more protracted **transient hypogammaglobulinemia of infancy**, characterized by recurrent respiratory infections, is associated with low IgG levels that often return to normal by 4 years of age. There is a deficiency in the number of circulating lymphocytes and in their ability to generate help for Ig production by B-cells activated by pokeweed mitogen, but this becomes normal as the disease resolves spontaneously.

Primary T-cell deficiency (Table 14.4)

Patients with no T-cells or poor T-cell function are vulnerable to opportunistic infections and, as B-cell function is to a large extent T-dependent, T-cell deficiency also impacts negatively on humoral immunity. Dysfunctional T-cells often permit the emergence of allergies, lymphoid malignancies and autoimmune syndromes, the latter presumably arising from inefficient negative selection in the thymus or the failure to generate appropriate regulatory cells.

Defective thymic development

The **DiGeorge syndrome**, in which mutations in the TBX1 transcription factor involved in embryonic development are present, is characterized by a failure of the thymus to develop properly from the third and fourth pharyngeal pouches (DiGeorge syndrome children also lack parathyroids and have severe cardiovascular abnormalities). Consequently, hematopoietic stem cells cannot differentiate to become T-lymphocytes and the "thymus-dependent" areas in lymphoid tissue are sparsely populated; in contrast, lymphoid follicles are seen but even these are poorly developed. Cell-mediated immune responses are undetectable and, although the infants can deal

Table 14.4. Deficiencies affecting T-lymphocytes.

Defective gene	Disorder	Typical infections
AIRE	Autoimmune polyendocrine syndrome-1	*Candida albicans*
ATM	Ataxia telangiectasia	Bronchopulmonary
CIITA	MHC class II deficiency	Bronchopulmonary
CD3γ	*CD3γ* deficiency	Bacteria and viruses
CD40L, *CD40*, *AID*, *NEMO* or *UNG*	Hyper-IgM syndrome	*Pneumocystis jirovecii*, *Toxoplasma*, *Cryptosporidium parvum*
FAS or *FASL*	Autoimmune lymphoproliferative syndrome	None
Foxp3	Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)	None
γC, *RAG-1*, *RAG-2*, *artemis*, *ADA* or *IL-7R α chain*	Omenn syndrome	Broad (viral, bacterial, fungal) including *Pneumocystis jirovecii* and *S. aureus* sepsis
NBS1	Nijmegen breakage syndrome	Bronchopulmonary
PNP	PNP deficiency	Broad (viral, bacterial, fungal)
SH2DIA	X-linked lymphoproliferative disease type 1	Epstein–Barr virus
STAT3	Hyper-IgE syndrome	Extracellular bacteria, staphylococci, *Aspergillus* spp., *C. albicans*
TAP-1, *TAP-2* or *tapasin*	MHC class I deficiency	Brochopulmonary
TBX1	DiGeorge syndrome	Multiple
WASP	Wiskott–Aldrich syndrome	Encapsulated extracellular bacteria
XIAP	X-linked lymphoproliferative disease type 2	Epstein–Barr virus
ZAP70	ZAP70 deficiency	Broad (viral, bacterial, fungal)

with common bacterial infections, they may be overwhelmed by live attenuated vaccines such as measles or bacille Calmette–Guérin (BCG) if given by mistake. Antibodies can be elicited, but the response is subnormal, reflecting the need for the cooperative involvement of T-cells. (The similarity of this condition to neonatal thymectomy and of B-cell deficiency to neonatal bursectomy in the chicken should not go unmentioned.) Treatment by grafting neonatal thymus leads to restoration of immunocompetence, but some matching between the MHC on the nonlymphocytic thymus cells and peripheral cells is essential for the proper functioning of the T-lymphocytes (p. 122). Complete absence of the thymus is pretty rare and more often one is dealing with partial DiGeorge syndrome in which the T-cells may rise from 6% at birth to around 30% of the total circulating lymphocytes by the end of the first year (compared with 60–70% in normal 1-year olds); antibody responses are adequate.

Arrest of early T-cell differentiation

Mutation of the gene encoding the purine degradation enzyme, **purine nucleoside phosphorylase**, results in the accumulation of the metabolite deoxy-GTP, which is toxic to T-cell precursors through its ability to inhibit ribonucleotide reductase, an enzyme required for DNA synthesis. Targeting of the T-cell lineage by this deficiency could well be linked to a relatively low level of 5′-nucleotidase. Some T-cells "leak through" but they give inadequate protection against infection and the disease is usually fatal unless a hematopoietic stem cell transplant life-line is offered. In addition to recurrent infections, patients usually suffer from neurologic dysfunction and autoimmunity.

Quite a few different genes, including for RAG-1, RAG-2, Artemis, IL-7 receptor α chain, adenosine deaminase, and the γC shared interleukin receptor chain, have been linked to the development of **Omenn syndrome.** As we shall see very shortly mutations of these genes are also responsible for severe combined immunodeficiency (SCID), but in Omenn syndrome the particular mutations involved are "leaky" and result in a less devastating phenotype. For example, the mutations in RAG allow some T-cells to sneak through because VDJ recombination is not completely abolished. Patients often exhibit eosinophilia and raised IgE, and sometimes have autoimmune disease affecting the skin and gut.

MHC class II deficiency (sometimes referred to as "bare lymphocyte syndrome") is associated with recurrent bronchopulmonary infections and chronic diarrhea occurring within the first year of life, with death from overwhelming viral infections at a mean age of 4 years unless these affected infants are successfully treated with a hematopoietic stem cell transplant. The condition arises from mutations affecting any of several transcription factors controlling the expression of class II genes, for example the *c*lass *II t*rans*a*ctivator (CIITA). Feeble expression of class II molecules on thymic epithelial cells grossly impedes the positive selection of CD4 T-helpers, and those that do leak through will not be encouraged by the lack of class II on antigen-presenting cells. Note also that rare patients with mutations in the *TAP-1*, *TAP-2* or *tapasin* genes have MHC class I deficiency.

Deficiencies leading to dysfunctional T-cell–B-cell collaboration

Cell-mediated immunity (CMI) is depressed in immunodeficient patients with thrombocytopenia and eczema (**Wiskott–Aldrich syndrome**) or with **ataxia telangiectasia.** The *W*iskott–*A*ldrich *s*yndrome *p*rotein (**WASP**) plays a critical role in linking signal transduction pathways and the actin-based cytoskeleton by clustering physically with actin through the GTPase Cdc42 and the Arp2/3 (*a*ctin-*r*elated *p*rotein) complex that regulates actin polymerization. Mutations in the *WASP* gene on the X chromosome thus adversely affect T-cell motility, phagocyte chemotaxis, dendritic cell (DC) trafficking and the polarization of the T-cell cytoskeleton towards the B-cells during T-cell–B-cell collaboration. Poor cell-mediated immunity and impaired antibody production in affected boys are hardly surprising consequences. **Ataxia telangiectasia,** a chromosomal breakage syndrome, is an autosomal recessive disorder of childhood characterized by progressive cerebellar ataxia with degeneration of Purkinje cells, a hypersensitivity to X-rays and an unduly high incidence of cancer. The *a*taxia *t*elangiectasia *m*utated (*ATM*) gene encodes the Atm protein kinase, a member of the phosphatidylinositol 3-kinase family involved in regulating cell cycle and DNA double-stranded break repair. Furthermore, the Atm kinase is required for hematopoietic stem cell self-renewal by inhibiting oxidative stress in these cells. Another disease characterized by immune dysfunction, radiation sensitivity and increased incidence of cancer is the **Nijmegen breakage syndrome** in which there is a mutation in the *NBS1* gene encoding nibrin, a component of the double-stranded DNA break repair complex that becomes phosphorylated by Atm. Both Atm and nibrin are required for efficient class switch recombination in B-cells.

It is exciting to see the molecular basis of diseases being unraveled and an excellent example of Nature yielding its secrets has been provided by studies on the **hyper-IgM syndrome**, a rare disorder characterized by recurrent bacterial infections, very low levels or absence of IgG, IgA and IgE and normal to raised concentrations of serum IgM and IgD. Most patients have an X-linked form of the disease involving point mutations and deletions in the T-cell CD40L (CD154). These mutations largely map to the part of the molecule involved in the interaction with B-cell CD40 (cf. p. 221), thereby rendering the T-cells incapable of transmitting the signals needed for Ig class switching in B-cells. Less commonly, mutation of the X-linked *NEMO* gene (NFκB essential modifier, alternatively known as IKKγ), or the autosomal *CD40*, activation-induced cytidine deaminase (*AID*) or uracil-DNA glycosylase (*UNG*) genes are responsible. In these

cases it is the B-cells, rather than the helper T-cell, that are defective.

The most common genetic cause of **hyper-IgE syndrome** (HIES) is a mutation in the *STAT3* gene. In addition to elevated IgE levels there are decreased numbers of Th17 cells. The HIES phenotype also includes several distinctive anatomical features such as hyperextensible joints and a failure or delay in shedding primary teeth so that patients have two sets of teeth.

Rare cases of T-cell functional deficiency arise from mutation in the γ chain of the CD3 complex, in which patients have normal levels of circulating T-cells but with a reduced expression of T-cell receptors on their cell surface, and ZAP-70 kinase mutations that result in reduced numbers of $CD8^+$ T-cells.

Some immunodeficiencies can rather paradoxically cause an overactive immune response

We have already mentioned that excessive production of certain classes of antibody (IgM or IgE, for example) can result from particular gene defects. It is now also clear that "immunodeficiency" affecting regulatory or tolerance mechanisms will result in an undesirable enhancement of particular types of immune response. Thus, given the critical role of Foxp3 in the induction of regulatory T-cells, it will come as no surprise to hear that loss-of-function mutations in the *Foxp3* gene have a profound effect, being responsible for the **IPEX** (*i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked) syndrome in which unregulated T-cell activity leads to multisystemic and often fatal autoimmune disease. The somewhat less severe clinical condition **autoimmune polyendocrine syndrome-1** (APS-1, sometimes referred to as APECED—*a*utoimmune *p*oly*e*ndocrinopathy with *c*andidiasis and *e*ctodermal *d*ystrophy)—is due to mutations in the *AIRE* gene leading to inadequate central tolerance of T-cells. In contrast APS-2 is genetically much more complex and, like the vast majority of autoimmune diseases (see Chapter 18), is not caused by a single gene defect.

Defects in either Fas (CD95) or Fas ligand (CD95L) lead to **autoimmune lymphoproliferative syndrome** (ALPS) in which there is defective lymphocyte apoptosis resulting in increased numbers of $CD4^-CD8^-$ (double negative) T-cells and the development of autoimmune disease.

Combined immunodeficiency

In the primary T-cell deficiencies described above there are at least some mature T-cells present, albeit functionally defective. However, in **severe combined immunodeficiency disease** (SCID) there is normally an absolute failure in T-cell development and therefore SCID represents the most severe form of primary immunodeficiency, affecting one child in approximately every 80 000 live births. These infants exhibit profound defects in cellular and humoral immunity and without medical intervention death occurs within the first year of life due to severe and recurrent opportunistic infections. Prolonged diarrhea resulting from gastrointestinal infections and pneumonia due to *Pneumocystis jirovecii* are common; *Candida albicans* grows vigorously in the mouth or on the skin. If vaccinated with attenuated organisms these immunocompromised infants usually die of progressive infection.

Several different gene defects can be responsible for the development of SCID

Mutations in several different genes can cause SCID, which involves a block in T-cell development together with a direct or indirect B-cell deficiency. In some cases NK cells also fail to develop (Figure 14.7).

Cytokine signaling pathway defects

Approximately 40% of patients with SCID have mutations in the **common γ (γ_c) chain** of the receptors for interleukins IL-2, -4, -7, -9, -15 and -21. Of these, IL-7R is the most crucial for lymphocyte differentiation, and mutations in the **IL-7R α**

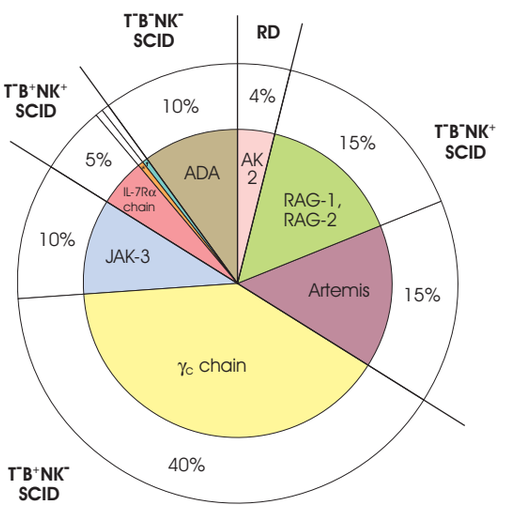

Figure 14.7. Genetic defects responsible for severe combined immunodeficiency (SCID).

The SCID phenotype is dependent upon the particular gene defect that is responsible. For example, in the 15% of SCID cases caused by mutation of the *Artemis* gene there is a complete lack of both T- and B-cells but NK cells are present (i.e. $T^-B^-NK^+$ SCID) whereas in the 10% of cases due to ADA gene defects NK cells are also lacking ($T^-B^-NK^-$SCID). Mutations in CD3δ, CD3ε, CD3ζ or CD45, (*) or the actin-regulator coronin-1A (†) each account for <1% of SCID cases. Mutations in the AK2 gene give rise to reticular dysgenesis (RD). There may be a few rare cases of SCID in which other gene mutations are responsible.