PNP deficiency is often accompanied by neurological disorder. Adenosine deaminase (ADA) deficiency accounts for about half of the autosomal-recessive forms of SCIDs. ADA follows PNP in purine nucleoside catabolism, but deficiency in this enzyme causes more severe symptoms. In addition to immunological defect, most patients with ADA deficiency also have skeletal abnormalities.

HIM syndrome represents a group of related diseases, the majority of which are X-linked. XHIM is caused by a genetic defect in the gene for the CD40 ligand (CD154). The patients have severely reduced IgG, IgA and IgE...
serum levels, but normal or even raised IgM levels. XHIM is a failure in heavy-chain class switch from IgM to IgG and IgA. Interaction between CD40L on T cells and CD40 on B cells is a key signal in the generation of memory B cells and in the formation of germinal centres. The production of immunoglobulins and subclasses is regulated and the defective CD40L prevents the production of certain antibodies. CD40 is also a receptor on macrophages and dendritic cells; it induces IL-12 secretion and thereby elicits an immune response to intracellular microorganisms.

Recently, two new forms of HIM have been identified. In one, the defect is in activation-induced cytidine deaminase (AID) which is a ribonucleic acid (RNA) editing enzyme. The other form is NEMO deficiency, in which patients have also hypohydrotic ectodermal dysplasia and incontinentia pigmenti.

T-cell activation triggers cascades of reactions. Zap-70 is a tyrosine kinase that binds with its SH2 domains to the TCR’s phosphorylated immunoreceptor tyrosine-based activation motif (ITAM) sequences. In Zap-70 deficiency, signalling through the TCR is defective, influencing T-cell development.

In XLP, EBV infection causes mononucleosis by the vigorous uncontrolled expansion of both T and B cells (Morra et al., 2001). The disease is usually associated with hypogammaglobulinaemia, or Burkitt lymphoma, or carcinoma, or some forms of Hodgkin disease, or several of them. Mortality is complete by 40 years of age. A mutation of SAP, an SH2-domain protein, is responsible for the disease.

CD3 is a multicomponent T-cell complex formed of nonidentical subunits that interact with the TCR. Interaction with antigen activates cytokine release and cell proliferation. Rare CD3 deficiencies are caused by mutations in the γ and ε subunits.

The MHC is expressed in B cells as surface molecules, which present processed peptide fragments to the TCR of CD4+ T helper cells, triggering the antigen-specific T-cell response. MHC class-II deficiencies impair transcription of MHC II genes. Four forms have been found. Three of the affected proteins are parts of regulatory factor (RF) X, a complex binding to the X box of MHC II promoters in the nucleus. RFX5 has a DNA-binding domain. RFX-associated protein (RFXAP) binds to RFX5. Mutations appear also in RFXANK, ankyrin repeat containing regulatory factor X-associated protein. Class-II transcription activator (CIITA) is a positive regulator of MHC class-II gene transcription, but it does not bind directly to DNA. CD4+ T cells are decreased in all the forms, although circulating lymphocyte numbers are normal and immunoglobulin levels can also be decreased. See also: Major histocompatibility complex: human

Other combined B- and T-cell deficiencies include MHC class-I deficiency, which is due to peptide transporter protein 1 (TAP1) and TAP2 mutations. TAP1 and TAP2 transport peptides from the cytoplasm into endoplasmic reticulum, where MHC I molecules can bind to them. Cells degrade foreign proteins by proteolysis and generate peptides. Processed peptides bind to MHC I molecules, which are transported to the cell surface. Then, cytotoxic T cells recognize the antigen-presenting MHC proteins and kill the infected cells. RAGs are proteins that activate V(D)J recombination in the antibody and T-cell receptor genes required for generation of the diversity of the receptors. Both RAG proteins are involved in cleaving double-stranded DNA during recombination. In the Omenn syndrome, recombination is only partially deficient.

Artemis, which is activated by phosphorylation by DNA-PK, functions in hairpin opening of V(D)J recombination and 5' and 3' overlap processing in nonhomologous DNA end joining. Ligase IV, in which mutations lead to PID, is one of several nonhomologous DNA end-joining proteins which form complexes functional in coding and recombination signal joining.

Three processes modify antibody genes further. Somatic hypermutations add randomly point mutations through error-prone DNA repair. In gene conversion, pseudogene V element stretches are copied to the genes. There are several Ig classes, which are produced by class switching recombination of repetitive switch regions. AID, whose actual function is still unknown, is essential for all the three processes. Mutations in AID lead to hyper-IgM syndrome.

Several other types of PID have been studied, including ataxia telangiectasia, a partial CID with complex symptoms, Wiskott–Aldrich syndrome, Bloom syndrome, chronic granulomatous diseases and a number of complement deficiencies. Thus, PIDs can be caused by a wide spectrum of alterations in several different genes and proteins ranging from transcription and translation to recognition of nonself proteins and microorganisms and signal transduction. PIDs, especially XSCID, ADA and Jak3 deficiency, have been good targets for gene therapy. In the first successful trial for γc XSCID, however some of the patients developed later leukaemia, so more research is needed.

References


Further Reading