Immunodeficiency, Primary: Affecting the Adaptive Immune System

Mauno Vihinen, *University of Tampere, Tampere, Finland*

Secondary article

Article Contents

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.

More than 70 primary immune deficiencies (PIDs) are now known, and have been grouped according to the components of the immune system affected (WHO Scientific Group, 1997). 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.

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.

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 and leucocytes (B and T cells) are produced in stem cells in bone marrow. In SCIDs bone marrow transplantation 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. 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 (Ochs *et al*., 1998). 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.

Table 1 Some primary immunodeficiences

T-cell immunodeficiences
Purine nucleoside phosphorylase
Zap-70 deficiency
X-linked lymphoproliferative disease
CD3 subunit deficiency
Nezelof syndrome
B-cell immunodeficiences
X-linked agammaglobulinaemia
Hyper-IgM syndrome
IgA deficiency
IgG subclass deficiences
Common variable immunodeficiency
Severe combined immunodeficiencies
IL-2 receptor γ chain deficiency
JAK3 deficiency
Adenosine deaminase deficiency
Recombination activating gene 1 deficiency
Recombination activating gene 2 deficiency
Omenn syndrome
Major histocompatibility complex class I and class II deficiencies

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 up from a number of regions by gene rearrangement. Both the heavy and light chains contain constant and variable regions. Antibody coding regions are clustered in chromosomes. 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. 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. There are several immunoglobulin classes, and antibodies can undergo class switching by combination with different constant regions. Class switching is largely regulated by chemokines. Related mechanisms also produce a great diversity of antigen-specific TCRs by gene rearrangement.

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. There are two classes of MHC complex. 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 processed within specialized antigen-presenting cells, and present them to helper CD4+ T cells.

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

In RAG1 (recombination activating gene 1) and RAG2 deficiencies and the Omenn syndrome, recombinase-activating proteins are defective and both the BCR and the TCR are deficient, leading to severe combined immunodeficiency (SCID) (**Figure 1**). SCID can also result from the modifications in γ chain (γc)–Janus Kinase 3 (JAK3) signalling pathway. Several cytokine receptors, including the interleukin (IL)-2 receptor, contain γc and IL-2 is required for the growth and differentiation of B, T and natural killer (NK) cells. MHC class II deficiencies are caused by defective promoter-binding proteins, which effect transcription of MHC genes. In B cells, production of IgG, IgA and IgE isotypes is stimulated by cytokines and contact with helper T cells. In hyper-IgM syndrome (HIM) these class-switching signals are impaired because of defective CD40 ligand molecule.

Signal transduction in lymphocytes

The cells producing adaptive immunity are regulated by a complex network of molecules and their interactions. Surface receptors transmit signals inside the cells, where further cascades of reactions are triggered. Defects in the signalling pathways can result in immunodeficiencies (**Figure 1**).

Typically, about one third of X-linked PIDs are new, sporadic cases, where the mutation has occurred in the patient. 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. The majority of known mutations (altogether more than 300) lead to truncation of the protein, due to either nonsense or frameshift mutations because of insertions, deletions or splice site defects. Mutations causing several immunodeficiencies, including XLA, have been collected into databases (Vihinen *et al*., 1998). Although the mutations are evenly distributed in the *BTK* gene, the most mutable single sites in many genetic disorders, including XLA, are CpG dinucleotides.

In addition to the catalytic tyrosine kinase domain, Btk contains modules for protein–protein interactions, namely

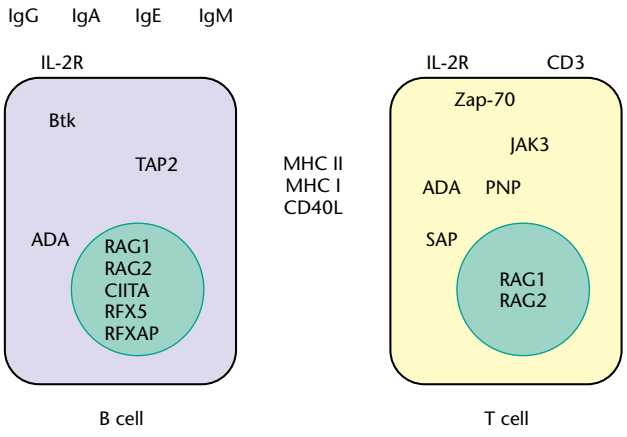

Figure 1 Proteins affected in primary immune deficiencies. Major histocompatibility complex (MHC) class II deficiencies are due to defective transcription by mutated nuclear proteins class II transcription activator (CIITA), regulatory factor (RF)X5 and RFX-associated protein (RFXAP). RAG1 and RAG2 deficiencies, as well as the Omenn syndrome, arise from impaired nuclear recombination in B cells. Adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP) are purine nucleoside-catabolizing enzymes. TAP2 transports degraded protein fragments from cytoplasm to endoplasmic reticulum to bind MHC I molecules before presentation to T cells. Bruton tyrosine kinase (Btk) is an intracellular enzyme, which when mutated prevents B cell maturation and immunoglobulin production. CD3 is a membrane protein complex that activates cell proliferation. Interleukin receptor (IL-2R) contains a common γ chain, which is also shared by several other cytokine receptors. Downstream of the IL-2R in the signalling pathway is Janus Kinase 3 (JAK3), a tyrosine kinase. Zap-70 is another protein kinase in T cells. SAP regulates the function of SLAM protein, which is more important for the control of the interaction between B and T cells and the proliferation of the cells. Ig, immunoglobulin.

Tec homology (TH), Src homology (SH) 2 and SH3 domains. Pleckstrin homology (PH) domain is responsible for membrane localization of the protein by binding to the phosphatidyl inositol groups of membrane lipids. Btk has been shown to have several signalling partners, but the detail of the reactions is incomplete. The specificity of the kinase domain may be increased by simultaneous binding of the SH2 and/or SH3 domain into their recognition sites in the substrate. The TH domain binds Zn^{2+}, which is essential for stability. Btk is activated by stepwise phosphorylation, first by Src family kinases and then by autophosphorylation.

Although many of the mutations cause truncation of the Btk protein, there are also other types of alteration. For example, a number of structural mutations lead into misfolded proteins. Three-dimensional structures of the Btk domains have been used to describe the consequences of the disease-causing mutations. Of the amino acid-changing missense mutations, many alter structurally or functionally significant conserved residues. In the PH domain, the majority of mutations are in the binding region; in the SH2 domain, most are in the phosphotyrosine-containing protein binding region; and in the kinase domain most are in adenosine triphosphate, Mg^{2+}, or substrate-binding regions.

IgG, IgA and IgE levels are severely reduced in X-linked HIM (XHIM) syndrome, but IgM levels are normal or increased, indicating that there is an immunoglobulin isotype-switching problem. The disease is caused by mutations in the CD40 ligand (CD40L) in T cells. CD40–CD40L interaction is fundamental for T-cell dependent B-cell responses, including generation of memory B cells.

CD40 belongs to the tumour necrosis factor (TNF) superfamily of transmembrane proteins. Signalling through CD40 activates phospholipase Cγ2 and phosphatidylinositol-3 kinase, upregulates CD23, CD80 and CD54, and induces transcription factors such as nuclear factor-κB. The XHIM-causing mutations can appear in any of the domains of CD40L (intracytoplasmic, transmembrane, extracellular unique, and TNF homology regions). However, mutations cluster into the TNFH domain, suggesting functional importance of this module. The most common alterations are point mutations, which typically result in truncation of the polypeptide chain.

In X-linked lymphoproliferative disease (XLP) or Duncan disease, patients are exceptionally susceptible to Epstein–Barr virus (EBV). SAP (SLAM (signalling lymphocyte activation molecule)-associated protein, also called for DSHP and SHD1A) is a short SH2-domain-containing molecule. SLAM, also known as Cdw150, appears on the surface of T cells, where it has a crucial function in stimulation. Phosphorylation of SLAM provides docking sites for SH2-domain-containing proteins including protein phosphatase SHP-2. SAP regulates the binding by competing for SLAM. Mutations in SAP affect the interaction between T and B cells to uncontrolled B-cell proliferation in EBV infection.

Combined B- and T-cell immunodeficiencies result from a large group of diverse defects. There are both autosomal recessive and X-linked forms of SCID. In the X-SCID, mutations appear in the common γ chain of the receptors for cytokines IL-2, 4, 7, 9, and 15, affecting the differentiation and growth of lymphocytes. IL-2 receptor (IL 2R) α-chain (CD25) deficiency has also been described. More than 100 families have been reported with IL-2R γc mutations. Binding to IL-2 causes dimerization of the receptors and leads to activation of 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. Many defective genes can cause similar symptoms. Mutations in the γc chain lead to abrogated or defective JAK3-mediated

signal transduction. About 30–40% of T^- B^+ SCIDs are caused by JAK3 mutations. JAK3 is a tyrosine kinase composed of seven JAK homology (JH) domains. JH1 is the kinase domain and JH2 a kinase-like module. SCID-causing mutations have been found in several domains. This seems to be typical for multidomain signalling proteins since function can be impaired even when the kinase activity is normal if the enzyme cannot bind effectively to its substrate(s) or partner(s). Immunodeficiencies can also be caused by deficiencies in the factors controlling lymphocyte activation and proliferation as indicated by Fas (CD95) mutations.

T-cell Immunodeficiency

Deficiencies in T cells usually also affect other components of the immune system and lead to CIDs; for example, T cells have cytotoxic and helper functions. Included amongst T-cell deficiencies are PNP deficiency, Zap-70 (ζ-associated polypeptide of 70 kDa) deficiency, XLP, Nezelof syndrome and CD3 deficiency, all of which can also have effects on other cell types (**Table 1**, **Figure 1**). Affected patients have a progressive decrease in the number of circulating T cells, whereas numbers of circulating B cells and serum immunoglobulin levels are usually normal. Autoimmunity is a frequent complication of T-cell immunodeficiencies.

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 further DNA synthesis and proliferation. PNP deficiency is often accompanied by neurological disorder. The enzyme following PNP in purine catabolism is adenosine deaminase, mutations of which also cause SCID.

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. 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 reponsible for the disease. SAP controls the function of SLAM protein.

Nezelof syndrome is a T-cell deficiency with little or no abnormality of gammaglobulins. Patients have very small thymuses, also antibody synthesis is impaired and IgA can be deficient, whereas IgD or IgE levels can be elevated. Nezelof syndrome is the most likely PID to be confused with AIDS.

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.

T-cell deficiencies and CIDs are severe conditions, and bone marrow transplantation is in many cases the only long-lasting therapeutic option.

B-cell Immunodeficiency

B-cell immunodeficiencies are antibody deficiency disorders that are restricted to antibody function (**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.

XLA is a typical antibody deficiency in which production of antibodies is prevented due to a block in B-cell maturation (Smith *et al*., 1998). 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. Patients with XLA have a normal response to viral infections and have normal V(D)J rearrangement. 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.

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 (Ramesh *et al*., 1998). 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. Infections in patients with HIM are similar to

those in XLA, except for greater tendency for persistent or recurrent neutropenia and thrombocytopenia.

IgA deficiency can be selective, affecting only IgA levels, or it may be combined with the lack of other isotypes. IgA deficiency is the most prevalent PID (1:5000 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, but patients have a high incidence of autoantibodies.

Selective deficiencies of IgG subclasses, with or without IgA deficiency, are caused by defects in several genes. IgG2 deficiency is most common in children, whereas adults more often have low levels of IgG3.

Common variable immune deficiency (CVID) includes a group of undifferentiated disorders, in all of which antibody formation is defective. The incidence is approximately 1:25 000. Patients with CVID usually have normal numbers of circulating B cells, but low serum levels of IgG and IgA. However, the B cells are defective. CVID affects females and males equally and it usually has a later age of onset than other antibody immunodeficiencies. Patients have an unusually high incidence of lymphoreticular and gastrointestinal malignancies and the incidence of autoimmune disorders is also increased. CVID forms arise from several different genetic defects.

Other B-cell deficiencies have also been described, including, for example, μ heavy chain deficiency, λ5 surrogate light chain deficiency, and 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.

X-linked SCID, about 50–60% of SCID cases, is caused by IL-2 receptor γ chain mutations which lead to very low numbers of T and NK cells, whereas B cells are present in high numbers (Candotti *et al*., 1998). 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. IL-2 stimulates the receptor and induces tyrosine phosphorylation and further activation of JAK3. The γc–JAK3 pathway transmits the signal to the nucleus via STATs and effects the transcription of genes that respond to cytokines (**Figure 1**).

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. ADA degrades toxic adenosine and deoxyadenosine, which accumulate in the cells of patients. Immature lymphoid cells are particularly sensitive to these nucleotides. In addition to immunological defect, most patients with ADA deficiency also have skeletal abnormalities. ADA deficiency has been one of the first diseases in which gene therapy trials have been established with some success, although more research is needed.

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. Three forms have been found. The affected proteins in these groups are parts of regulatory factor (RF) X, a complex binding to the X box of MHC II promoters in the nucleus. In complementation group A, class II transcription activator (CIITA) is mutated. CIITA is a positive regulator of MHC class II gene transcription, but it does not bind directly to DNA. RFX5 is mutated in complementation group C deficiency and it has a DNA-binding domain. RFX-associated protein binding to RFX5, is mutated in the complementation group D. CD4+ T cells are decreased in all three forms, although circulating lymphocyte numbers are normal and immunoglobulin levels can also be decreased.

Other combined B- and T-cell deficiencies include MHC class I deficiency, which is due to peptide transporter protein 2 (TAP2) mutations, and RAG1 and RAG2 deficiencies. TAP2 transports 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.

Several other types of PID have been studied, including ataxia telangiectasia, a partial CID with complex symptoms, Wiskott–Aldrich syndrome, Bloom syndrome, chronic granulomatous disease, and a number of complement deficiencies. 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.

References

Candotti F, O'Shea J and Villa A (1998) Severe combined immune deficiencies due to defects of the common γ chain–JAK3 signaling pathway. *Springer Seminars in Immunopathology* **19**: 401–415.

Ochs HD, Smith CIE and Puck J (1998) *Primary Immunodeficiency Diseases. A Molecular and Genetic Approach*. Oxford: Oxford University Press.

Ramesh N, Seki M, Notarangelo LD and Geha RS (1998) The hyper-IgM (HIM) syndrome. *Springer Seminars in Immunopathology* **19**: 383–399.

Smith CIE, Bäckesjö C-M, Berglöf A *et al*. (1998) X-linked agammaglobulinemia: lack of mature B lineage cells caused by mutations in the Btk kinase. *Springer Seminars in Immunopathology* **19**: 369–381.

Vihinen M, Brandau O, Brandén L *et al*. (1998) BTKbase, mutation database for X-linked agammaglobulinemia (XLA). *Nucleic Acids Research* **26**: 242–247. [http://www.helsinki.fi/science/signal]

World Health Organization Scientific Group (1997) Primary immunodeficiency diseases. *Clinical and Experimental Immunology* **109** (Supplement 1): 1–28. [http://www.jmfworld.com/html/WHO_Report.PDF]

Further Reading

Belmont JW (1995) Insights into lymphocyte development from X-linked immune deficiencies. *Trends in Genetics* **11**: 112–116.

Buckley RH (1987) Immunodeficiency diseases. *Journal of the American Medical Association* **258**: 2841–2850.

Fischer A and Arnaiz-Villena A (1995) Immunodeficiencies of genetic origin. *Immunology Today* **16**: 510–514.

Ochs HD, Smith CIE and Puck J (1998) *Primary Immunodeficiency Diseases. A Molecular and Genetic Approach*. Oxford: Oxford University Press.

Genetics and Treatment of Primary Immunodeficiencies (1998) *Springer Seminars in Immunopathology* **19**(4): 363–508. [Immunodeficiency special issue.]

Immunology Today (1996) **17**(11): 495–539. [Special issue.]

World Health Organization Scientific Group (1997) Primary immunodeficiency diseases. *Clinical and Experimental Immunology* **109** (Supplement 1): 1–28. [http://www.jmfworld.com/html/WHO_Report.PDF]