Annu. Rev. Immunol. 1997. 15:93–124

NATURALLY OCCURRING PRIMARY DEFICIENCIES OF THE IMMUNE SYSTEM

A. Fischer, M. Cavazzana-Calvo, G. De Saint Basile, J. P. DeVillartay, J. P. Di Santo, C. Hivroz, F. Rieux-Laucat, F. Le Deist

Unité INSERM U 429, Hôpital Necker-Enfants Malades—149, Rue de Sèvres, 75 743 Paris cedex 15, France

KEY WORDS: primary immunodeficiencies, severe combined immunodeficiencies, T lymphocytes, regulation, apoptosis

ABSTRACT

Naturally occurring genetic disorders of the immune system provide many models for the study of its development and function. In a way, their analysis complements the information provided by the generation of genetic defects in mice created using homologous recombination techniques. In this review, the recent findings made in three areas are focused upon deficiencies in T cell differentiation and in T lymphocyte activation, and on the control process of peripheral immune response.

INTRODUCTION

In the last few years an explosion of knowledge has occurred in the understanding of the molecular basis of the many primary deficiencies of the immune system (1–4). This advance mainly results from the appropriate utilization of the modern tools of molecular biology, leading to gene identification by a variety of techniques including positional cloning and complementation. Table 1 lists the murine and human diseases for which the gene hunt has been successful. Study of these diseases provided much information on all aspects of the immune system, i.e. lymphocyte subset differentiation, cell function, immunity to various microorganisms, and lymphocyte activation regulation. Comparison of human diseases with phenotypes of mutant mice generated by homologous

0732-0582/97/0410-0093$08.00

Table 1 Primary genetic disorders of the immune system for which the gene has been identified

Diseases	Gene
♦ Severe combined immunodeficiencies	Adenosine deaminase
	γc
	JAK-3
	Rag 1/2
scid (m)[a]	DNA-PK
♦ T cell immunodeficiencies	Purine nucleoside phosphorylase
	CD3 ε
	CD3 γ
	ZAP-70
♦ HLA class II deficiency	C II TA
	RFX 5
♦ HLA class I deficiency	TAP2
♦ X-L hyper IgM syndrome	CD40 ligand
♦ Wiskott-Aldrich syndrome	WASP
♦ Ataxia telangiectasia	ATM
♦ Combined T and B cell immunodeficiency	DNA ligase I
♦ Nude (m, r)	Winged helix protein
♦ X-L agammaglobulinemia Xid (m)	btk
♦ Defective control of lymphocyte/macrophage activation and/or proliferation	
motheaten (m)	HCP Phosphatase
lpr (m)	fas
gld (m)	fas ligand
beige (m)/Chediak-Higashi	beige
♦ Phagocytic cell deficiencies	
chronic granulomatous diseases	cytochrome b p91, p22
	cytosolic phox 47 and 67
leukocyte adhesion deficiency	β 2 integrin
idiopathic mycobacterial infections	Interferon γ receptor, α chain

[a](m, r) murine, rat diseases.

recombination techniques, in which an immune deficiency results, has also been successful in increasing the understanding of several human diseases.

The scope of this review is not to detail all of these many findings but to focus on some conditions characterized by an absence of T lymphocytes and a deficiency in T cell activation or in the control of peripheral immune response. As listed in Table 2, many more genetic diseases of the immune system, including those with a nonmendelian inheritance such as common variable immunodeficiency and the closely related IgA deficiency, have kept their secret... for a little longer anyway.

Table 2 Main primary genetic disorders for which the genes have not been identified

- ♦ Severe combined immunodeficiencies (see Table 3)
- ♦ Other T cell immunodeficiencies
  - Omenn's syndrome
  - Di George syndrome*
  - IL2 production deficiency
  - Ca^{2+} influx deficiency
  - Cartilage hair hypoplasia**
- ♦ B cell immunodeficiencies
  - Common variable immunodeficiency***
  - Isotype deficiency (IgA, IgG2. . .)***
  - Hyper IgM syndrome (Autosomal recessive inheritance)
  - Hyper IgE syndrome
- ♦ Defective control of lymphocyte (macrophage) activation and/or proliferation (see Table 4)
- ♦ Phagocytic cell deficiencies
  - Leukocyte adhesion deficiency type II
  - Severe congenital neutropenia****

*Candidate genes exist.
**Gene localized.
***Susceptibility gene localized.
****Acquired mutation of the G-CSFR in some cases.

SEVERE COMBINED IMMUNODEFICIENCIES

Severe combined immunodeficiencies (SCID) represent the most severe form of primary immunodeficiencies. Their overall frequency is approximately 1 in 75,000 births. SCID conditions share the characteristic of a profound block in T cell differentiation (1–4) and are lethal within the first year of life because of absent T cell–mediated immunity. Opportunistic infections, sometimes caused by live vaccines, associated with failure to thrive are usually responsible for death. At least seven different forms of human SCID have now been recognized (Table 3) and can be grouped according to inheritance, phenotype, and, for some of them, identification of the mutated genes.

These conditions represent many models for the study of T cell and, for some, B and NK cell differentiation. Significant progress has been made within the last years in the identification of SCID-associated gene mutations, thereby providing insight into the role of key molecules involved in either lymphocyte precursor proliferation or differentiation [like V(D)J gene recombination]. The overall picture is far from complete, and its complexity is growing. Indeed, different mutations in one gene can give rise to distinct SCID phenotypes, including "attenuated" phenotypes. This is illustrated by mutation of the γc cytokine receptor gene in SCID-X1 (see below). Alternatively, a given

Table 3 Severe combined immunodeficiency (SCID) condition

Disease	Inheritance	Cells affected	Gene
Reticular dysgenesis	AR	T, B, NK, myeloid	?
Adenosine desaminase	AR	T, B, NK	ADA
scid (mouse)	AR	T, B,	DNA-PK
"Alymphocytosis"*	AR	T, B	Rag 1–2
"Alymphocytosis"**	AR	T, B	"recombination process"
SCID-X1	XL	T, NK	γc
SCID with B cells	AR	T, NK	JAK-3
T cell deficiency	AR	T, NK	?

*Without increased cell radiosensitivity.
**With increased cell radiosensitivity.

syndrome can result from mutations of several identified (or as-yet-unidentified) genes.

Alymphocytosis

About 20% of patients with SCID have a phenotype characterized by an absence of mature T and B lymphocytes, while functional NK cells are detectable (5). Usually, thymus is found to be hypoplastic. The condition can be cured by allogeneic bone marrow transplantation (5). This T(−) B (−) form of SCID has autosomal recessive inheritance. These characteristics are strikingly similar to those observed in the naturally occurring mouse mutant strain scid, where a block in T and B lymphocyte differentiation results from defective V(D)J recombination of T cell receptor and Ig gene elements (6). More precisely, while the junction of recombination signal sequences occurs almost normally, formation of coding joints is profoundly impaired (7). Initiation of the recombination process as induced by the Rag-1 and -2 proteins is normal. There is, however, accumulation of hairpin structures of the coding ends, a normal intermediate in V(D)J recombination, that is not normally resolved (8). In addition, scid mice cells exhibit an excessive radiosensitivity, demonstrated to be the consequence of abnormal DNA doublestrand break repair mechanisms (DSBR) (9). Recent genetic studies have brought major advances in the understanding of the molecular basis of the scid defect. The scid deficient gene was first localized on murine chromosome 16 close to genes encoding the surrogate light chains (10). It was then shown that transfer of human chromosome 8 could complement the defect in cell lines. Scid mice cells were found to exhibit the same double defect [DSBR and V(D)J rearrangement] as a hamster cell line, named V3, since they did not complement each other in cell fusion experiments. In contrast, complementation occurred with other DNA–repair deficient hamster cell lines such as xrs-6 and XR-1 (12, 13). Both scid cells and V3 were found

to be defective in DNA-dependent protein kinase (DNA-PK) activity, whereas a yeast artificial chromosome containing the human DNA-PK gene complemented the V3 cell defect (14, 15). Furthermore, chromosome 8 fragments containing the DNA-PK gene complemented the scid phenotype (14).

DNA-PK is a nuclear protein–serine/threonine kinase whose activity depends on binding to free DNA ends. Binding to DNA is mediated through its association with KU 70 and 80 proteins (16) in a multiprotein complex. DNA-PK phosphorylates several substrates including Rag-1, Rag-2, and p53. That scid mice lack DNA-PK activity illustrates the importance of this enzyme in the V(D)J recombination and DSBR processes. The precise function of DNA-PK is presently unknown. As recently discussed (17), DNA-PK could act as an alignment factor juxtaposing coding ends to be joined. In addition, DNA-PK may also recruit DNA repair components such as ligases, terminal deoxyribonucleotide transferase, and exonucleases. Phosphorylation of yet unidentified substrates is a crucial step in this process, either for protein activation and/or inactivation, to regulate the process of ongoing DSBR (17).

A naturally occurring SCID condition with a somewhat similar phenotype has also been described in Arabian foals. Cells from these animals also exhibit excessive radiosensitivity and defective DNA-PK activity (18). A defect in the V(D)J recombination process affects both signal and coding joint ligation as was observed in the KU80 deficient xrs-6 hamster cell line (13, 19). It is not known yet what the precise genetic/molecular defect is, although protein levels of DNA-PK were found to be reduced in equine scid (18). Altogether, these observations stress that the V(D)J recombination machinery utilizes a mammalian DSBR process.

In T(−) B(−) SCID patients, evidence for abnormal V(D)J recombination has also been provided. Schwarz et al described absent or abnormal DH Q52 to JH rearrangements in marrow pre B cells of T(−) B(−) SCID patients (20). Absence of detectable rearrangements in pre B cells were also reported by another group while leaky B cells exhibit restricted junctional and combinatorial diversity with long P nucleotide insertion (21, 21a). We recently showed that fibroblast cell lines transfected with Rag1 and Rag2 genes from some T(−) B(−) SCID patients did not properly rearrange coding joints (N Nicolas, JP De Villartay, unpublished results). Cells from many T(−)B(−) SCID patients also exhibit excessive sensitivity to ionizing radiation (22). It therefore appears that T(−)B(−) SCID can be at least subdivided into two groups, i.e. one characterized by excessive cell radiosensitivity and the second by normal cell radiosensitivity. In the second group, Schwarz et al have found mutations of either Rag-1, Rag-2, or both genes accounting for defective initiation of the V(D)J rearrangement process (23). Defects in Rag gene transcription have also been detected in the marrow of other T(−)B(−) SCID patients (24).

The phenotype of the former group is very similar to that of the scid mouse. However, use of a pulse-field gel electrophoresis method did not detect abnormal DSBR in patients' fibroblasts (25), and a normal DNA PK activity was found (25). Yet, the mechanism(s) underlying the radiosensitive T(−)B(−) SCID phenotype are not clear; a DSBR defect has not been demonstrated despite the existence of abnormal V(D)J rearrangement. Gene products known to be involved in V(D)J recombination, such as of the recently identified XRCC-4 gene, could be good candidates for this immunodeficiency (26).

X-Linked SCID

X-linked SCID (SCID-X1) accounts for 50–60% of cases of SCID (27). It is characterized by an absence of mature T and NK lymphocytes, whereas B cells are present in increased numbers. Histologically, the thymus lacks a cortex/medullar differentiation, lymphoid precursors are scarce, and Hassal's corpuscles are not detectable (1, 27). Peripheral lymphoid organs are also hypoplastic. These data indicate that there is an early block in the T cell differentiation pathway in this disease. Peripheral B cells exhibit a normal phenotype. SCID-X1 is curable by allogeneic bone marrow transplantation, indicating that the defect is intrinsic to the lymphoid lineage (27). Studies of X-chromosome inactivation patterns in obligate carriers have shown a skewed pattern in T and NK cells as well as in B cells, whereas a random pattern was usually detected in the other hematopoietic lineages (28, 29). The SCID-X1 gene product is therefore expressed and involved in the maturation of the T−, B−, and NK-cell lineages. Of note is the observation that the X chromosome inactivation pattern is more skewed in mature than immature B cells (28).

The SCID-X1 locus was mapped to Xq12–13.1 (30). It was then recognized that the gene encoding the γ chain of the IL-2 receptor (now renamed γc) was localized to the same region, and mutations of the γc gene were found in SCID-X1 patients (31). That γc mutations cause SCID-X1 has now been proven in several ways: All patients with SCID-X1 have the γc gene mutation (31–39); in vitro gene transfer of γc into patient's EBV-transformed B cells and marrow cells corrects the high-affinity, IL-2-receptor deficiency and NK cell differentiation block, respectively (40–42, 42a); canine XL-SCID is also associated with a mutation in the γc gene (43); and finally, γc(−) mice exhibit a similar, although not entirely identical, phenotype (see below) (44, 45).

γc belongs to the hematopoietic cytokine receptor family, characterized by four conserved cysteines and the repeated WS motif (46). The γc chain is constitutively expressed by T cells, B and NK cells, as well as myeloid cells and erythroblasts (reviewed in 47). γc expression together with the IL-2R α and β subunits generates the high-affinity receptor for IL-2 (Kd 10^{-11}) by enhancing fourfold the association constant and decreasing fivefold the dissociation

constant. γc is involved in IL-2 endocytosis and plays a major role in signal transduction through activation of its associated tyrosine kinase JAK-3 (47, 48). JAK-3 deficiency (see below) induces a phenotype identical to that of SCID-X1, indicating (*a*) that the main role of γc is to transduce signals through JAK-3 and (*b*) that JAK-3 function is primarily (if not exclusively) to relay γc-induced signals. For IL-2-mediated signaling, heterodimerization of the cytoplasmic regions at IL-2Rβ and γc chains juxtaposes the JAK1 and JAK3 kinases that phosphorylate each other and, once activated, phosphorylate the STAT 3- and 5 proteins. The latter, as dimers, can then translocate to the nucleus where they participate in the induction of the expression of several genes such as *c-myc*, *c-fos*, and *c-jun*, involved in the cell division process (reviewed in 49–51).

A number of mutations of the γc gene have now been reported in SCID-X1 patients (31–39). Since the disease is lethal, a 30% rate for new mutations is expected for each generation, accounting for the variety of mutations found. It is remarkable to note that many single aminoacid substitutions in the extracellular domain are sufficient to abrogate T and NK cell differentiation. Some affect conserved cysteines and the WS motif, the structure of which is likely to be required for the overall configuration of the molecule (33). Others, like an ala$\longrightarrow$val substitution in position 156, create a molecule that is expressed but fails to bind IL-2 or to transduce signals (32). So far, no phenotype/genotype correlations have been detected.

SCID-X1 deficiency was first thought to be the consequence of defective IL-2/IL-2R interaction during thymocyte differentiation. This hypothesis has been proven wrong: In IL-2 (−) mice, and in patients with primary immunodeficiency characterized by defective IL-2 production, T cells develop normally (52–55). γc is a member not only of the IL-2 receptor but also of the IL-4, IL-7, IL-9, and IL-15 receptors (56–62), augmenting in each case the affinity for the cytokine and participating in signal transduction. The SCID-X1 phenotype appears therefore to be the complex association of defects in these five cytokine/cytokine receptor systems.

Recent studies in mutant mice generated by homologous recombination have brought significant insight into the role of IL-7 in T cell differentiation. γc(−) mice have a profound immunodeficiency (44–45). The T cell phenotype of γc mice is very similar, virtually identical with the one of IL-7(−) and IL-7Rα(−) mice, i.e. a 20-fold reduction in thymocyte number, a relative block at the double negative (CD4−, CD8−) stage and reduction in the peripheral T cell pool (63, 64). These data strongly argue for a major role of IL-7 in inducing proliferation of early T cell progenitors in the thymus (65). Also $\gamma\delta$ T cells are completely lacking in γc(−) mice. Despite the profound block in T cell differentiation, in γc(−) mice crossed with transgenic mice for the H-Y-specific TCR, positive and negative selection of H-Y-specific T cell can occur

in the thymus. However, these T cells are almost absent in the periphery, thus showing the role of γc in the maintenance of the mature T cell pool (66).

In γc(−) mice, NK cells are not detectable, whereas B cells are reduced in numbers (44, 45). From the age of 3–4 weeks, γc(−) mice develop a peripheral pool of CD4(+) T cells that appear, at least in part, to be activated (44, 45). The reason for peripheral CD4 T cell expansion, which is not observed in SCID-X1 patients, is unknown (44). Also, in contrast to human γc deficiency, enhanced extramedullary hematopoiesis appeared in γc(−) mice, possibly reflecting a role for the CD4($^+$) T cell pool in promoting nonlymphoid hematopoiesis (67; L Sharara, A Anderson, D Guy-Grand, A Fischer, JP Di Santo, submitted).

Remarkably, in a naturally occurring SCID-X1 model observed in a dog strain created by γc deficiency related to a 4-bp deletion within the first exon, the phenotype was found to be very similar to that of γc(−) mice (43). The role of the γc in T lymphocyte generation is therefore distinct between humans and other species.

The NK cell deficiency observed in SCID-X1 is likely to be the main consequence of defective IL-15-induced signaling. Indeed, IL-15 (with SCF) can trigger CD56$^+$ NK cell generation from CD34$^+$ marrow progenitors (68). We found that following γc gene transfer into SCID-X1 patients' marrow, functional NK cells (CD56$^+$) can differentiate in the presence of SCF and IL-15 (42a).

SCID-X1 B cells can make IgE in the presence of IL-4 and a CD40 mediated–signal (69). However, SCID-X1 EBV-B cells do not activate JAK-3 and STAT6 in the presence of IL-4 (70). These results are accounted for by the presence of γc-independent IL-4 receptor able to transduce at least some signals after IL-4 binding. As expected, IL-2 and IL-15 do not induce Ig switch of SCID-X1 B cells, in contrast to their effects on control B cells (69). These results are likely to account for the in vivo B cell deficiency observed, for instance, after a haploidentical bone marrow transplantation that resulted in selective donor T cell engraftment (71). V(D)J elements of Ig normally rearrange in SCID-X1 B cells, while most JH are in germ-line configuration, probably reflecting a lack of T cell help (72).

In rare instances, γc gene mutations have been found in patients lacking not only T and NK cells but also B cells. No obvious explanation appears for this "atypical" phenotype. This fact further stresses the lack of demonstrable correlation between genotype and phenotype observed so far. It may very well be that modifier gene(s) could play a role.

A combined X-linked immunodeficiency characterized by progressive loss of T and B cell function leading to death during childhood has been described in two pedigrees. In both families, patients' T cells were found to be oligoclonal (73, 74). In one family, the X-chromosome inactivation pattern in obligate

carriers together with gene mapping by RFLP studies was consistent with a form of X-linked SCID. Analysis of the γc gene in the propositus demonstrated two transcripts, one truncated and one normal size, which accounted respectively for 80% and 20% of total γc mRNA (75). A single base-pair substitution in the last position of exon 1 was found that probably disturbed splicing of intron 1 (resulting in the abnormal mRNA product), while a less frequent, normal splicing generated the normal sized mRNA encoding a protein with a conservative Asp$\longrightarrow$Asn substitution in position 39. The γc chain could be detected in EBV-B cells from the patient and showed levels of 20% of normal, high-affinity IL-2 binding sites. Moreover, peripheral T cells from this patient, while poorly functional, were found to use a restricted TCRβ repertoire (75). This case suggests that reduced expression of the γc may profoundly disturb T cell differentiation, with only a relatively small number of clones progressing along the T cell differentiation pathway. As mentioned above, a seemingly identical phenotype has been reported with a γc mutation that reduced JAK-3 binding and T cell activation (48, 74, 76).

More surprisingly, we recently described a profound change in SCID-X1 phenotype following an unsuccessful attempt at bone marrow transplantation (77). Despite a γc gene deletion encompassing most of the intracellular domain of γc, the child developed partially functional T cells that were of host origin. Such T cells were detected over a six-year period following bone marrow transplantation, though in declining numbers. The mechanism by which, in the absence of possible direct JAK-3 activation, these T cells have differentiated and, in part, have functioned remains to be understood (77). It suggests that alternative pathways could exist that compensate for the γc/JAK-3 signal in T cell differentiation in a way similar to that seen in γc-mice and XL-SCID dogs (43–45).

Finally, a SCID-X1 patient developed an unusual phenotype characterized by the presence of 500–800 μl T cells of his own, able to respond (albeit not normally) to mitogens and antigens (V Stephan, et al, *New Engl. J. Med.* In press) Although γc expression could not be detected on the patient's B cells, monocytes or granulocytes while NK cells were not detectable, T cells did express γc. In B cells, γc gene was found to be mutated, (Cys$\longrightarrow$Arg substitution at position 115) with impaired γc expression. In T cells, however, the mutation could not be found. The mother is a carrier of the mutation. These results could be accounted for by a reverse mutation that occurs in a T lineage–committed cell. The latter cell gave rise to a somewhat differentiated pool. This observation provides two interesting pieces of information:

1. Such a rare event restored, at least for an 18 month period, a stable, albeit incomplete, T cell pool

2. The selective advantage conferred to this cell lineage appears very high, giving support for the feasibility of gene transfer as a treatment of SCIDXI, even if conditions of hematopoietic stem cell transduction are very inefficient with the presently available vectors.

A similar reversion has been recently described in a patient with adenosine deaminase deficiency (78): The γc deficiency model reflects how the study of a human primary immunodeficiency can provide much fruitful information in the understanding of lymphocyte differentiation.

JAK-3 Deficiency

A non-X-linked form of SCID characterized by a phenotype similar to SCID-X1 had been known for some time (79). Mutations of the JAK-3 kinase gene were found associated with autosomal recessive inherited T(−) NK(−) B(+) SCID (80). As discussed above, these findings elegantly demonstrated that the γc signal is mediated by JAK-3 activation. A second report has independently confirmed this observation (81). In the three cases reported so far, mutations of the JAK-3 gene led to an almost complete absence of protein and lack of JAK-3 kinase activity (80, 81). Two of the four mutations found in these three patients affected the JH2 kinase domain. Systematic study of non-X-linked T(−) NK (−) B (+) SCID cases has shown that most, but not all, patients exhibit JAK-3 deficiency (G De Saint Basile, unpublished results; 82). As in γc deficiencies, JAK-3-deficient B cells were in part abnormal because IL-4 did not induce STAT 6 phosphorylation (81). The role of JAK-3 deficiency in impairing responses to IL-2 and IL-4 signaling was recently confirmed by restoration of JAK-3 expression and phosphorylation as well as cell proliferation upon IL-2 and IL-4 stimulation, following JAK-3 gene transfer into patients' EBV-transformed B cells (83).

JAK-3 gene inactivation in mice led to a phenotype comparable to γc(−) mice, further confirming that the γc-induced proliferative signal depends on JAK-3 recruitment, phosphorylation, and activation (84–86). Phosphorylation of tyrosine residues within the intracytoplasmic region of γc creates docking sites for SH2 proteins. Three transduction pathways can be triggered following JAK activation by γc-containing receptors. STAT proteins, once phosphorylated, dimerize and are translocated to the nucleus where they bind to gene transcriptional enhancers (87–90). Phosphorylation of insulin receptor substrates leads to activation of phosphatidylinositol 3-kinase (35). Finally, the Shc-Grb2-Sos-Ras activation pathway can also be triggered, inducing transcription of *c-fos* and *c-jun* transcription factor genes. JAK-3(+) T(−) NK(−) B(+) SCID of autosomal recessive inheritance occurs rarely, possibly caused

by a deficiency in an element of this cascade of events provided that it is specific for γc signal.

Other Forms of SCID

As stated above, some forms of SCID, characterized by defective T and possibly NK cell differentiation with autosomal recessive inheritance, have not been molecularly described. Similarly, the molecular basis of the very rare condition reticular dysgenesis (RD) (91) in which there is an almost complete block in lymphocyte subset differentiation, as well as in myelopoiesis, has not been unraveled. There is, however, a striking similarity of RD with the phenotype of mice in which the gene encoding the Pu-1 transcription factor has been inactivated (92).

Adenosine desaminase (ADA) deficiency also induces a profound decrease in the maturation of lymphocyte precursors (93). Its pathophysiology is now well characterized. Defective enzymatic activity in lymphocyte precursors results in the selective accumulation of deoxyATP, which inhibits cell division. Recently, several interesting observations have been reported regarding this disease. A variety of ADA gene mutations have been characterized (94). Some of them are compatible with residual ADA activity enabling some lymphocyte differentiation to occur. The disease has now been detected in adults with "partial" deficiency associated with infections, and also with autoimmunity (94).

ADA deficiency has attracted a lot of interest in the quest for new therapeutic strategies. Besides allogeneic bone marrow transplantation therapy, enzyme substitution with ADA coupled with polyethylene glycol was found capable of restoring sufficient T cell immunity to prevent, in more than 40 patients, major infections for periods of 2 to 8 yr (95). Exogeneous ADA cannot however fully normalize immune functions, for reasons which remain unclear. Major efforts in the treatment of ADA deficiency by gene transfer have therefore been developed. Ex-vivo T lymphocyte transduction works in that transduced T cells persisted and were functional for a period of 2 yr in one patient (96). Gene transfer into stem cells has met with little success so far, likely because the defective retroviruses used as vectors do not integrate into the genome of noncycling stem cells (97–99). The selective advantage conferred by ADA gene expression may, however, enable transduced cells progressively to give rise to a sufficient T cell pool. Although some reports indicate a persistence in the periphery of a small number of ADA-transduced T cells, concomitant treatment by PEG-ADA could mask this potential advantage. Unfortunately, experiments in animal models cannot be performed because ADA gene inactivation in mice is lethal at birth because of poor liver differentiation (100, 101). Although

hepatic dysfunction has recently been reported in ADA-deficient patients (102), an obvious major difference appears in the consequences of ADA deficiency between murine and human species.

T CELL IMMUNODEFICIENCIES

A number of primary immunodeficiency phenotypes have been described in which T lymphocytes, in contrast to SCID conditions, can be detected in the periphery. T cell numbers are in normal or reduced numbers, while T cell functions are, at least in part, disturbed. Although functional defects and, when known, genetic defects show considerable heterogeneity (Table 1), these conditions share many phenotypic features that deserve consideration.

Patients with these forms of T cell immunodeficiency do not usually develop life-threatening infections during the first months of life; rather, they develop a variety of complications caused directly or indirectly by the T(+B) cell immunodeficiency. These consist of infections, autoimmunity, allergies, and malignancies (103). Autoimmunity is a very frequent complication of T cell immunodeficiency. It occurs in at least 50% of patients, whatever the precise diagnosis, at some time during childhood or early adulthood. The autoimmunity is mostly caused by autoantibodies against blood cells (anemia, thrombocytopenia, neutropenia), although hepatitis and vasculitis that involve the brain and kidney have been observed. Many of these patients suffer intractable diarrhea caused by diffuse enteropathy, which shows a striking similarity to the inflammatory bowel disease seen in mice defective in IL-2 (52), IL-2Rβ, or CD3 ζ T lymphocyte proteins (104–105), for instance. The mechanism(s) by which T cell dysfunction leads to severe autoimmunity could rely on faulty negative selection and/or peripheral "anergy induction" of both T, and indirectly, B cells (106).

Identified Causes of T Cell Immunodeficiencies

This group currently consists of partial CD3ϵ expression deficiency, CD3γ subunit expression deficiency (107–108), and ZAP 70 tyrosine kinase deficiency (109–112). Findings in the latter groups of 7 patients from 4 families were instrumental in demonstrating the key role of ZAP 70 in T lymphocyte activation. In all cases, it resulted in the occurrence within the first years of life of recurrent and opportunistic infections. CD8 T cells were virtually absent, in contrast to CD4 T cells. The latter cells, however, proliferated poorly in the presence of mitogens and did not produce IL-2; Ca^{2+} influx triggered by anti-CD3 antibody was severely impaired. IL-2 addition could restore CD4 lymphocyte proliferation. Tyr-phosphorylation of cellular proteins was markedly reduced following anti-CD3 antibody cell triggering. This led to the discovery of an

absence or abnormal ZAP 70 protein. Three mutations of the ZAP 70 encoding genes have been characterized. In two families, a homozygous insertion of three residues in the kinase domain resulted from a G⟶T intronic mutation, creating a new splice site. This mutation caused an unstable protein. In a third family, a C⟶A mutation at nucleotide 1763 caused a Ser-to-Arg substitution in residue 518. The siblings carrying this mutation were also heterozygous for the previously described mutation. Interestingly, position 518 is conserved in the kinase domain between ZAP 70 and the related syk kinase. In the third family, the affected sibling had a homozygous deletion of 13 bp (1719 to 1731). A translational frameshift ensued from position 503 in the kinase domain. A premature termination occurred 35 residues downstream. Though expressed, this protein had lost major functional positions in the kinase domain.

Functional consequences of the ZAP 70 tyrosine kinase deficiency emphasize its role in signal transduction following TCR ligation. ZAP 70 binds to Tyr-phosphorylated CD3 subunits (ITAM motifs) and phosphorylates various substrates including PLC γl. The intriguing selective deficiency of CD8 T cells that has been confirmed to occur in the thymus (109) led to the interesting hypothesis that the related syk protein, which is expressed fourfold more in thymocytes than in mature T cells, could substitute for the deficient ZAP 70 to enable CD4, but not CD8, T cell differentiation to occur. CD8 T cell maturation would fail because a primary signal mediated by the tyrosine kinase lck-bound to CD8 would not be powerful enough to allow sufficient Tyr-(P) of CD3 subunits in order to allow syk to bind and be activated. Indeed, lck binding to CD8 is much reduced compared to CD4/lck interaction (111, 112). Of interest in ZAP 70(−) mice is that there is neither CD4 nor CD8 T lymphocyte development (113).

T cell immunodeficiency secondary to defective HLA class II molecule expression is beyond the scope of this review; it has been described in a recent comprehensive review (114).

T Cell Immunodeficiencies with an As-Yet-Unidentified Molecular Basis

LYMPHOKINE DEFICIENCIES In recent years, functional T cell immunodeficiencies have been described in conjunction with abnormal cytokine production. Five patients have been reported with this form of immunodefiency, with opportunistic and viral infections, chronic diarrhea, failure to thrive, and erythroderma. Blood lymphocyte counts were normal. The phenotype and distribution of T lymphocytes were normal except in one patient who had circulating immature T cells [CD3(+), CD1(+), CD4(−), CD8(−)]. The main feature in common was poor mitogen-induced T lymphocyte proliferation that was restored by the addition of exogenous IL-2. This T cell dysfunction was

associated with hypogammaglobulinemia (53–55). These immunodeficiencies are related to an IL-2 production defect, which is associated, in one case, with other lymphokine (IL-4, IL-5, IFNγ) production defects (55). In all cases, it results from IL-2 gene transcription failure after T cell activation, even though early steps in T cell activation are normal (53–55, 114a). The precise molecular defects have not been identified. In the multi-lymphokine defect, abnormal binding of the transcription complex NF-AT to the enhancer region of the IL-2 gene was identified by transfection of a reporter gene (115). Since the molecular definition of the NF-AT complex has been recently identified, the basis of this immunodeficiency could be soon elucidated. In other cases, the IL-2 production defect could result either from a mutation in regulatory sequences of the IL-2 gene interfering with binding of regulatory proteins or from an abnormality in a regulatory protein.

DEFICIENCY OF TRANSMEMBRANE CA^{2+} INFLUX We have recently studied three unrelated cases of severe T cell immunodeficiency characterized by defective T cell proliferation and IL-2 synthesis to mitogens (anti-CD3 antibody and antigens), while T lymphocyte subsets were normal in the periphery (116, 117). This functional T cell immunodeficiency was detected early in life (6 months to 5 years of age) because of the occurrence of severe bacterial and viral infections leading to early death of two other siblings. Whereas the early steps in T cell activation, i.e. tyrosine phosphorylation, lck/fyn kinase activities, and phosphoinositide turnover, were found to be normal following TCR cross-linking, anti-CD3 antibody-induced Ca^{2+} flux was, in contrast, grossly abnormal. Ca^{2+} release from endoplasmic reticulum stores was detectable as tested in the presence of anti-CD3 antibody or of thapsigargin following cell membrane depolarization in a K+ rich medium, whereas extracellular entry of Ca^{2+} was defective. The latter abnormality was not secondary to defective K+ channels' function, which were normal. A similar defect was found in other hematopoietic cell lineages, fibroblasts, and myocytes as evaluated by both cytometry and digital video imaging experiments at a single cell level. This primary T cell immunodeficiency appears thus to be due to defective Ca^{2+} entry through the plasma membrane.

These data are very similar to findings recently reported in Jurkat mutants (118, 119). In both patients cells and Jurkat mutant cells a deficiency appeared in the transmembrane calcium current induced by depletion of endoplasmic reticulum stores (as triggered by thapsigargin, IP3, or low concentration of ionomycin) (120). This capacitative calcium entry plays a major role in T cell activation by enabling calcium-dependent signals to occur through calcineurin activation (121). As a consequence of the rise of defective intracytosolic calcium concentration, NF-AT complex cannot be detected in patients' lymphocyte

nuclear extracts, probably because the preexisting cytoplasmic subunit of NF-AT, i.e. the NF-ATc/NT-ATp complex, is not translocated into the nucleus. Conversely, NF-κB complex was normally detected.

The underlying molecular defect is yet to be found. The CAML gene encoding a transmembrane protein necessary for transmembrane Ca^{2+} influx (122) is normally expressed, and the sequence of the coding region is normal in cells tested from two of these patients (JP De Villartay, unpublished observation).

Recently, two groups cloned the homolog of a *Drosophila* calcium released-activated Ca channel (CRAC), called TRPC 1 and 3 for transient receptor potential channel-related protein 1 and 3 (htrp1 and htrp3) in mouse and humans, respectively (123, 124). These channels mediate Ca^{2+} entry with characteristics similar to the ones defective in patients' cells and Jurkat mutant cells. Mutation of gene(s) from this family are therefore potentially good candidates for this T cell immunodeficiency. A very intriguing observation made in this condition is that hematopoietic cells, other than T cells, appear to function normally despite the same Ca^{2+} current defect having been found in B cells, platelets, and granulocytes (116, 117). For instance, anti-μ antibody-induced B cell proliferation was found to be normal as was platelet aggregation triggered by several reagents (116). Calcium current deficiency was also detected in nonhematopoietic cells such as fibroblasts and cultured myocytes, whereas excitable current induced by acetylcholine was found to be normal in the latter cells (125). We recently recognized that the muscular calcium current deficiency found in myocytes, as evidenced following stimulation with thapsigargin, could have symptomatic consequences because the two live patients, at the respective ages of 4 and 5 years, have presented with progressive muscular weakness and abnormal electromyographic features. How this CRAC influences muscle function, in addition to T lymphocyte activation but not other cell functions, is presently unknown.

INHERITED DISEASES RESULTING IN DEFECTIVE CONTROL OF LYMPHOCYTE ACTIVATION/PROLIFERATION/SURVIVAL

Many conditions have now been characterized that share a deficiency in the control of lymphocyte and macrophage activation and proliferation (106).

FAS Deficiency

lpr mice exhibit a progressive lymphoproliferative syndrome consisting of an accumulation of abnormal CD4(−) CD8(−) T cells associated with variable autoimmune manifestations, depending on the genetic background (126). The mutation results in faulty Fas (CD95) expression and thereby defective Fas-triggered lymphocyte apoptosis (127). Insertion of a transposon into intron

Table 4 Genetics disorders with impaired "off" signals in T and B cells

	(m) mice (h) human	Gene	Affected cells
1pr	(m)	fas	T, B
Lymphoproliferation with auto immunity	(h)	fas	T, B
gld mice	(m)	fas-L	T, B
Lymphoproliferation with auto immunity	(h)	?	T, B
motheaten	(m)	HCP phosphatase	B myeloid cells
beige mice	(m)	beige	T*, macrophages
Chediak-Higashi syndrome	(h)	beige-equivalent?	
Familial hemophagocytic lymphohistiocytosis	(h)	?	T*, macrophages
Immunodeficiency with partial albinism	(h)	?	T*, macrophages
X-linked proliferative syndrome	(h)	?	T*, macrophages
Omenn's syndrome	(h)	?	T** usually oligoclonal

*TH1 phenotype.
**TH2 phenotype.

2 of the Fas gene dramatically reduces normal splicing of the Fas transcript. A similar, albeit less severe, condition, *lpr*^{cg}, is associated with a missense mutation within the so-called "death domain" encoding part of the Fas gene (128). Mutations of the Fas-ligand gene also result in lymphoproliferation (*gld* mutation) (129).

Recently, a human disease also characterized by lymphoproliferation, consisting in the accumulation of CD4(−) CD8(−) T cells and variable autoimmunity, has been described (130) and found to be associated in several cases with Fas-encoding gene mutations (131,132).

Three different conditions deserve attention: (i) human lymphoproliferation associated with an absence of Fas expression, i.e. equivalent of a null mutation; (ii) human lymphoproliferation associated with heterozygous Fas gene mutation; and (iii) human lymphoproliferation without a detectable Fas defect.

HOMOZYGOUS FAS DEFICIENCY The first condition has only been described in a single case so far (131). The child born to related parents had massive lymphoproliferation evident at birth, suggesting a process that had started in the prenatal period. This is different from both *lpr* and Fas (−/−) mice (131, 133). Lymphoproliferation involved both CD4(−), CD8(−), CD45 RA(+),

HLA class II, CD57(+) T cells and B cells and was associated with mild autoimmunity causing thrombocytopenia (133). Lymphocytes from this patient did not express Fas following stimulation and were insensitive to treatment by an agonist anti-Fas antibody (131). A homozygous genomic deletion from nucleotides 1110 to 1400 led to transcript lacking the region encoding the last 28 residues from the intracytoplasmic domain of Fas and part of the 3′ untranslated region (131). It is thought that, as in *lpr* mice, the CD4($^-$) CD8($^-$) T cells were derived from CD4($^+$) and CD8($^+$) mature T cells that had lost CD4 or CD8 expression in an "attempt" to downregulate cell activation (134).

Some characteristics of the T/B lymphoproliferation in this child deserve further comment. Numerous mitotic figures were observed in spleen and lymph node sections, suggestive of active lymphocyte division and not only of passive lymphocyte accumulation. The rapid rise in circulating lymphocyte counts seen following chemotherapy treatment also supports this hypothesis (133). In the absence of Fas expression on peripheral lymphocytes, an early onset (prenatal) activation, proliferation, and therefore accumulation of autoreactive T and B cells is assumed.

In lymphoid organ sections, although architecture was preserved, few B lymphoid follicles were detected (133). This observation fits with the proposal of Rathmell and Goodnow that autoreactive peripheral B cells chronically stimulated by antigens migrate to T cell zones where, in the absence of Fas expression, they can actively proliferate instead of dying following CD40 activation (135).

Finally, it was striking to note the presence of lymphocytes undergoing apoptosis on blood smears as well as in the spleen sinuses as detected by using the Tunel method (133). These results suggest that an alternative pathway(s) of lymphocyte apoptosis is engaged in an attempt to compensate for the Fas deficiency. The observation that TNF receptor I deficiency accelerates the lymphadenopathy and autoimmunity onset in *lpr* mice also indicates that distinct ways of inducing peripheral lymphocyte death do exist (see below) (136). The human Fas deficiency has been found to be curable by allogeneic bone marrow transplantation (M Benkerrou, M Benberrou, F Le Deist, JP DeVillartay, S Caillot-Sucman, F Ruux-Larcat, N Jabado, M Carazzana-Calro, A Fischer, submitted).

HETEROZYGOUS FAS MUTATION Seven children from six unrelated families were found to exhibit lymphadenopathy and variable autoimmunity in association with heterozygous Fas gene mutations (131, 132). Clinical manifestations related to lymphadenopathy were detected between birth and the age of 5 years. Three of the children developed autoantibodies to red cells, platelets, and granulocytes; one had glomerulonephritis, but none developed lupus manifestations. Overall, features of this condition were similar, albeit less severe, to the ones

observed in the patient with homozygous Fas deficiency. Distinct mutations (splice site mutations, deletions, and missense mutations) were detected in all cases on one single Fas allele. Fas-mediated apoptosis of lymphocytes was impaired in all cases. Mutations were inherited from one parent, though cells from one parent were mosaic for the Fas mutation (132). Interestingly enough, five out of the six parents harboring a Fas mutation had neither clinical nor immunological features of lymphoproliferation or autoimmunity. Two parents had Hodgkin's disease, which suggests that Fas mutation could favor the development of lymphomas. Fas-mediated apoptosis in carriers was found to be reduced in two out of five cases tested.

It has been proposed that Fas mutation could induce transdominant negative effects because the Fas-induced apoptotic signal requires Fas trimer formation (137). Transfection experiments performed with mutated cDNA from five cases support this hypothesis (132). These data do not account, however, for the lack of symptoms in most carrier parents. Considering the disease as digenic provides an alternative hypothesis. Single allele Fas mutation would therefore combine with an unknown mutation from another gene, which also favors the development of lymphoproliferation and autoimmunity. This hypothesis is supported by two pieces of data: 1. Heterozygous *lpr*^{cg} mice with a missense mutation in the death domain have no symptoms; and 2. Two unrelated parents from patients with heterozygous Fas mutations exhibit reduced Fas-induced apoptosis of lymphocytes, although they have no mutation in the Fas-encoding gene and their lymphocytes express Fas normally (131, 132). It is therefore believed that mutation gene(s) encoding proteins involved in the transmission of the "death signal" contribute to the observed deficiency. Genes encoding proteins known to interact directly with Fas such as MORT 1/FADD or RIP or to mediate further downstream signals such as MACH/FLICE or ICE family related proteins are good candidates (138–144). Possible identification of as-yet-unknown proteins involved in triggering death may also provide other candidates.

If this second hypothesis turns out to be correct (possibly in conjunction with transdominant negative effect), one could assume that genetic predisposition to lymphoproliferation and/or autoimmunity should also be associated with Fas-independent apoptotic defects. Also, variability in autoimmune manifestations, observed within one family (131), likely indicates involvement of other susceptibility genes as observed in mice where *lpr* mutation on different genetic backgrounds leads to distinct autoimmune manifestations. Given the observation that central tolerance (negative selection) occurs normally in *lpr* and Fas (−/−) mice, it is likely that autoimmune disorders detected in Fas-deficient patients result from faulty peripheral tolerance mechanism(s) only (145, 146).

Taken together, the human Fas mutant condition tells us that the Fas molecule is a major component in the control of the lifespan of T and B lymphocytes in

the peripheral compartment. It delivers a potent "off" signal to autoimmune clones in the periphery.

LYMPHOPROLIFERATION WITHOUT FAS DEFICIENCY Patients with a similar phenotype (both children and adults) have now been recognized with normal Fas expression and Fas signaling leading to lymphocyte death. We have detected five such cases. An obvious possible explanation of this condition relies on Fas ligand deficiencies by analogy with the *gld* mice (129). This hypothesis has been now excluded at least in one case (JP DeVillartay, unpublished data). However Wu et al recently reported the finding of an hetrozygous loss of function mutation of the Fas-L gene in an adver with systemic lupus erythematosis C146a. Overall, these data therefore open the search for defects in FasL/Fas-independent pathways that control lymphocyte death. This is an important finding because it tells us that several death-triggering molecular pathways exist to control activation of human peripheral lymphocytes, although they cannot efficiently compensate for Fas pathway deficiencies (see above). Whether TNF receptor type I (147), type II (148), or other related molecules such as TRAIL (149) or, as yet, unknown receptors mediate this (these) alternative pathway(s) remains to be determined.

It is also worth noting the recent description of acquired clonal loss of function Fas mutation in CD4(−) CD8(−) T cells in two patients with hypereosinophilia. These T cells expanded and produced cytokines promoting eosinophil production (150).

Inherited Diseases with Defective Control of T (B) Lymphocyte Activation

MOTHEATEN MUTATIONS A complex phenotype consisting of inflammatory lesions associated with myeloid hyperplasia and B cell autoimmunity has been described in the so-called motheaten mice. Patchy alopecia, inflamed paws, lung infiltrates, extramedullary myelopoiesis with splenomegally, hypergammaglobulinemia, and the production of autoantibody by B1 lymphocytes associated with impaired T and B cell development are the hallmarks of this disease (151).

A lethal as well as a less severe phenotype have been described, named respectively me/me and me^v/me^v (v = viable) mutations (152, 153). The hematopoietic cell phosphatase (HCP), also called PTPIC, is deficient in *motheaten* mice (154, 155). HCP is a cytosolic phosphatase, widely expressed among hematopoietic cells, that can be activated to bind membrane molecules such as CD22 or Fc receptor γ IIb cells and to counteract phosphorylation events triggered by antigen receptor engagement (156). B cells from motheaten mice exhibit an increased intracellular calcium rise following antigen stimulation. Consequences of the

faulty control of B cell activation through the antigen receptor are twofold. It leads to elimination of precursor B cells, whether avidity to self-antigen is high or low, and to exaggeration of antibody production, including autoantibodies by peripheral residual B cells (106). The regulatory role of HCP is obviously important in other cell lines because most motheaten phenotype manifestations persist in me^v/me^v Rag1 −/− B cell–deficient mice (157). This example was, nevertheless, the first description of a naturally occurring genetic deficiency in a regulatory pathway of lymphocyte activation.

CHEDIAK-HIGASHI SYNDROME/BEIGE MICE Chediak-Higashi syndrome (CHS) and its murine counterpart, the beige mutation, are complex conditions characterized by partial skin and ocular albinism associated with increased susceptibility to infections, deficient cytotoxic lymphocyte activity, and the presence of large intracytoplasmic granulations in many cell types (158, 159). These large granules result from defective vesicular trafficking of the late endosome/lysosome compartment (160). The contents of lysosomes do not normally accumulate. Defective T cell and, above all, natural killer cell cytotoxicities ensue because giant granules are not exocytosed and lytic proteins are not properly delivered (161, 162). Following localization of the beige locus on chromosome 13, the beige gene was recently identified by positional cloning (163, 163a). It encodes a novel cytoplasmic protein that may control lysosome traffic through interaction with microtubules.

The CHS gene localization was found to be syntenic to *beige* on human chromosome 1 (164). It is therefore very likely that mutations of the human *beige equivalent* gene cause the CHS. Also, two murine yeast artificial chromosomes that complement beige mutation complement Chediak-Higashi fibroblasts (164a). Most patients with CHS develop a lethal complication, called the "accelerated phase," characterized by unremitting T and macrophage cell activation in multiple organs (165). Allogeneic bone marrow transplantation is the only way to control this intriguing complication (166). Onset of the "accelerated phase" usually follows an infection. This suggests that, once triggered, T lymphocyte activation never terminates in this condition. It is presently unclear whether the uncontrolled T lymphocyte/macrophage activity in CHS patients results from a defect in a cytotoxic cell pathway surveying cell activation or in another unknown regulatory mechanism. An "accelerated phase" does not usually occur in beige mice.

FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (FHL) A similar T lymphocyte/macrophage activation syndrome also occurs in other human inherited diseases, such as partial albinism with immunodeficiency (167), familial hemophagocytic lymphohistiocytosis (FHL) (168), and X-linked proliferative syndrome (XLP) (169). FHL is the prototypic disease in which T lymphocyte

and macrophage activation occurs early in childhood and continues until death. Liver, spleen, bone marrow, and central nervous system are infiltrated by activated T cells and macrophages that phagocyte blood cells, a process called hemophagocytosis. T cell activation is demonstrated by the detection of HLA DR+ T cells in blood (and tissues) mainly of $CD8^+$ phenotype, high serum levels of soluble CD8 and IL-2 receptors (170), and high levels of interferon γ in the serum (171). Activated T cells express α/β form of the TCR and are polyclonal (F Rieux-Laucat, unpublished observation). Hemophagocytosis, high serum levels of TNFα, and IL-1 reflect macrophage activation in this condition. The trigger for persistent T and macrophage cell activation is largely unknown. FHL is inherited as an autosomal recessive disorder indicating that a single gene defect can cause this severe syndrome. It is likely that activation of T cells with a TH1 phenotype proceeds and induces macrophage activation since treatment by T lymphocyte targeting agents such as cyclosporin A and antithymocyte globulins are effective (172). This disorder somewhat resembles the phenotype of CTLA4 ($-/-$) mice in which activated T cells accumulate and induce early death (173). Genetic linkage analysis has however excluded CTLA4 as a candidate gene in several families (R Dufourcq, G De Saint Basile, unpublished results).

Patients with CHS and FHL conditions share a common feature, i.e. deficiency in NK cell activity. Speculations on the role of NK cells in the control of T/macrophage activation might thus be put forward. There is however no evidence for downregulation of HLA class I by the latter cells, a condition necessary for being a target for NK cell activity (174). Also recently described, deficiencies in NK cells associated with CD16 (Fcγ RIIIa) gene polymorphism and loss of the B73.1 epitope were found in patients with recurrent viral infections who had no undue T and macrophage cell activation (175, 176).

It is worth noting that the CHS "accelerated phase" and FHL conditions can be cured by allogeneic bone marrow transplantation even when only a mixed chimerism is achieved (166, 177, 178). These data indicate that the unknown defective mechanism of T/macrophage activation control can act as a transeffector.

OMENN'S SYNDROME Another enigma is raised by the immunological manifestations of the Omenn's syndrome (179). This rare disorder has an autosomal recessive mode of inheritance. It is characterized by the occurrence in infants of diffuse erythrodermia, alopecia, protracted diarrhea, and failure to thrive, and eventually death. There is massive infiltration of the epidermis and dermis as well as of gut epithelium and lamina propria by activated T cells that can also be detected in the patient's blood. T cell proliferation and activation are associated with marked eosinophilia. Proliferative T cells are thought to exhibit a TH2 phenotype because high levels of IL-4 and IL-5 were found in

patients' sera as well as in T cell supernatants (180,181). In many cases, the T cell pool was restricted with a very low number of clones exhibiting variable phenotype; i.e. TCR $\alpha\beta+$, $CD4^+$, $CD8^+$ or $CD4^-$, $CD8^-$ or T TCR $\gamma\delta+$ (182, 183). Therefore, at least in these cases, Omenn's syndrome represents oligoclonal proliferation of T cells exhibiting a TH2 phenotype possibly reactive toward epithelia. In contrast, peripheral lymphoid organs and the thymus are essentially devoid of lymphocytes, indicating profoundly defective T cell differentiation. The B cell pool is also extremely reduced. Why a small number of T cell clones escape a block in cell differentiation and exert autoimmune-like reactivity is presently unknown. In two families, patients with Omenn's syndrome had siblings with severe combined immunodeficiency characterized by a block in T and B cell differentiation. Omenn's syndrome could therefore reflect, at least in some cases, a leakiness in a lymphocyte differentiation block.

It thus appears that further genetic and molecular studies of human disorders resulting in uncontrolled immunity should bring fruitful information on the still poorly understood mechanisms underlying the regulatory processes in lymphocyte function.

CONCLUSION

This review has discussed some aspects of how the observation of natural mutants of the immune system contribute to the knowledge of lymphocyte function. Many models still remain unraveled and will, no doubt, provide more information. It is also clear that complexity is growing because immunodeficiency-susceptibility genes, i.e. genes creating susceptibility to infections, are also associated with a predisposition to autoimmunity, allergy, and often uncontrolled cell growth. Also, we have learned that mutations from one single gene like γc, btk, WASP, or CD40 L (184–190) can lead to various phenotypes possibly because of the intervention of environmental factors or, more likely, modifier genes. Conversely, one given phenotype can be the consequence of several gene mutations as shown by severe combined immunodeficiency impairing both T and B lymphocyte differentiation or lymphoproliferative syndrome with autoimmunity.

Although these observations will create a lot of difficulties for clinical immunologists trying to ascertain molecular diagnosis in patients and families, it is a source of continuing excitement for immunologists to understand the basis of the increasing complexity. One way to help resolve these new questions perhaps relies on the establishment of an international registry collecting phenotypic and genotypic information on individual cases as illustrated by recent efforts (191, 191a,b).

ACKNOWLEDGMENTS

We would like to thank Drs M Blaese, B Belohardsky, E De Vries, L Notarangelo, J Regueiro, K Schwarz, and J Vossen for providing us with unpublished information. We are grateful to Dr J Peake for reading the manuscript.

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