Partial defects of T-cell development associated with poor T-cell function

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For many years, severe combined immune deficiency diseases, which are characterized by virtual lack of circulating T cells and severe predisposition to infections since early in life, have been considered the prototypic forms of genetic defects of T-cell development. More recently, advances in genome sequencing have allowed identification of a growing number of gene defects that cause severe but incomplete defects in T-cell development, function, or both. Along with recurrent and severe infections, especially cutaneous viral infections, the clinical phenotype of these conditions is characterized by prominent immune dysregulation. (J Allergy Clin Immunol 2013;131:1297-305.)

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Severe combined immune deficiency (SCID) includes a heterogeneous group of genetic disorders characterized by severe impairment of T-cell development, with a virtual lack of circulating autologous T lymphocytes and absence of functional T-cell responses.[1] Clinical manifestations of SCID include early-onset life-threatening infections and failure to thrive. In contrast, especially in recent years, several conditions have been described in which T-cell development and function are impaired but not abrogated. These disorders have a broader spectrum of clinical manifestations that often includes autoimmunity, inflammation, and lymphoproliferative disease, indicating disturbance of immune homeostasis. In this review we will focus on this heterogeneous group of disorders. We will focus our attention to diseases with a molecular basis that has been defined in the last few years for which novel clinical and immunologic phenotypes have been reported or novel insights into the pathophysiology of clinical manifestations of immune dysregulation associated with these conditions have been recently provided. Purine nucleoside phosphorylase deficiency,[2] MHC class I[3] and class II[4] deficiencies, and CD8α deficiency[5] also belong to this group of partial defects of T-cell development and function, but their clinical and immunologic phenotype is well known and will not be discussed further here.

Abbreviations used

AIRE:	Autoimmune regulator
CMV:	Cytomegalovirus
CRAC:	Calcium release–activated channel
DOCK8:	Dedicator of cytokinesis 8
$InsP_3$:	Inositol 1,4,5-trisphosphate
ITK:	IL-2–inducible tyrosine kinase
LAT:	Linker of activation in T cells
Lck:	Lymphocyte-specific protein tyrosine kinase
MAGT1:	Magnesium transporter 1
MST1:	Macrophage stimulating 1
NKT:	Natural killer T
OS:	Omenn syndrome
PLCγ:	Phospholipase Cγ
RAG:	Recombination activating gene
RHOH:	Ras homology family member H
SCID:	Severe combined immune deficiency
STIM1:	Stromal interaction molecule 1
Syk:	Spleen tyrosine kinase
TCR:	T-cell receptor
T_{EMRA}:	T effector memory $CD45RA^+$ cells
TREC:	T-cell receptor excision circle
Treg:	Regulatory T
UNC119:	Uncoordinated 119
ZAP70:	ζ Chain–associated protein of 70 kDa

COMBINED IMMUNODEFICIENCIES CAUSED BY HYPOMORPHIC MUTATIONS IN SCID-ASSOCIATED GENES

Although SCID is typically associated with lack of T-cell development and function, hypomorphic mutations in SCID-causing genes can allow residual development of autologous T cells and reduced (but not absent) T-cell function. The clinical phenotype associated with this condition is not limited to typical manifestations of SCID but often includes immune dysregulation and lymphoproliferative disease.[1,6]

Omenn syndrome (OS) represents the prototypic form of a severe inflammatory/autoimmune condition associated with hypomorphic mutations in SCID-causing genes with severe restriction of T-cell development associated with profound abnormalities of the mechanisms that govern immune tolerance.[7] In particular, there is a reduced number of medullary thymic epithelial cells expressing autoimmune regulator (AIRE), a transcription factor that permits expression of tissue-restricted peptides that are

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presented to nascent thymocytes, enabling clonal deletion of self-reactive T cells.[8,9] Moreover, the development and function of regulatory T (Treg) lymphocytes are severely compromised.[10] As a result of inefficient deletion and suppression of self-reactive T cells, oligoclonal expansion of distinct T-cell clonotypes is observed in patients with OS.[7,9] From a mechanistic standpoint, the abnormalities of immune tolerance in patients with OS reflect defective lymphostromal cross-talk in the thymus and have been observed also in cases of OS caused by genetic defects other than recombination activating gene *(RAG)* mutations,[8] indicating that normal T-cell development is essential to support the maturation and function of thymic epithelial and dendritic cells. It is likely that similar abnormalities might contribute to clinical manifestations of immune dysregulation in other conditions with impaired T-cell development and function, as described below.

More recently, hypomorphic *RAG* mutations have been identified in patients with milder phenotypes, such as delayed-onset disease and granulomatous or autoimmune manifestations,[10-13] dysgammaglobulinemia with a hyper-IgM phenotype,[14] and idiopathic CD4 lymphopenia.[15] In these cases the functional activity of mutated RAG proteins was significantly higher than in patients with SCID or OS.

Somatic mutations are another mechanism that can modify the disease phenotype in patients with SCID-associated gene defects. Originally reported in patients with adenosine deaminase deficiency,[16] the occurrence of somatic mutations that can restore, at least in part, expression and function of the mutated protein have been subsequently demonstrated in patients with other SCIDs.[17] In some cases this resulted in a shift of phenotype from SCID to OS[18,19]; more rarely, restoration of T-cell function has been observed,[20,21] providing a strong basis for the development of gene therapy.

Finally, environmental factors can also shape the phenotypic spectrum of SCID and associated disorders, especially in patients with hypomorphic mutations, as indicated by expansion of T cells expressing T-cell receptor (TCR) γδ after cytomegalovirus (CMV) infection[22,23] and by conversion of SCID into the OS phenotype after viral infection.[24]

TCRα CONSTANT GENE DEFECTS LEADING TO SELECTIVE LACK OF TCRαβ$^+$ T LYMPHOCYTES

TCRαβ$^+$ lymphocytes comprise approximately 80% to 85% of all circulating T cells. Morgan et al[25] have reported the cases of 2 patients who presented with a history of recurrent respiratory tract infections, *Candida* species–associated diarrhea, failure to thrive, autoimmunity (hemolytic anemia and vitiligo), eczema, eosinophilia, lymphadenopathy, and organomegaly. One of the patients showed increased susceptibility to severe herpes virus (EBV, varicella zoster virus, and human herpes virus 6) infections. All T cells expressing CD3 at normal density also coexpressed TCRγδ; an unusual population of CD3^{lo} cells expressed TCRαβ at a very low level. *In vitro* proliferative responses to mitogens and antigens were decreased, but specific antibody production was preserved. In both patients mutation analysis disclosed a homozygous splicing mutation in the TCRα constant gene *(TRAC)*, with loss of TCRα transmembrane and intracytoplasmic domains. Although several aspects of the disease remain unclear (including the developmental history of CD3^{lo} cells and the nature of signals that might promote their expansion *in vivo*), this novel combined immunodeficiency illustrates the nonredundant role played by TCRαβ$^+$ T cells in immune defense and homeostasis.

LYMPHOCYTE-SPECIFIC PROTEIN TYROSINE KINASE DEFICIENCY

The lymphocyte-specific protein tyrosine kinase (Lck) is constitutively associated with CD4 and CD8 proteins and plays a key role in the initial steps of the TCR signaling process by mediating phosphorylation of immunoreceptor tyrosine activation motifs in the intracytoplasmic domains of CD3 subunits and of the ζ chain–associated protein of 70 kDa (ZAP70).[26]

Defective expression of Lck had been reported in 3 patients with variable clinical and immunologic phenotypes[27-29]; however, *LCK* gene mutations could not be demonstrated. More recently, Hauck et al[30] have reported the case of a child with recurrent respiratory tract infections, protracted diarrhea, failure to thrive, nodular skin lesions, arthritis, retinal vasculitis, and autoimmune thrombocytopenia. Genetic studies showed that the child carried a maternal uniparental isodisomy of chromosome 1 and was homozygous for a missense mutation (L341P) that affected Lck protein expression and abrogated its kinase activity.

The immunologic phenotype was characterized by severe CD4$^+$ T-cell lymphopenia with oligoclonal TCRαβ$^+$ T cells, markedly reduced expression of both CD4 and CD8 molecules on the surface of CD3$^+$ T cells, and an increase in central memory (CD45R0$^+$CCR7$^+$) CD4$^+$ cell and CD45RA$^+$CCD27$^-$CD62L$^-$ "exhausted" T effector memory CD45RA$^+$ (T_{EMRA}) CD8$^+$ cell numbers. Upon *in vitro* activation with anti-CD3, early tyrosine phosphorylation events during T-cell activation were markedly reduced and Ca^{2+} mobilization was abrogated, resulting in a severe proliferation defect. Serum IgM levels were increased, and autoantibodies to multiple self-antigens were present. The low number of Treg cells, and the reduced activation-induced cell death of the patient's T cells might have contributed to the immune dysregulation.

IDIOPATHIC CD4 LYMPHOPENIA CAUSED BY UNCOORDINATED 119 DEFICIENCY

Uncoordinated 119 (UNC119) is a chaperone involved in Lck-mediated signaling by transporting myristoylated Lck to the cell membrane and disrupting intramolecular interactions that keep Lck in a closed inactive conformation.[31,32] A heterozygous dominant negative missense mutation of *UNC119* affecting the N-terminus of the molecule has been identified in an adult with a history of recurrent upper and lower respiratory tract infections, frequent episodes of shingles, chronic cutaneous and nail fungal infections, and a diagnosis of idiopathic CD4 lymphopenia.[33] The *in vitro* proliferative response to mitogens and antigens was markedly decreased. An abnormal intracellular distribution of Lck protein was demonstrated, with sequestration in the endosomal compartment and a reduced amount at the cell membrane. Expression of mutant UNC119 in primary CD4$^+$ lymphocytes and Jurkat cells blocked activation of Lck, confirming the dominant negative effect of the mutant.[33]

RAS HOMOLOGY FAMILY MEMBER H DEFICIENCY

The Ras homology family member H (RhoH) is an atypical small GTPase. Mainly expressed in hematopoietic cells,[34] it plays an important role in T-cell activation. On TCR stimulation, RhoH undergoes tyrosine phosphorylation and mediates recruitment of Zap70 and Lck to the TCR/linker of activation in T cells (LAT) signalosome (Fig 1).[35]