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Inherited immunodeficiencies associated with proximal and distal defects in T cell receptor signaling and co-signaling

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ABSTRACT

T lymphocytes are central cells of adaptive immunity. Activation of T lymphocytes by the antigen receptor of T cells (TCR) and co-stimulatory molecules involve specific signaling components and cascades. Those are essential for development, differentiation and effector responses of T lymphocytes. Over the last three decades, identification of primary immunodeficiencies associated with defects in development and activation of T lymphocytes provided new and unexpected insights into TCR signaling and co-signalling and their relation with protective immunity in humans. Mutations in components of the proximal and distal TCR signaling like the TCR-CD3 complex, protein tyrosine kinases and phosphatases, adaptor proteins, second messengers like Ca^{2+} mobilization and the MAPK kinase and nuclear factor kappa B (NFκB) pathways impede T cell development and functions, causing immunodeficiency and immune dysregulation manifestations such as autoimmunity and inflammation. Mutations that impair co-signaling delivers by co-stimulatory molecules of the tumor necrosis factor (TNF), the CD28 and the signaling lymphocytic activation molecule (SLAM) receptor families, have no effect or slight impact on T-cell development but impair T cell responses such as expansion. Interestingly, these latter are often associated with infectious susceptibility restricted to particular pathogens like Epstein-Barr virus (EBV) and human papillomavirus (HPV), highlighting the molecular "specialization" of co-stimulatory molecules to shape TCR-dependent T cell responses to specific pathogens or infected cells.

Following recognition of antigenic peptides presented by major histocompatibility molecules (MHC) on antigen presenting cells, signals delivered by the antigen receptor of T cells (TCR), are essential for the development, the differentiation and the activation of T lymphocytes. The TCR is made of a heterodimer of αβ or γδ chains involved in the recognition of antigenic

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peptides that associates with a signal transducting module, the CD3 complex. The CD3 complex is formed of two heterodimers of CD3ε–CD3γ or CD3ε–CD3δ chains associated with a homodimer of the zeta chains (also termed CD3ζ/CD247). Following TCR engagement, tyrosines in immunoreceptor tyrosine-based activation motifs (ITAMs) within CD3 cytoplasmic domains are rapidly phosphorylated by protein tyrosine kinases (PTKs) from the SRC family, the lymphocyte-specific protein tyrosine kinase (LCK), and (to a lesser extent) FYN [1,2]. LCK constitutively associates with the T-cell coreceptors CD4 and CD8, which interact directly with MHC molecules. Activation of LCK occurs during CD4/CD8 co-engagement with the TCR, upon the recognition of antigenic peptides. This initial tyrosine phosphorylation signal is amplified and propagated by activation of the zeta chain-associated protein tyrosine kinase of 70 kDa (ZAP-70) following its recruitment to the phosphorylated ITAMs of the CD3 complex and its phosphorylation by LCK. In turn, ZAP70 phosphorylates downstream cytoplasmic and transmembrane substrates, notably the adaptor/scaffold molecules LAT (for linker of activated T cells), CD6 and SLP-76 [3,4]. Although these adaptor proteins lack enzymatic and transcriptional activities, they are essential for T cell signaling by their ability to organize and coordinate formation of signaling complexes (also referred as signalosomes), and thus they diversify the initial signal. The signalosomes formed via recruitment of additional adaptors and enzymes activate second messengers and downstream signaling cascades. The most important downstream events include production of 1,4,5-triphosphate inositol (InsP3 or IP3) and diacylglycerol (DAG), Ca^{2+} fluxes/mobilization and activation of mitogen-activated protein serine/threonine kinases (MAPKs-ERK1/2, AKT)) and guanidine exchange factors. These steps are followed by reorganization of the actin cytoskeleton and activation of transcription programs via nuclear translocation of transcription factors such as nuclear factor κB (NF-κB) and nuclear factor of activated T cells (NFAT). Integration of these different cascades and signals ultimately result in specific T-cell responses (see Fig. 1).

In addition to the CD4/CD8 co-receptors, co-stimulatory molecules (such as CD28 and members of the TNF receptor (TNFR) family like 4-1BB) provide supplemental signals (along with CD4/CD8/TCR signaling) when engaged by their ligands expressed on professional antigen presenting cells, infected cells and tumor cells [5]. These signals are required to sustain and achieve efficient T-cell activation and/or to diversificate and adapt T-cell responses.

General clinical and immunological features to defects in TCR signaling

Inherited primary immunodeficiencies associated with impaired TCR signaling or defect(s) in T cell activation can be divided in two groups depending of the presence or not circulating T cells [Table 1]. Severe combined immunodeficiency (SCID) is characterized by absence or very low numbers

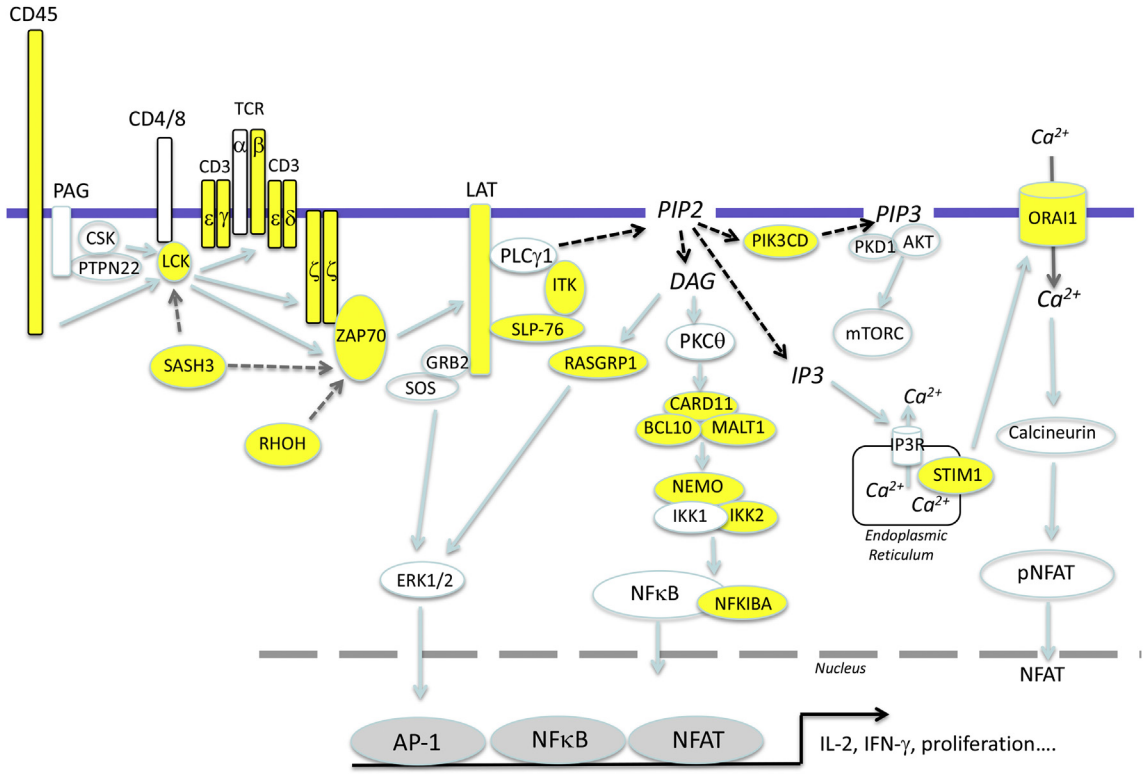

Fig. 1 **Defects in TCR signalisation leading to SCID and CID**. The figure depicts key molecules in the TCR signaling machinery and the downstream pathways. Components that have been found genetically impaired in humans and to cause immunodeficiency are highlighted in yellow. Role/function not clearly defined are marked grey dashed arrows. The names of second messengers are written in italics, and active transcription factors are shown in grey. Black dashes arrows indicate enzymatic pathways for production of second messengers.

of T cells, while combined immunodeficiency (CID) is defined by reduced or normal numbers of T cells with altered functions. In most of cases, the thymic output is reduced and patients exhibit low counts of peripheral blood thymus emigrants associated with progressive loss of T cell naivety and CD4 lymphopenia. A notable exception concerns CIDs affecting the NFκB pathway which are characterized by normal or inflated naïve T cell counts associated with decreased or absence of memory T cells.

Patients with T-cell signaling defects are highly susceptible to opportunistic and recurrent infections and often developped immune dysregulations [6–9]. The most frequent and severe clinical phenotypes are early-onset infections associated with protracted gut disease, failure to thrive, autoimmunity and skin/mucosal inflammatory disorders. Immune dysregulations encompass variable autoimmune, inflammatory and lymphoproliferative manifestations that can be associated with abnormal expansions of oligoclonal T-cell populations (often CD8+) with a chronic active and/or exhausted effector memory phenotype (EMRA) and skin-homing TCR γδ cells. The emergence of these self-reactive T cells is probably due to impaired TCR signaling during positive and negative selection in the thymus.

Lymphopenia-induced proliferation driven by residual TCR-dependent (including aberrant tonic TCR signaling) or TCR-independent stimuli (such as cytokines) or/and alterations of peripheral immune tolerance mechanisms may also favor escape of self-reactive T cells. Indeed, T cells in these settings are often refractory to activation-induced cell-death (AICD) (also referred to as restimulation-induced cell death/RCID), which requires intact TCR signaling. AICD is an essential inhibitory pathway that controls activated T cells by apoptosis through interactions between the cell-death receptor FAS and its ligand FasL on activated lymphocytes. Importantly, mutations in *FAS* result in autoimmune lymphoroliferative syndrome [10]. Moreover, development and/or function of regulatory T cells are frequently compromised. Thus, the above-mentioned mechanisms contribute individually or jointly to the build-up of often complex, variable and highly deleterious immune dysregulations. Lastly, patients frequently present dysgammaglobunemia which ranges from severe hypogammaglobunemia to hypergammaglobunemia. Patients can also fail to mount antigen specific antibody responses in response to vaccination or infections and frequently display low numbers of CD27+ memory B cells. Most of these phenotypes result from abnormalities in the T-cell help, due to defects in T-helper cell maturation and/or activation, although intrinsic defects in B-cell development and function may also contribute directly to the dysgammaglobunemia in some deficiencies.

Several immunodeficiencies discussed here are also associated with extra-immunological manifestations that are not discussed in the context of the present review.

Defects in TCR/CD3 complex

The different subunits of the CD3/TCR complex are required for its proper assembly in the endoplasmic reticulum and then its surface expression [11]. Autosomal recessive mutations leading to the complete loss of TCRα, CD3δ, CD3γ, CD3ε and CD237/CD3ζ deficiency have been reported [12–16]. These defects result in a strong decreased or lack of CD3/TCR surface expression. With the exception of the CD3γ deficiency, patients suffering from these genetic defects developped a severe combined immunodeficiency (SCID). This SCID is denoted as T-B + NK + SCID since patients have no (or only a few) T cells but normal B and NK cells.

CD3γ deficiency

Patients with CD3γ deficiency (resulting from bi-allelic mutations in *CD3G*) developped CID with normal or slightly reduced αβ T and γδ T cell counts, indicating the CD3γ is dispensable for T cell development in humans (in contrast to mice) [17–21]. The severity of the immunodeficiency is variable ranging from early lethal onset to an absence of susceptibility to infection. However, all patients presented with autoimmune and inflammatory features [19]. CD3γ-deficient T cells displayed low levels of CD3-TCR surface expression (one third of the amount found in healthy individuals), skewed reperoire toward self reactivity and impaired functions with poor proliferative responses to TCR stimulation. Treg also had diminished suppressive function. CD3γ appears to be more important for signal transduction than for assembly and surface expression of the TCR-CD3 complex.

TCRα/CD3δ/CD3ε/CD3ζ deficiencies

TCRα/CD3δ/CD3ε/CD3ζ deficiencies (caused by bi-allelic mutations in *TRAC, CD3D, CD3E* and *CD247* respectively) result in a severe or almost total block in T cell development; in TCRα deficiency, only αβT cells are impacted and γδ T cell development is unaffected [12]. Patients have normal NK and B counts, indicating that these defects have no impact on NK and B cell differentiation. However, cytolytic responses by NK cells are abrogated in patients with CD3ζ deficiency. CD3ζ is also a transducing module for CD16 (FcγRIIIA), NKp46 and NKp30– all of which are key activator receptors of cell cytotoxicity in NK cells.

Defects in tyrosine kinases and phosphatases

PTKs and protein tyrosine phosphatases (PTPs) are essential for the initiation and amplification of tyrosine-phosphorylation-based signals in the early steps of TCR signaling [22,23]. Four different classes of non-receptor PTKs and several PTPs have been involved and act sequentially. Firstly, LCK is responsible for initiating the signaling cascade. LCK is activated by the transmembrane tyrosine phosphatase CD45, which dephosphorylates the C-terminal inhibitory tyrosine Y505 in LCK (when phosphorylated Y505 maintains LCK in an inactive conformation). Secondly, ZAP70 amplifies and diversifies the initial signal. Thirdly, ITK is involved in the activation of the calcium signaling pathway downstream the LAT signalosome. Fourthly, the kinase CSK inactivates LCK by selectively phosphorylating the Y505 in LCK, together with the PTPN22

Table 1 Characteristics of immunodeficiencies caused by gene defects in TCR signaling and co-signaling.

Gene	T cells	Immune dysregulation symptoms	Infections	Functional T cell defects
DEFECTS IN TCR SIGNALING				
Defects in the TCR/CD3 complex				
TRAC (TCRα)[a]	SCID T-B + NK+ • Normal T γδ cells		+	
CD3G (CD3γ)	CID: • Abnormal skewed repertoire (self-reactive)	+	+	• Decreased CD3/TCR expression • Low proliferation • Reduced Treg suppression
CD3D (CD3δ)	SCID T-B + NK+		+	
CD3E (CD3ε)	SCID T-B + NK+		+	
CD247 (CD3ζ)	SCID T-B + NK+		+	
Defects in tyrosine kinases and phosphatases				
PTPRC (CD45)	SCID T-B + NK+		+	
LCK	CID: • Severe T CD4 lymphopenia • TEMRA and γδT cells accumulation • Skewed repertoire	+	+	• Weak Tyr-P signals, no Ca^{++} flux • Decreased CD4/CD8 expression • Impaired T cell responses (prolif., AICD)
ZAP70	CID: • Severe T CD8 lymphopenia	+/−	+	• Weak Tyr-P signals, no Ca^{++} flux • Impaired T cell responses (prolif.)
ITK	CID: • Progressive T lymphopenia • Reduced iNKT cells	+/−	EBV (HPV, CMV)	• Decreased Ca^{++} flux
Defects in adaptor proteins				
LAT^{null}[b]	SCID T-B + NK+		+	
$LAT^{hypomorphic}$	CID: • Progressive T lymphopenia with low naive T cells • Th2 and γδ T cell expansions	+	+	• Decreased CD3 expression • Weak ERK1/2 activation
$LCP2^{hypomorphic}$ (SLP-76)	CID: • TEMRA accumulation • Skewed repertoire	+	+	• Weak Tyr-P signals, Ca^{++} flux, ERK1/2
SASH3	CID: • TEMRA accumulation • Skewed repertoire	+	+	• Weak Tyr-P signals, Ca^{++} flux, ERK1/2 • Impaired T cell responses • Increased basal apoptosis, decreased thymocyte survival
Defects in store-operated calcium entry				
ORAI *STIM1*	CID: • Reduced iNKT (for *STIM1*)	+	+	• No Ca^{++} flux • Impaired NFAT activation • Impaired T cell responses
Other defects				
MAGT1	CID (XMEM)[c]: • CD4 T lymphopenia with low naive T cells	+/−	EBV (other viral and bacterial infections)	• Decreased intracellular Mg2+ ? • Decreased Ca flux ? • Decreased N-glycosylation of NKG2D and CD28 • Impaired NKG2D-mediated cytotoxicity towards EBV-infected B cells

RHOH	CID: • Lymphopenia with low naive T cells • Reduced T cells with integrin B7 expression • TEMRA accumulation		HPV	• Decreased ZAP70 expression
Defects in the downstream cascades				
CARD11 (CARMA) *MALT1* *BCL10*	CID: • Reduced T_{reg} and Th17 • Reduced memory T cells	+	+	• Impaired NFκB activation • Impaired T cell responses
RASGRP1	CID: • Lymphopenia with low naive T cells • TEMRA and γδT cells accumulation with skewed repertoire	+	EBV (fungal, bacterial infections)	• Impaired ERK1/2 activation • Impaired proliferation • Decreased CTPS1 expression
PIK3CD^{GOF}	CID (APDS)	+	+ (EBV)	• Increased senescence • Impaired T cell responses
DEFECTS IN T-CELL COSTIMULATORY SIGNALING				
CD27 *CD70*	CID	+/−	EBV (other viral and bacterial infections)	• Impaired proliferation towards EBV-infected B cells • Impaired CD8+ late differentiation
TNFRSF9 (4-1BB/CD137) *TNFSF9* (4-1BBL/CD137L)	CID	+/−	EBV (HSV)	• Impaired proliferation towards EBV-infected cells
TNFRSF4 (OX40)	CID		HHV-8	• Impaired CD4 T cell responses
CD28	CID		HPV (EBV and CMV viremia)	• Impaired CD4 T cell responses (T_{FH} cells)
CARMIL2 (RLTPR)	CID: • Reduced memory CD4 cells • Reduced T_{reg}	+	+ (EBV, HPV)	• Impaired CD28 responses (proliferation) • Increased Th2 and decreased Th1, Th17, T_{FH}
ICOS-ICOSLG	CID: • Reduced memory CD4 cells	+	+	• Impaired cytokine production • Impaired Th differentiation
SH2D1A (SAP)	CID (XLP syndrome): • Absence of iNKT cells		EBV	• Impaired SLAMF-R-mediated responses • Impaired 2B4-mediated T/NK cell cytotoxicity towards EBV-infected B cells

Abbreviations: CID: combined immunodeficiency; SCID T-B + NK+: severe combined immunodeficiency with B and NK cells but no T cells; HPV, human papillomaviruses; EBV: Epstein Barr virus; CMV: cytomegalovirus; HHV-8: human gamma herpes virus 8; TEMRA: terminally differentiated effector memory T cells; Th: T helper lymphocyte; Treg: regulatory T lymphocytes; iNKT cells: invariant NKT lymphocytes; Tyr-P: tyrosine phosphorylation; TFH: follicular helper T lymphocyte; APDS: Activated PI3 kinase delta syndrome; XLP: X-linked lymphoproliferative syndrome; XMEN: X-linked immunodeficiency with magnesium defect, EpsteineBarr virus (EBV) infection, and neoplasia; GO: gain-of-function mutation; AICD: activation-induced cell death.

[a] Alternative name of gene/protein in brackets.

[b] Nature of mutations (null, hypomorphic and GOF) in superscript.

[c] Name of the disease underlined in brackets when there is one.

phosphatase (also known as PEP), which dephoshorylates the activating Y314 in the kinase domain of LCK [23,24].

CD45 deficiency

Patients with CD45 deficiency caused by bi-allelic mutations in *PTPRC* barely expressed any of the CD45 isoforms at the cell surface and present early-onset, severe T-B + NK + SCID [25–27]. Peripheral T cell counts are very low, with the exception of one patient who had an expansion of nonfunctional γδ T cells. All patients exhibited severe hypogammaglobunemia, despite their normal B cell counts.

LCK deficiency

A homozygous deleterious mutation in the LCK resulting in a very weak expression LCK without kinase activity was identified in a child with CID features with predominant early-onset inflammatory and autoimmune manifestations [8]. The child displayed a severe CD4+ T-cell lymphopenia and low levels of CD4+ and CD8 surface expression on the T cells. The residual T lymphocytes had an exhausted memory phenotype with an oligoclonal T-cell repertoire and displayed profound TCR signaling defects consisting of very weak tyrosine phosphorylation signals and absence of calcium mobilization in response to TCR stimulation. Late responses to TCR activation were also compromised, since these T cells failed to proliferate and were resistant to apoptosis. Three adult siblings with LCK deficiency (caused by a hypomorphic mutation in *LCK*) were also recently described; their clinical phenotype was less severe and consisted of recurrent skin (keratinocyte) infections by human papilloma virus (HPV). All patients had CD4+ T cell lymphopenia [28]. These findings suggest that the development of CD4+ T cells is highly dependent on LCK.

ZAP70 deficiency

More than 15 different mutations in ZAP70 causing the complete loss of ZAP70 expression have been reported [29–31]. The majority of ZAP70-deficient patients presented with CID in the infancy and a third of the patients showed signs of immune dysregulation [32]. ZAP70 deficiency is characterized by a non-functional CD4+ T cells and a profound CD8+ T cell lymphopenia, indicative of a differential role of ZAP70 in the CD4+ and CD8+ T-cell development. Like LCK-deficient T cells, ZAP-deficient T cells from patients exhibited a profound impairment in early and late events in the TCR signaling cascade: weak tyrosine phosphorylation signals, no calcium flux, and defective proliferation. The few residual CD8+ T cells retained some TCR signalling and functions that correlated with the expression the ZAP70-related tyrosine kinase SYK in these cells. SYK might compensate – at least to some extent – for the absence of ZAP70 [33].

ITK deficiency

ITK deficiency has been reported in more than 20 individuals [34–38]. These patients were particular susceptible to infection by Epstein Barr virus (EBV) and suffered from EBV-driven B cell lymphoproliferative disorders (including lymphoma), which were often associated with pulmonary infiltration/involvement [39]. Some patients also presented other viral infections (HPV, varicella-zoster virus (VZV) and cytomegalovirus (CMV)) and autoimmune and inflammatory symptoms. ITK deficiency is characterized by progressive CD4 lymphopenia and hypogammaglobunemia [36]. Some patients also displayed low numbers of CD8+ T cells and a strong reduction in innate-like invariant NKT cells (iNKT) [36]. Ca^{2+} mobilization is impaired in ITK-deficient T cells [38]. It is not clear why ITK deficiency is associated with a particular susceptibility to EBV infection. It could be attributed to the requirement of ITK in the expansion of effector CD8+ T cells during viral infection [40,41]. It is possible that the absence of iNKT cells also contributes to this susceptibility, as suggested elsewhere [42].

ITK is selectively expressed in T cells and it belongs to the TEC family of kinases, several members of which have been involved in T-cell activation and responses. In the TCR signalling cascade, ITK is recruited into the LAT signalosome by interacting with LAT, SLP-76 and the phospholipase C gamma-1 (PLC-γ1) [43]. ITK phophorylates PLC-γ1, which is necessary for full lipase activity. When activated, PLC-γ1 cleaves the membrane lipid phosphatidylinositol-4, 5 diphosphate (PIP2) into IP3 and DAG; these two key second messengers then respectively activate the PKCtheta and Ca^{2+} mobilization.

Defects in adaptor proteins

LAT deficiency

Several humans with LAT deficiency have been reported. Five had a complete loss of LAT and developed a T-B + NK + SCID with failure to thrive [44]. Patients had extremely low counts of T cells. Residual T cells failed to proliferate in response to mitogens. NK and B cells were normal. The three other siblings (in a consanguineous family) carried a hypomorphic homozygous premature stop codon that led to a truncated form of LAT with the removal of most of the intracytoplamic domain of LAT, which contains all major sites of phosphorylation [45]. These patients presented with a CID characterized by progressive CD4+ and B cell lymphopenia, reduced CD3 expression and low naïve T cells. The main clinical symptoms were reccurent infections and immundysregulation symptoms characterized by expansions of Th2-like effector lymphocytes and γδ T cells. The T cells did not proliferate in response to TCR stimulation. TCR-mediated ERK1/2 activation was impaired, while ITK phosphorylation, Ca^{2+} mobilization and NFκB activation were preserved. This is quite surprising because all these signals are known to depend of tyrosine phopshorylation sites absent in the truncated LAT. This partial signaling is attributed to the recruitement of a putative unknown adaptor protein via the transmembrane domain of the truncated LAT. Furthermore, LCK might be also abnormally activated when the LAT intracytoplasmic domain is lacking, since this latter is also known to mediate regulatory/negative effects on TCR signaling. It is postulated that this weak signal results in tonic TCR signaling leading to CD3 downregulation and the development and expansion of activated aberrant Th2-like cells [46].

SLP-76 deficiency

A homozygous mutation in *LCP2* (better known as SLP-76) considered as hypomorphic was recently identified in a single patient with a CID and autoimmune manifestations [47]. The patient had normal T cell counts and inflations of memory CD4+ T cells and terminally differentiated CD8+ T cells associated with a skewed T cell repertoire. TCR signaling was weak showing a reduction in ERK and PLC-γ1 activation and Ca^{2+} mobilization. The patient also presented marked B cell, NK cell, neutrophil, and platelet aggregation defects, in line with the known roles of SLP-76 (apart from its role in T cells). Partial T-cell development and immune dysregulation manifestations are also observed in genetically modified mice with less than 10% of the normal levels of SLP-76, supporting that there was a residual expression of functional SLP-76 in the patient.

SASH3 deficiency

Four adult male patients having developped a CID with immune dysregulation symptoms were recently identified with SAM and SH3 domain containing member 3 (SASH3) deficiency [48]. SASH3 (also referred to as SH3-containing lymphocyte protein (SLY1)) is a lymphoid-specific adaptor protein encoded by an X-linked gene. In addition to the SAM and the SH3 domains, SASH3 also contains two nuclear localization signals (NLS). The exact role of SASH3 in antigen receptor signaling is unknown. Patients manifested CD4+ T, B and NK lymphopenia, and neutropenia. SASH3 deficiency impeded T cell proliferation and cell cycle progression in response to TCR stimulation, whereas T cell apoptosis was elevated; this might participate to the proliferation defect. In vitro study of T cell differentiation suggested that survival of thymocytes was impaired. Accordingly, proximal and distal TCR signaling were found to be strongly impaired, with a marked reduction in the phosphorylation (activation) of ZAP-70, LAT and PLC-γ1 and decreased activation of ERK, NFκB and AKT/mTOR pathways. These findings suggest that SASH3 has an important role in early TCR signaling, possibly by acting on ZAP-70 and/or LCK activation.

Defects in store-operated calcium entry

The calcium ion Ca^{2+} is one of the key second messenger in T cell signalling [49]. Ca^{2+} is needed for activation of transcription factors of the NFAT family, which are essential for cytokine production by activated T cells and for their proliferation. A first influx of Ca^{2+} from the ER is triggered by intracellular IP3, a product of the enzymatic activity of the PLC-γ1. IP3 binds to IP3 receptors expressed on the ER membrane and activates the release of calcium from stores in the ER, leading to decreased concentration of Ca^{2+} in the ER. In response to this diminution, STIM1 a sensor of Ca^{2+} localized at the ER translocates to the plasma membrane, where its activates the CRAC (Ca^{2+} release-activated Ca^{2+}) channel ORAI1. The opening of ORAI1 provokes a sustained rise of intracellular concentration of Ca^{2+} via the influx of external Ca^{2+}; this is referred to as the store-operated Ca2+ entry (SOCE) [50].

ORAI deficiency

ORAI1 deficiency is the prototypical example of how studying of immunodeficient patients enabled a breakthrough in our understanding of T cell signaling. Observations of patients with CID and symptoms of immune dysregulation led to the discovery of ORAI1 as the channel responsible for SOCE [51–54]. ORAI1 deficiency severely impeded T cell activation but had no effect on lymphocyte development. All patients presented with normal lymphocyte counts and subsets. ORAI-deficient T cells had impaired SOCE in response to TCR stimulation which compromised activation of NFAT, impaired production of IL-2, IL-4, IL-10, IFN-γ and TNFα cytokines and cell proliferation. In contrast, activation and memory markers (such as HLADR+ and CD45RO+) were normally expressed on activated T cells. SOCE is also required for the degranulation of cytotoxic granules of CD8+ cells and NK cells [55]. Even though B cells usually express ORAI1 and show SOCE, patients have normal immunoglobulin levels. Hence, ORAI1 appears to be less important in B cells than in T cells.

STIM1 deficiency

Several cases with STIM1 deficiency have been reported [53,56–58]. The immunodeficiency caused by STIM1 mutations is very similar to ORAI1 deficiency. As in ORAI1 deficiency, defects in STIM1 abolish SOCE in T cells and thus result in a severe impairment of T-cell activation, whereas T lymphocyte development is largely unaffected. Some patients had decreased numbers of CD4+ naive T cells and recent thymic emigrants. NK cell cytoxicity was also found to be impaired (as in ORAI1 deficiency), and iNKT cells were absent, suggesting a possible role for STIM1 in NK and iNKT cells [57].

MAGT1 deficiency

In 2011, a novel T-cell immunodeficiency caused by mutations in the magnesium transporter gene *MAGT1* was identified in humans with CID phenotypes associated with a specific T-cell deficiency [59]. Most of the patients were highly susceptible to EBV infection and developed lymphoma. The original study showed that the magnesium ion Mg^{2+} had a MAGT1-dependent role as a second messenger in TCR signaling by activation of $Ca2^{+}$ mobilization. Recent studies rather tend to indicate that the major role of MAGT1 in immunity is related to its other function as a non-catalytic subunit of the oligosaccharyl transferase (OST) complex. OST is responsible for the asparagine (N)-linked glycosylation of specific substrates including CD28 and the killer activating receptor NKG2D [60,61]. MAGT1-deficient CD8+ T and NK cells displayed a defect in the glycosylation of NKG2D, which impeded its expression and function leading to impaired cytotoxicity against EBV-infected B cells.

Defects in the downstream cascades

Deficiencies of the NFκB pathway

NFκB is a central and key transcription factor for T-cell activation and responses. Its activates the transcription of genes involved in T-cell maturation, survival, proliferation and late responses such as cytokine production. Once activated, NFκB translocates from the cytoplasm into the nucleus after dissociation from the intracytoplasmic inhibitor IκBα (encoded by the gene *NFKIBA*), following the phosphorylation of its latter by the IkB kinase complex (IKK). The IKK complex is composed of three subunits: IKK1/IKKα (encoded by *CHUK*), IKK2/IKKβ (encoded by *IKKB*) and NEMO/IKKγ (encoded by *IKBKG*). The upstream activation of NFκB by the TCR-CD3 receptor is specifically controlled by the CBM complex, a signalosome made of the assembly of CARMA (*CARD11*), BCL10 and MALT1 proteins, whose the formation is dependent on TCR signaling. The oligomerization of the CBM complex activates the IKK complex, which in turn triggers the phosphorylation and the proteosomal degradation of IκBα and the activation of NFκB. Autosomal recessive mutations in CARMA1, BCL10 and MALT1 have been reported to cause CID [62–64]. These defects result in alterations of T-cell maturation and functions. Patients presented with normal total T counts, but low counts of Treg and TH17 cells, and T cells failed to proliferate in response to CD3/CD28 stimulation. B cell numbers were normal or sometimes diminished with a developmental arrest at the transitional stage. NFκB activation was defective in response to TCR and BCR stimulation.

Autosomal recessive mutations in *IKBKG* (NEMO) and *IKKB* (IKK2) and autosomal dominant mutations in NFKIBA causing increased inhibitory function of IκBα, and mutations in NFkB subunits NFkB1 and C-rel have been also described [65–67]. Some of these mutations are associated with a more severe immunodeficiency, characterized by impairments in both adaptive and innate immune responses. Indeed, the impact of NEMO, IKK2 and NFKIBA deficiencies in the immune system is much broader than that of deficiencies in the CBM complex, as these three proteins are ubiquitous downstream components of the NFκB cascade.

Importantly, and in a stricking contrast to other deficiencies affecting the TCR signaling (most of which are associated with a loss of naive T lymphocytes), all these defects are characterized by the total or partial lack of circulating memory T cells and B cells associated with normal or increased counts of naive lymphocytes. Hence, the NFkB pathway in T lymphocytes appears to have a unique and crucial role in the development of the memory compartment. However, the exact mechanism(s) underlying of this function is not known.

RHOH deficiency

Deficiency in RHOH was identified in two siblings with a CID characterized by T-cell lymphopenia and reduced numbers of T cells expressing the β7 integrin, which directs the homing of T cells to lung, gut, and skin [68]. Most of circulating T cells showed an exhausted memory phenotype and proliferated poorly to TCR stimulation. RHOH is an atypical Rho GTPase that is predominantly expressed in hematopoetic tissues. Interestingly, ZAP70 activation and phosphorylation were strongly impaired in RHOH-deficient T cells due to defective localization of ZAP70 to the plasma membrane. However, the exact role of RHOH in T cell activation is still not known.

RASGRP1 deficiency

The DAG-regulated guanidine exchange factor RAS guanyl nucleotide-releasing protein 1 (RASGRP1) is selective for the small GTPase protein RAS. RASGRP1 is considered to be one of the master activators of the RAS/MAPK/ERK pathway in T and NK cells. Biallelic mutations in *RASGRP1* resulting in complete loss of protein expression have been identified in several patients with CID characterized by reduced T cell numbers in association with reduced naïve T cells and recent thymic emigrants [69–73]. Low TCR excision circles and TCR-β repertoire diversity associated with increased TCR-γδ frequencies were suggestive of an alteration in TCR rearrangements during thymic differentiation. Patients presented with recurrent viral infections and most of them developed severe EBV-driven lymphoproliferative disorders. Some had also fungal and/or bacterial infections and showed immune dysregulation symptoms [69]. RASGRP1-deficient T cells exhibited a marked decrease in ERK activation and failed to proliferate in response to TCR stimulation. T cells were also poorly able to migrate, which correlated with an impairment in RhoA activation [69]. Rasgrp1-deficient mice also develop autoimmunity, perhaps because of abnormal pre-TCR signaling and positive selection, which depend on RASGRP1.

The development of severe EBV-driven lymphoproliferative disorders in RASGRP1-deficient individuals probably results from the defective expansion and function of EBV-specific T cells [69]. Interestingly, RASGRP1-deficient T cells showed low expression levels of CTPS1, a cytidine triphosphate (CTP) synthethase required for *de novo* production of the CTP nucleotide. Under normal circumstances, CTPS1 is strongly upregulated in activated T cells in a TCR-dependent manner and is required for TCR-induced proliferation. Importantly, CTPS1 deficiency in humans causes a CID characterized by high suceptibility to viral infections and EBV in particular [74].

PIK3CD deficiency

The PI3 kinase (PI3K) activity is considered to be an important downstream pathway in TCR signaling. Notably, PI3K delivers survival signals and modulates metabolic programs required for differentiation, proliferation, effector function and memory generation of T cells via activation of the AKT-p70-S6K-mTOR pathway [75]. PI3K catalyzes the phosphorylation of the phosphatidylinositol-4, 5 diphosphate (PIP2) contained within the plasma membrane into phosphatidylinositol-3,4,5-triphosphate (PIP3). The PIP3 facilitates the recruitement and activation of proteins containing pleckstrin homology (PH) domains, such as phosphoinositide-dependent kinase (PKD1) and AKT, and possibly also ITK, VAV1 and WASP. PH domains bind to various phosphatidyl lipids, including PIP2 and PIP3.

PIK3CD encodes the p110δ, the catalytic subunit of PI3K. p110δ is highly expressed in lymphocytes and is the main active form of the PI3K catalytic subunits in human T cells. p110δ associates with the regulatory p85α subunit (encoded by *PIK3R1*). In activated T cells, PI3K is mostly activated by the co-stimulatory molecule CD28 via the recruitment of p85α. However, there is some evidence that PI3K is also directly activated by the TCR through the LAT signalosome.

Recently, four patients with severe infections, inflammatory colitis, hypogammaglobulinemia and loss of B cells were reported to carry homozygous deleterious mutations in *PIK3CD* that led to the absence of p110δ expression or removed its catalytic domain [76–78]. These patients had normal T cell subsets and counts, and proliferation of T cells in response to various stimuli was preserved or enhanced. Given the importance of the PI3K pathway in T cells, the absence of clear defects in T cell responses is rather surprising. The clinical and immunological phenotypes might be due (at least in part) to a recently described compensatory mechanism related to a balance between PLCγ-1- and PI3K-dependent pathways in T cells [79]. Indeed, PIP2 is a substrate for both PIK3CD and PLC-γ1. Hence, the absence of PI3K activity would provide more PIP2 for PLCγ-1 and so would increase activation of PLCγ-1-dependent pathways including proliferation. Other catalytic subunits (p110γ and p110α) might also compensate for the absence of the p110δ.

Of note, activated phosphoinositide 3-delta syndrome (APDS) is a primary immunodeficiency caused by heterozygous gain-of-function mutations in *PIK3CD* or bi-allelic loss-of-function in *PIK3R1* (p85α). Clinically, this syndrome has the features of CID characterized by accumulation of senescent and exhausted T cells that impaired T cell differentiation and responses [80,81].

Defects in costimulatory receptors

Cosignals are important to proper and efficient activation of T lymphocytes during immune responses by modulating or increasing T-cell receptor (TCR) signals [5]. These signals are delivered by co-stimulatory or co-inhibitory molecules (not discussed in the present review) expressed at the membrane of T cells, following their engagement by specific ligands expressed on antigen-presenting cells. These molecules contain intracyplasmic and/or transmembrane signaling motifs such as tyrosine-based motifs enabling the recruitment of dowstream effectors. Over the last few decades, several key costimulatory receptors on T cells have been identified: CD28, ICOS, members of the TNF receptor (TNFR) family like CD27, TNFRSF9 (4-1BB/CD137), OX40 (CD134), DR3 and TNFRSF14 (HVEM) and receptors of SLAM family (SLAMF-R) such as SLAMF1 (SLAM) and CD244 (2B4). CD28, CD27 and 4-1BB have been shown to deliver pro-survival, differentiation and proliferation signals via activation of the PI3K and NFκB pathways. Engagement of 4-1BB and CD28 have been also associated with enhanced mitochondrial biogenesis and respiration and metabolic changes [82,83]. Although these co-signals are clearly important for T-cell activation and responses, it is not yet known how they connect to and integrate into TCR signaling cascades. However, several of these receptors can deliver signals and trigger T-cell responses independently of TCR signaling. Interestingly, the recent identification of human gene defects impairing co-stimulatory molecules and signals suggests a molecular "specialization" of co-stimulatory molecules to adap TCR-dependent T cell responses to specific pathogens or infected cells/tissues.

Deficiencies of the CD27-CD70 and TNFRSF9-TNFSF9 receptors

Bi-allelic mutations in *CD27, CD70, TNFSFR9* and *TNFSF9* causing a complete loss of CD27, CD70 (the ligand of CD27), CD137 and CD137L (the ligand of CD137) expression respectively, have been recently reported in several patients with a CID characterized by a high susceptibility to EBV infection (and to develop EBV-driven lymphoproliferative disorders) [72,79,84–86]. Some patients with CD27 deficiency also exhibited autoimmune manifestations. T cell counts were normal, although slight abnormalities in T memory and naïve populations were noticed in some patients. Various studies of these patients highlighted a selective impairment of TCR-dependent expansion of EBV-specific CD8+ T cells towards EBV-infected B cells (B cells being the main target of EBV infection) and abnormaities in CD8 terminal differentiation. The selectivity for EBV is explained by the preferential expression of CD70 and CD137L on EBV-infected B cells (upon infection) [87]. T cells from CD70-deficient and CD137L-deficient patients did not show intrinsic defects but failed to expand when challenged with autologous EBV-infected B cells (that did not express CD70 or CD137L). CD27 and 4-1BB have been shown to deliver signals by the recruitment of TRAF2 and 5 adaptor molecules that are known to activate the NFkB pathway [88].

OX40 deficiency

OX40 deficiency was reported in a single patient with Kaposi syndrome (KS) due to human herpes virus 8 infection [89]. The patient had normal T cell counts with low proportions of memory effector CD8+ T cells. The proportion of EBV-specific CD8+ T cells was normal. CD4+ T-cell responses were impaired to recall antigens. Interestingly, OX40L was abundantly expressed in KS lesions.

CD28 deficiency

Three related patients with CD28 deficiency have been reported recently. All three patients presented recurrent HPV infections with manifestations raging from skin papillomas, warts to "tree man syndrome" [90]. Patients also had abnormally high blood loads of EBV and CMV virus but did not show overt signs of disease. Interestingly, vaccination (to diphtheria, tetanus and HPV) in the patients did not produce a clear vaccine-specific antibody response, highlighting the potentially specific role of CD28 signals in CD4+ T cells, particularly in CD4+ T follicular helper cells that are key to help B cells for antibody production. The importance of CD28 for optimal activation and expansion of CD4+ T cells was also emphasized by the presence of a pool of CD28-expressing

"somatically revertant" memory CD4+ T cells in one patient. However, this narrow (HPV-restricted) infectious phenotype is quite unexpected, if we considered the vast body of literature data generated over the last 30 years on CD28, showing CD28 co-signaling in T cells is critical and mandatory role for effective or optimal activation and responses [82]. Instead, the features of CD28 deficiency in humans rather indicate that CD28-dependent signals are dispensable and redundant for protective immunity against most pathogens with the exception of papilloma-viruses (and perhaps EBV and CMV).

Interestingly, a deficiency in RLTPR (also known as CARMIL2) was shown to cause a selective defect in CD28 co-stimulation of T cells. RLTPR is large scaffold protein that associates with CD28, and thus connects CD28 to the PKCtheta and CARMA1 for activation of NFkB [91]. RLTPR deficiency was reported in more than 20 patients with CID associated with reccurent various infections [92,93]. Several patients had abnormal persistant EBV viremia, and five developed EBV-associated smooth muscle tumors.

Deficiencies in ICOS-ICOSL receptors

ICOS belongs to CD28 family of co-stimulatory molecules. Unlike CD28, ICOS is selectively upregulated on activated T cells, but like CD28, it triggers activation of PI3K signaling-dependent pathways [94]. ICOS also activates calcium mobilization and TANK-binding kinase 1. ICOS deficiency was first reported to cause 'common variable immunodeficiency' (CVID) in individuals with recurrent respiratory tract infections, hypogammaglobulinemia, and low switched memory B cell counts [95]. However, subsequent reports described patients with a more severe phenotype (close to a CID), with T-cell defects, susceptibility to infections (suggestive of impaired T cell responses) and immune-dysregulation manifestations [96–98]. The T-cell defects include reduction of memory T cells and T_{FH} cell numbers, abnormal CD4+ Th polarization and impaired cytokine production. In agreement with studies in mice, signals deliver by ICOS appears to be particularly important for CD4+ T helper responses (including germinal formation and B-cell help). ICOS ligand (ICOSL) deficiency was recently identified in a single patient and mimics ICOS deficiency [98,99]. ICOSL is expressed on antigen presenting cells and non-hematopoietic tissues.

SH2D1A deficiency

Mutations in *SH2D1A* in humans have been shown to cause the X-linked lymphoproliferative syndrome. Patients are only prone to EBV infection and to develop subsequent severe EBV-driven lymphoproliferative disorders (including lymphoma) and hemophagocytic lymphohistiocytosis (HLH), a rare inflammatory disorder triggers by persistence of virally infected cells. *SH2D1A* codes SLAM-associated protein (SAP), a small adapter protein composed of a single SH2 domain, and which is only expressed in T and NK cells [42,100]. All patients with SAP-deficiency have normal T cell populations, other than a complete absence of iNKT cells. It has been shown that SAP-deficient CD8+ T and NK cells failed to eliminate to EBV-infected B cells. Furthermore, SAP-deficient T cells are resistant to AICD. SAP binds to phosphorylated tyrosine-based switch (ITSM) motifs found in the intracytoplasmic domains of SLAM family receptors (SLAMF-R) [101]. With the exception of 2B4 (that recognizes CD48), SLAMF receptors are self-ligands involved in homotypic interactions. SAP behaves as a *bona fide* adapter protein by recruiting the FYN kinase to SLAMF receptors, which then initiates tyrosine phosphorylation signals and the recruitment of additional signaling molecules to SLAMF-R. Furthermore, SAP acts as a blocker protein by inhibiting the recruitment of SH2-containing phosphatases to SLAMF-R. Convergent studies in mice and human show that functions of SLAMF-R are profoundly impaired in the absence of SAP, and explain the cellular phenotypes observed in patients. SAP-SLAMF-R-dependent signals are essential for the development of iNKT cells, AICD in T cells, and to trigger NK and CD8+ T cell-cytotoxic responses towards EBV-infected B cells (that expressed high amounts of SLAMF-R upon infection).

Conclusive remarks

As discussed in the present review, the identification of the genetic causes of primary immunodeficiencies associated with T-cell defects has revealed unique and unexpected aspects of the TCR signaling and T cell activation in humans. Now up to 400 gene defects have identified to cause immunodeficiencies. A large proportion of these defects are associated with impaired T cell-mediated immunity, often not directly linked to impaired TCR signaling or co-stimulatory signaling, and so have not been discussed here. Notably, another group of T-cell immunodeficiencies (not reviewed here), is characterized by the loss of naive T cells due to survival defects and/or abnormalities in lymphocyte cytoskeleton remodeling, migration or immunological synapse formation. These immunodeficiencies that include DOCK8, MST1/STK4, WASP and CORO1A deficiencies lead to severe defects in T cell responses [102–105].

Conflicts of interest

The authors have no financial or ethical conflicts of interest to report.

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