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

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Abstract

For many years, Severe Combined Immune Deficiency (SCID) diseases, 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 and/or function. Along with recurrent and severe infections, and especially cutaneous viral infections, the clinical phenotype of these conditions is characterized by prominent immune dysregulation.

Keywords

Immunodeficiency; T cell development; thymus; autoimmunity; tolerance

Introduction

Severe combined immune deficiency (SCID) includes a heterogeneous group of genetic disorders characterized by severe impairment of T cell development, with virtual lack of circulating autologous T lymphocytes and absence of functional T cell responses¹. 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 whose molecular basis has been defined in the last few years, for which novel clinical and immunological 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 deficiency², Major Histocompatibility Complex (MHC) class I³ and class II⁴ deficiencies, and CD8α deficiency⁵ also belong to this group of partial defects of T cell development and function,

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but their clinical and immunological phenotype is well known and will not be discussed further here.

Combined immunodeficiencies due to 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 may 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 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 tolerance⁷. In particular, there is reduced number of medullary thymic epithelial cells expressing *Autoimmune Regulator* (AIRE), a transcription factor that permits expression of tissue-restricted peptides that are presented to nascent thymocytes, enabling clonal deletion of self-reactive T cells^{8,9}. Moreover, development and function of regulatory T (Treg) lymphocytes are severely compromised¹⁰. 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 OS reflect defective lymphostromal cross-talk in the thymus, and have been also observed in cases of OS due to genetic defects other than *RAG* mutations⁸, indicating that normal T cell development is essential to support maturation and function of thymic epithelial and dendritic cells. It is likely that similar abnormalities may contribute to clinical manifestations of immune dysregulation in other conditions with impaired T cell development and function 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 hyper-IgM phenotype¹⁴, and idiopathic CD4 lymphopenia¹⁵. 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 may modify the disease phenotype in patients with SCID-associated gene defects. Originally reported in adenosine deaminase deficiency¹⁶, the occurrence of somatic mutations that may restore, at least in part, expression and function of the mutated protein, have been subsequently demonstrated in other SCID disorders¹⁷. 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 may also shape the phenotypic spectrum of SCID and associated disorders, especially in patients with hypomorphic mutations, as indicated by expansion of T cells expressing TCR $\gamma\delta$ following CMV infection^{22,23}, and by conversion of SCID into OS phenotype following viral infection²⁴.

TCR α gene (*TRAC*) defects leading to selective lack of TCR $\alpha\beta$ ⁺ T lymphocytes

TCR $\alpha\beta$ ⁺ lymphocytes comprise approximately 80–85% of all circulating T cells. Morgan et al. have reported on two patients who presented with a history of recurrent respiratory infections, candidiasis diarrhea, failure to thrive, autoimmunity (hemolytic anemia, vitiligo),

eczema, eosinophilia, lymphadenopathy and organomegaly²⁵. One of the patients showed increased susceptibility to severe herpes virus (EBV, VZV, HHV6) infections. All T cells expressing CD3 at normal density also co-expressed TCR $\gamma\delta$; an unusual population of CD3^{lo} cells expressed TCR $\alpha\beta$ at very low level. In vitro proliferative responses to mitogens and antigens were decreased, but specific antibody production was preserved. Mutation analysis disclosed in both patients a homozygous splicing mutation in the TCR α constant (*TRAC*) gene, with loss of TCR α 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 may promote their expansion in vivo), this novel combined immunodeficiency illustrates the non-redundant role played by TCR $\alpha\beta$ ⁺ T cells in immune defense and homeostasis.

Lck 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 T cell receptor (TCR) signaling process, by mediating phosphorylation of Immunoreceptor Tyrosine Activation Motifs (ITAMs) in the intracytoplasmic domains of CD3 subunits and of the *Zeta-Associated Protein of 70 kDa* (ZAP70)²⁶.

Defective expression of Lck had been reported in three patients with variable clinical and immunological phenotypes^{27–29}, however, *LCK* gene mutations could not be demonstrated. More recently, Hauck et al. have reported on a child with recurrent respiratory infections, protracted diarrhea, failure to thrive, nodular skin lesions, arthritis, retinal vasculitis, and autoimmune thrombocytopenia³⁰. 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 immunological phenotype was characterized by severe CD4⁺ T cell lymphopenia with oligoclonal TCR $\alpha\beta$ ⁺ T cells, markedly reduced expression of both CD4 and CD8 molecules on the surface of CD3⁺ T cells, increase of central memory (CD45R0⁺ CCR7⁺) CD4⁺ cells and of CD45RA⁺ CCD27[–] CD62L[–] “exhausted” T effector memory (T_{EMRA}) CD8⁺ cells. Upon in vitro activation with anti-CD3, early tyrosine-phosphorylation events during T cell activation were markedly reduced, and Ca²⁺ mobilization was abrogated, resulting in a severe proliferation defect. Serum IgM was elevated and autoantibodies to multiple self-antigens were present. The low number of regulatory T cells, and the reduced activation-induced cell death of the patient’s T cells may have contributed to the immune dysregulation.

Idiopathic CD4 lymphopenia due to UNC119 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 infections, frequent episodes of shingles, chronic cutaneous and nail fungal infections, and a diagnosis of idiopathic CD4 lymphopenia³³. 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 reduced amount at the cell membrane. Expression of mutant UNC119 in primary CD4⁺ lymphocytes and in Jurkat cells blocked activation of Lck, confirming the dominant-negative effect of the mutant³³.

RHOH deficiency

The *Ras homology family member H* (RhoH) is an atypical small GTPase. Mainly expressed in hematopoietic cells³⁴, it plays an important role in T cell activation. Upon TCR stimulation, RhoH undergoes tyrosine phosphorylation and mediates recruitment of Zap70 and Lck to the TCR/LAT signalosome³⁵ (Fig. 1).

Créquer et al. have described two siblings who carried a homozygous nonsense mutation in the *RHOH* gene. Both patients suffered from persistent cutaneous human papillomavirus (HPV) infection resembling epidermodysplasia verruciformis (EV). The older sibling also developed Burkitt's lymphoma in childhood, granulomatous lung disease, and psoriatic-like lesions, whereas the younger sibling had molluscum contagiosum, psoriatic lesions, and gingivostomatitis³⁶. The immunological phenotype was characterized by reduced number of naïve CD4⁺ cells and of recent thymic emigrants, increased proportion of effector memory T cells and of T_{EMRA} cells, restricted T cell repertoire diversity, and reduced in vitro proliferation to anti-CD3. Interestingly, the proportion of T cells expressing skin-homing receptors (cutaneous lymphocyte antigen, CCR4, CCR6, CCR10 and β 7-integrin) was significantly reduced, possibly accounting for the EV-like cutaneous manifestations.

Severe T cell lymphopenia, with an incomplete block at double negative 3 (DN3) to double positive (DP) stage of differentiation, and abnormalities of peripheral T cells (in vivo activated phenotype, impaired proliferation and reduced cytokine release in response to CD3 engagement) have been reported in *RhoH*^{-/-} mice^{35,37,38}.

ZAP70 deficiency

Following CD3/TCR activation, the tyrosine kinase ZAP70 binds to the phosphorylated ITAM motifs of CD3 ζ ³⁹, and is tyrosine-phosphorylated by Lck, thereby enabling ZAP70 kinase activity, resulting in phosphorylation of the *Linker of Activation in T cells* (LAT)⁴⁰ and the *SH2 domain-containing Leukocyte Phosphoprotein of 76 kDa* (SLP-76)⁴¹ (Fig. 1).

The essential role played by ZAP70 during T cell activation was unraveled in 1991, when *ZAP70* mutations were identified in patients who lacked circulating CD8⁺ T cells and whose CD4⁺ lymphocytes failed to respond to CD3 stimulation⁴²⁻⁴⁴. By contrast, *Zap70*^{-/-} mice have a more profound block in T cell development, with an arrest at DP stage⁴⁵. This discordance may reflect species-specific differences in the pattern of expression of tyrosine kinases that control T cell differentiation. In particular, Syk expression is rapidly turned off during differentiation from DN to DP cells in mice, but is maintained in human DP cells⁴⁶. This observation, along with the requirement of higher levels of Zap70 expression for the development of CD8⁺ than of CD4⁺ SP thymocytes⁴⁷, may account for the generation of SP CD4⁺ lymphocytes in humans. However, peripheral human T cells do not express SYK, thus explaining the profound functional defect of circulating CD4⁺ cells in ZAP70-deficient patients, including impaired proliferation, aberrant gene expression profile and defective directional migration^{48,49}.

Reduced levels of T cell receptor excision circles (TRECs) have been reported in ZAP70 deficiency^{48,50}, indicating that this kinase plays an important role also in pre-TCR signaling.

Although most patients with ZAP70 deficiency present with selective lack of CD8⁺ lymphocytes and increased susceptibility to severe and recurrent infections, several patients have been reported in which residual expression of ZAP70 was associated with delayed onset and manifestations of immune dysregulation, including skin rash, wheezing and eosinophilia⁵¹⁻⁵³. In mice, *Zap70* mutations that reduce, but do not abrogate TCR signaling, are associated with arthritis⁵⁴ and hyper-IgE⁵⁵. Impaired TCR strength signaling in

peripheral T cells may affect activation-induced cell death. However, recent data indicate that reduced number of AIRE⁺ thymic epithelial cells and of FOXP3⁺ Treg cells⁵⁶ may also contribute to the immune dysregulation associated with hypomorphic *ZAP70* mutations

MST1 deficiency

Macrophage stimulating 1 (MST1), also known as *Serine Threonine Kinase 4* (STK4) is the homolog of the hippo protein, that in *Drosophila* controls cell proliferation and apoptosis⁵⁷. Evidence that MST1 plays a critical role in T cell survival came from *Mst1*^{-/-} mice, that show severe reduction in the number of naïve T cells due to increased apoptosis resulting from activation-induced oxidative stress⁵⁸. Moreover, Mst1 regulates transcription of *Foxo1*, a gene that encodes for a transcription factor that controls expression of IL-7R α in naïve T cells, thereby promoting IL-7-mediated survival⁵⁹. Foxo1 is also involved in the expression of L-selectin and CCR7, two important homing receptors. Consistent with this, *Mst1*^{-/-} mice show impaired thymocyte egress⁶⁰ and defective homing of T lymphocytes to peripheral lymphoid organs⁶¹. Moreover, inefficient migration of Mst1-deficient thymocytes is associated with defective recognition of self-antigens in the thymic medulla and impaired negative selection, thus accounting for T cell-dependent inflammatory infiltrates in peripheral organs and autoimmunity⁶².

Three groups have reported that autosomal recessive MST1 deficiency in humans is associated with recurrent bacterial and viral infections (the latter including warts, molluscum contagiosum and EBV-driven lymphoproliferative disease), mucocutaneous candidiasis, skin rash, and autoimmunity. Congenital heart disease and moderate neutropenia have been also reported⁶³⁻⁶⁵. The immunological phenotype of MST1 deficiency recapitulates what observed in *Mst1*^{-/-} mice, and includes severe reduction of naïve T cells with virtual absence of recent thymic emigrants, increased proportion of T^{EMRA} cells, oligoclonal T cell repertoire, impaired proliferation in vitro to mitogens and antigens, and increased apoptosis of T lymphocytes, associated with reduced expression of IL-7R α and increased expression of FAS^{63,64}. Furthermore, the number of circulating B cells is often reduced, with predominance of transitional B lymphocytes and few CD27⁺ memory B cells^{63,64}. Overall, these data identify MST1 as a molecule that plays a critical role in T cell development, selection, survival and migration, at the cross-road between immune surveillance and tolerance.

DOCK8 deficiency

The *dedicator of cytokinesis 8* (DOCK8) is a member of the DOCK180 superfamily of atypical guanine nucleotide exchange factors (GEFs) that activate GTPases of the Rho/Rac/Cdc42 family^{66,67}. The DOCK-homology region 1 (DHR-1) domain allows DOCK8 to bind phosphatidylinositol-(3,4,5)-trisphosphate (PIP₃) at the cell membrane, while the DHR-2 domain mediates interaction with GTPases⁶⁸ (Fig. 1). DOCK8 is encoded by a large gene that includes 48 exons, spanning 250 kb of genomic DNA; Although this gene is widely expressed, higher levels are detected in T and B lymphocytes⁶⁹.

DOCK8 mutations have been identified in patients with autosomal recessive combined immunodeficiency and a hyper-IgE phenotype^{69,70}. Most patients carry large intragenic deletions as the result of Alu-mediated recombination, and therefore lack DOCK8 protein expression.

Eczema and manifestations of food or environmental allergy, often with prominent eosinophilia, are present in >90% of the patients. Recurrent respiratory infections and mucocutaneous candidiasis are also very common. Viral cutaneous infections affect >80% of the patients in the form of recurrent orolabial, ocular, or genital herpes simplex infection,

molluscum contagiosum, and warts due to papillomavirus^{69–72}. Progressive multifocal leukoencephalopathy due to JC virus has been described⁷⁰. Papillomavirus infections often degenerate into squamous epithelial cell carcinoma⁷³, and the risk of other tumors (lymphoma, leiomyosarcoma) is also increased⁷⁴. Autoimmune manifestations include cytopenia and central nervous system vasculitis. The disease has a severe prognosis, with a high mortality rate due to infections and tumors, but definitive cure may be achieved with hematopoietic cell transplantation (HCT)^{75–78}.

Immunological abnormalities include a variable degree of T cell lymphopenia^{69,70,74}, with loss of naïve CD8⁺ cells and increased proportion of T_{EMRA} CD8⁺ lymphocytes⁷⁹. A low number of TRECs, indicating impaired generation of T cells in the thymus, has been reported⁸⁰. In vitro lymphocyte proliferative responses are often decreased, especially for CD8⁺ T lymphocytes^{69,70,79}. The reduced number of Th17 cells may contribute to candidiasis⁸¹. Several studies in mouse models have confirmed a critical role for Dock8 in T lymphocyte survival, activation and trafficking. The number of naïve T lymphocytes in peripheral lymphoid organs is markedly reduced in Dock8-deficient mice^{79,82}, a finding that may reflect impaired survival. Moreover, defective CD8⁺ T cell memory has been demonstrated in upon in vivo challenge with vaccinia virus and influenza virus^{79,82}. Defective trafficking of Dock8-deficient dendritic cells, and impaired homing of DCs to lymph nodes⁸³ may also contribute to poor T cell priming, defective generation of memory T cell responses and increased occurrence of chronic viral infections.

Humoral immune responses are also affected in DOCK8 deficiency. IgG levels may be normal or elevated; in contrast, IgM are often low, and IgE are significantly increased^{69,70}. Patients may mount specific antibody responses to antigens, however these are not sustained⁸⁴. Similar findings have been observed in Dock8-deficient mice, in which impaired formation of immunological synapse between B cells and follicular dendritic cells is associated with poor survival of germinal center B cells and inability to establish high-affinity and memory B cell responses⁸⁵. A recent study in humans has shown that TLR9 activation induces Pyk2-mediated DOCK8 tyrosine phosphorylation, allowing recruitment of Src and/or LYN and phosphorylation of SYK and STAT3⁸⁴. Consistent with these findings, CpG-induced proliferation of B lymphocytes and in vitro production of IgM and IgG are profoundly impaired in patients with DOCK8 deficiency⁸⁴. Overall, these observations indicate that DOCK8 plays a critical role in immune surveillance and homeostasis by affecting the function of multiple cell types.

ITK deficiency

Interleukin-2-inducible tyrosine kinase (ITK) is a member of the Tec family of nonreceptor tyrosine kinases that is expressed in T lymphocytes and participates at TCR signaling (Fig. 1). In particular, ITK pleckstrin homology domain binds to phosphatidylinositol monophosphates, allowing ITK recruitment to the cell membrane⁸⁶. Following TCR/CD3 cross-linking, ITK activation increases PLC- γ 1 activation and Ca²⁺ influx^{87–89}. It has been shown that ITK controls the spatiotemporal organization of T cell activation; in the absence of ITK, the distribution of several signaling molecules at the immunological synapse between T lymphocytes and antigen presenting cells is altered, causing impaired actin accumulation⁹⁰.

In 2009, Huck et al. described two sisters with EBV-associated lymphoproliferative disease and autoimmune cytopenias due to *ITK* mutation. One of the siblings also had a history of *Pneumocystis jiroveci* pneumonia, candidiasis, BK polyoma infection, and EBV-related Hodgkin lymphoma⁹¹. The immunological phenotype was marked by lymphopenia and predominance of T cells with activated/memory phenotype. Since then, several other cases

have been described, with increased susceptibility to EBV-mediated lymphoproliferation (often associated with development of pulmonary nodules and mediastinal involvement), but also to other herpes virus infections (varicella, CMV). Most cases have developed progressive hypogammaglobulinemia and T cell lymphopenia, with reduced proportion of naïve T cells and an increase of activated T cells^{92–94}. Studies in mice have shown that Itk-deficient T cells have defective cytotoxic activity, fail to mount primary or memory T cell responses^{95,96}, and are characterized by an aberrant transcriptional signature, with increased expression of eomesodermin⁹⁷, a transcription factor that promotes development of CD44⁺ CD122⁺ CXCR3⁺ innate, memory-like CD8⁺ T cells^{98–100}.

ITK controls also development and survival of NKT lymphocytes¹⁰¹. The lack of circulating NKT cells in ITK-deficient patients⁹¹ may contribute to EBV-associated lymphoproliferation, similarly to what observed in patients with X-linked lymphoproliferative disease^{102,103}.

Coronin-1A deficiency

Coronin-1a is a member of the Coronin family of proteins that bind F-actin and the Arp2,3 complex, thereby regulating cytoskeleton organization¹⁰⁴. In particular, coronin-1A inhibits F-actin formation, integrin outside-in signaling, and chemokine-induced migration in T lymphocytes¹⁰⁵. Severe reduction of naïve T cells, and accumulation of apoptosis-prone effector memory T lymphocytes, has been observed in *Coro1a*^{−/−} mice^{105,106}. Moreover, Coro1a-deficient T cells fail to migrate in response to various chemokines and to proliferate upon CD3 stimulation^{105–107}.

The only case of CORO1A deficiency so far reported in humans was a female child with a history of thrush, respiratory tract infections, severe varicella, protracted diarrhea, and developmental delay. The child was a compound heterozygote for a *CORO1A* dinucleotide deletion and a large deletion that encompassed also 24 other genes^{108,109}. Similar to *Coro1a*^{−/−} mice, the patient showed severe T cell lymphopenia, impaired in vitro proliferation to mitogens and antigens, and defective specific antibody response. These abnormalities were however less severe than in typical forms of SCID, and more typical of a combined immune deficiency. Consistent with this, the patient survived several years before she was treated with HCT. Identification of *CORO1A* mutations in other patients will be needed to better define the phenotype of the disease.

Defects of Calcium release-activated channels (CRAC): STIM1 and ORAI1 deficiencies

Ca²⁺ signaling plays a critical role in immune activation and homeostasis^{110,111}. In T lymphocytes, engagement of the TCR leads to phosphorylation of PLC-γ1, that converts phosphatidylinositol 4,5-bisphosphate (PIP₂) into inositol 1,4,5-trisphosphate (InsP₃) and diacylglycerol (DAG). Binding of InsP₃ to its receptor promotes release of Ca²⁺ from the endoplasmic reticulum (ER) stores. Depletion of Ca²⁺ ER stores is sensed by the *Stromal Interaction Molecule* (STIM) proteins, that oligomerize and bind to the ORAI proteins (ORAI1, -2, and -3) that form the pore of CRAC channels on the cell membrane, thereby permitting Ca²⁺ influx (Fig. 1). The increase of intracellular Ca²⁺ concentration induces activation of NFAT and ultimately promotes cell proliferation, cytokine production, and induction of cell-mediated cytotoxicity¹¹¹.

Biallelic loss-of-function mutations of *STIM1* and *ORAI1* have been identified in patients with bacterial, viral or fungal infections, non progressive myopathy, ectodermal dysplasia and a variable degree of immune dysregulation^{112–114}. Herpes virus infections (CMV, EBV,

HSV, VZV) are frequent; in one case with STIM1 deficiency, HHV-8 infection led to Kaposi sarcoma¹¹⁵. Autoimmune manifestations (cytopenias, lymphadenopathy, splenomegaly) are especially common in patients with STIM1 deficiency^{112,113,116}. Although T cell development is not compromised, peripheral T lymphocytes from affected patients show markedly defective in vitro proliferation to mitogens and antigens and a severe impairment of cytokine production^{112,113,117,118}. The function of NK lymphocytes is also affected in patients with *STIM1* or *ORAI1* mutations, as indicated by defects of degranulation and cytokine production, and impaired cytolytic activity^{116,119}. Furthermore, complete lack of circulating NKT cells was demonstrated in one patient with STIM1 deficiency¹¹⁶, suggesting that normal CRAC function may be required for their development.

The molecular mechanisms accounting for immune dysregulation in these patients are still unclear. A reduced number of Treg cells has been reported in some patients¹¹³, but not others¹¹⁶. Moreover, based on studies in *Orai1*^{-/-} mice¹²⁰, it is possible that resistance of CD4⁺ T cells to activation-induced cell death may also contribute to defective T cell homeostasis. Finally, impaired secretion of IL-10 by B cells may also be involved in autoimmunity associated with STIM1 deficiency¹²¹.

Defective degranulation of platelets, severe heart failure and impaired differentiation and function of osteoblasts have been observed in animal models of the disease^{122–124}, but not in patients.

Overall, these data indicate that integrity of CRAC channels is dispensable for lymphoid development (with the possible exception of NKT lymphocytes), but is required for effector and regulatory functions of peripheral T and NK lymphocytes.

MAGT1 deficiency

Mg²⁺ plays an important role in intracellular signaling¹²⁵. Several Mg²⁺ transporters have been identified, whose mutations lead to distinct clinical phenotypes^{126–128}. *MAGT1* encodes for a membrane-associated transporter with high selectivity for Mg²⁺¹²⁹. Recently, three male patients with mutations in the X-linked *Magnesium Transporter protein 1* (*MAGT1*) gene have been reported to suffer from X-linked immunodeficiency with magnesium defect and EBV infection and neoplasia (XMEN syndrome)¹²⁸. Respiratory tract infections, chronic diarrhea, and increased susceptibility to other viral infections (HSV-1) were also present¹²⁸. Immunological abnormalities of MAGT1 deficiency include CD4 lymphopenia, reduced number of recent thymic emigrants, and impaired T cell proliferation in response to CD3 stimulation. By contrast, T cell response to phorbol myristate acetate and ionomycin is intact, consistent with a role for Mg²⁺ in proximal intracellular signaling. Female carriers of MAGT1 deficiency exhibit skewed X chromosome inactivation in circulating T lymphocytes, indicating that Mg²⁺ signaling plays an important role in T cell development and/or survival.

MAGT1 deficiency compromises not only Mg²⁺ flux, but also Ca²⁺ influx¹²⁸. This reflects impaired activation of PLC- γ 1 and decreased generation of InsP³. Early signaling events (such as phosphorylation of CD3 ζ , ZAP-70 and LAT) in response to CD3 stimulation are intact, indicating that Mg²⁺ flux is activated downstream from these signals and upstream of PLC- γ 1 phosphorylation¹²⁸. However, the precise mechanisms by which TCR signaling activates MAGT1 and Mg²⁺ regulates PLC- γ 1 phosphorylation remain unknown.

Conclusions

Advances in genome sequencing have rapidly led to the identification of a growing number of conditions characterized by impaired T cell development and function, whose clinical phenotype is marked not just by increased susceptibility to infections, but also immune dysregulation. This series of discoveries has been also facilitated by increased collaboration with clinicians and scientists from countries with a high consanguinity rate. From a public health perspective, now that newborn screening for SCID based on enumeration of TRECs is becoming widely available, it will be very important to carefully annotate which ones of these conditions are also characterized by reduced thymic output, and to develop diagnostic platforms that may lead to correct identification of these diseases in the second-tier phase of the diagnostic process.

From a scientific perspective, the study of these conditions is providing important insights into the mechanisms that govern immune homeostasis. In particular, patients with partial defects of T cell development and function may develop immune dysregulation because of abnormalities that may variably affect the strength of TCR signaling, T cell survival, activation-induced cell death, positive and negative selection, Treg development and function, and trafficking of immune cells. Although many of the phenotypic features observed in patients with these disorders are also recapitulated in corresponding animal models, important differences have emerged which may reflect species-specific properties, pressure from environmental factors, and genotype-specific effects. Overall, this emphasizes the importance of studying inborn errors of immunity to decipher the mechanisms that control human immune system development and function. It can be anticipated that the list of partial defects of T cell function will increase substantially in the next few years, thus broadening our understanding of normal and pathological immune system development.

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Abbreviations

AIRE	Autoimmune regulator
CMV	Cytomegalovirus
CRAC	Calcium Release Activated Channels
DAG	Diacylglycerol
DHR	Dock-homology region
DN	double negative
DOCK8	Dedicator of Cytokinesis 8
DP	Double Positive
EBV	Epstein-Barr Virus
ER	Endoplasmic Reticulum
EV	Epidermodysplasia Verruciformis
GEF	Guanine Nucleotide Exchange Factor
HHV	Human Herpes Virus

HSV-1	Herpes Simplex Virus 1
IL	Interleukin
insP₃	inositol 1,4,5-trisphosphate
ITAM	Immunoreceptor Tyrosine Activation Motif
ITK	Interleukin-2-inducible Tyrosine Kinase
LAT	Linker of Activation in T cells
Lck	Lymphocyte-specific protein tyrosine kinase
MAGT1	Magnesium Transporter 1
MHC	Major Histocompatibility Complex
MST1	Macrophage stimulating 1
NFAT	Nuclear Factor of Activated T cells
NKT	Natural Killer T cells
OS	Omenn syndrome
PIP₂	Phosphatidylinositol 4,5-bisphosphate
PLC-γ	Phospholipase C- γ
RAG	Recombinase Activating Gene
RHOH	Ras homology family member H
SCID	Severe combined Immune deficiency
STAT	Signal Transducer and Activator of Transcription
STIM1	Stromal Interaction Molecule 1
STK4	Serine Threonine Kinase 4
TCR	T Cell Receptor
Th	T helper
T_{EMRA}	T effector memory CD45RA ⁺ cells
TRAC	T cell receptor α constant gene
TREC	T cell receptor excision circles
Treg	regulatory T cell
UNC119	Uncoordinated 119
VZV	Varicella Zoster Virus
ZAP70	ζ -associated protein of 70 kDa

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Figure 1.

Schematic representation of signaling through the T cell receptor (TCR)/CD3 complex. Molecules whose mutations have been associated with partial defect of T cell development and impaired T cell function are indicated in red and highlighted in bold.