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Primary immunodeficiencies associated with EBV-Induced lymphoproliferative disorders

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Contents

1. Introduction 110
2. PIDs associated with EBV-LPDs 110
   2.1. Ataxia-Telangiectasia 110
   2.2. ITK deficiency 111
   2.3. X-linked lymphoproliferative disease type 1 (SAP deficiency) 113
   2.4. Wiskott-Aldrich syndrome 114
   2.5. CD27 deficiency 114
   2.6. XMEN disease (MAGT1 deficiency) 114
   2.7. Coronin 1A deficiency 115
   2.8. Autoimmune lymphoproliferative syndrome (ALPS) 115
   2.9. *MST1* mutation (STK4 deficiency) 115
   2.10. Omenn syndrome 116
      2.10.1. Artemis 116
      2.10.2. DNA ligase IV 116
      2.10.3. RAG1 116
   2.11. DiGeorge syndrome 116
   2.12. Activated PI3K-δ 121
   2.13. WHIM syndrome 122
   2.14. CTPS1 deficiency 122
   2.15. MCM4 deficiency 122
   2.16. ZAP70 deficiency 122
   2.17. NF-κB1 haploinsufficiency 122
3. Conclusions 123
   Conflicts of interest 123
   References 124

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ABSTRACT

Primary immunodeficiency diseases (PIDs) are a subgroup of inherited immunological disorders that increase susceptibility to viral infections. Among the range of viral pathogens involved, EBV remains a major threat because of its high prevalence of infection among the adult population and its tendency to progress to life-threatening lymphoproliferative disorders (LPDs) and/or malignancy. The high mortality in immunodeficient patients with EBV-driven LPDs, despite institution of diverse and often intensive treatments, prompts the need to better study these PIDs to identify and understand the affected molecular pathways that increase susceptibility to EBV infection and progression. In this article, we have provided a detailed literature review of the reported cases of EBV-driven LPDs in patients with PID. We discuss the PIDs associated with development of EBV-LPDs. Then, we review the nature and the therapeutic

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outcome of common EBV- driven LPDs in the PID patients and review the mechanisms common to the major PIDs. Deep study of these common pathways and gaining a better insight into the disease nature and outcomes, may lead to earlier diagnosis of the disease, choosing the best treatment modalities available and development of novel therapeutic strategies to decrease morbidity and mortality brought about by EBV infection.

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1. Introduction

Epstein-Barr virus (EBV), a member of the gamma herpesviridae family, is considered to be one of the major oncogenic viruses due to its potential to transform normal cells and drive emergence of several human cancers, including B-lymphomas. In addition to invading B-cells and epithelial cells, recently it has been reported that some types of the virus can also infect T and NK cells (Coleman et al., 2014).

Proliferation of EBV-infected epithelial cells has a major role in spreading the virus, by means of shedding the mucosa into saliva. People can be infected by exposure to EBV-containing saliva or close oral contact. Furthermore, in immunocompromised individuals, EBV can transform oral or gastrointestinal epithelial cells leading to nasopharyngeal carcinoma and gastric carcinoma (Tsao et al., 2015).

There are two types of EBV: EBV-1 and EBV-2, which differ mostly in their EBV nuclear antigen 2 (EBNA2) genes (Sample et al., 1990). The prevalence of infection with EBV-1 is greater than EBV-2 in most regions (Gratama and Ernberg, 1995). In contrast to EBV-1, which readily transforms B cells, EBV-2 is poorly transforming. Instead, EBV-2 has a major affinity to invade T-cells. Infection of T-cells leads to dysregulation of T-cell immunity and cytokine production, and by stimulating an inflammatory background, it can also induce oncogenesis in T-cells (Coleman et al., 2014).

Even though it infects the vast majority of people by adulthood, those with normal immune system function usually exhibit subclinical or no evidence of disease because of efficient T cell/NK cell immunity against disease progression. This clears the majority of infectious virion; however, a residual low level of virus results in life-long latent infection in more than 90 percent of adults. There are several latency phases of the virus, based on the type and differentiation of the cells that are invaded and the degree of host immunity (Grywalska et al., 2013). Latency 0 refers to EBV infection of memory B-cells, in which the virus persists in a manner that the immune system cannot detect it. In this type of latency, the virus only expresses the transcripts of its two small RNAs, EBER1 and EBER2. Latency 1 is the state in which the virus expresses Epstein–Barr nuclear antigen 1 (EBNA-1) in addition to the EBERs. Expression of these genes is needed for division of the viral genome during cell division. The EBV genes expressed in latency type 2 include EBNA-1, EBERs, latent membrane protein (LMP)-1, LMP-2A and LMP-2B, which are required for differentiation of EBV-infected cells to long-lived memory cells (Kang and Kieff, 2015; Kempkes and Robertson, 2015). The third latency program of EBV involves expression of all EBNAs, EBERs and LMPs and induces proliferation and transformation of cells. Latency 3 is seen mainly in immunocompromised patients, which is followed by the adverse sequelae of EBV infection (Dolcetti et al., 2013).

NK cells and antigen-specific CD8+ T-cells are the main effectors that inhibit progression of primary EBV infection (Priatel et al., 2014). It is believed that these cells are activated by loss of some B-cell antigens and expression of lytic antigens, following primary infection. NK cells and CD8+ T-cells inhibit the virus-induced transformation and the unlimited proliferation of memory B-cells (Gurer et al., 2008).

The hazardous consequences of EBV infection are seen mostly in immunocompromised patients, in which the virus can be reactivated and cause transformation of cells. This uncontrolled proliferation of cells can lead to some adverse sequelae, such as increased emergence of malignant and non-malignant lymphoproliferative disorders (LPDs), such as B-cell, T-cell/NK cell and Hodgkin's lymphomas (HL) (Eminger et al., 2015; Sabattini et al., 2010) (Table 1).

Primary immunodeficiencies are a heterogeneous group of hereditary diseases that are associated with compromised immune responses, reducing the ability of immune system to combat infectious pathogens, malignant cells and autoimmune state (Rezaei et al., 2008). A major disability in most of PIDs is inefficient immunity against virus infected cells such as those infected by EBV. Survival of these cells increases the possibility of continued proliferation, activation, and ultimately oncogenesis.

There are several PIDs in which EBV-associated LPDs are a major component and others where EBV-LPDs have been reported to develop less frequently (Table 2). Even though about 290 PIDs have been reported (Picard et al., 2015), it is striking that all of the PIDs that present with EBV-driven LPDs are related to defects in the growth, differentiation and activities of B and/or T cells, which together account for about 10 percent of all PIDs. Conversely, PIDs associated with complement deficiencies, autoinflammatory disorders, innate immunity defects, congenital defects of phagocyte number or function and acquired immunodeficiencies are not known to be associated with an increased risk for EBV-LPDs, which may due to the less critical role of innate immunity in protection against the complications of EBV. On the other hand, combined T-cell and B-cell immunodeficiencies account for about two third of PIDs associated with EBV-driven lymphoproliferative disorders (Table 2).

In this review, we describe the PIDs associated with EBV-induced LPDs. In addition, we have provided a literature review on reported PID patients with EBV-LPD development to date with their age, manifestations, treatment and outcome. Studying the altered immune pathways in each of these diseases will give us insight to normal host immunity against this virus, and establish new ideas for more effective methods of prevention and treatment. Moreover, studying the age distribution, prevalence of different LPDs and the outcome of treatment in the PIDs may help the physicians in making an early diagnosis and choosing the most efficient treatment method available.

2. PIDs associated with EBV-LPDs

2.1. Ataxia-Telangiectasia

Ataxia telangiectasia (AT), a rare PID associated with a high risk to develop cancers (Suarez et al., 2015), is caused by biallelic mutations in *ATM* which encodes a serine-threonine kinase of the phosphoinositidyl 3-kinase–related protein kinase family. ATM acts in pathways contributing to post-DNA damage cellular responses like control of cell cycle checkpoints, repair of DNA double-strand breaks and apoptosis (Lavin, 2008; Shiloh, 2003) (Fig. 2-A). The major presentations of AT include progressive

Table 1
EBV-associated LPDs. (Hodgkin's lymphoma HL, Burkitt lymphoma BL, Diffuse large B cell lymphoma DLBL).

Lymphoproliferative category	Lymphoproliferative disorders	Rate of EBV associated lymphoproliferation
B-cell associated	BL	15–20% (sporadic BL)(Geng and Wang, 2015) >90% (endemic BL)(Geng and Wang, 2015)
HL	Lymphomatoid granulomatosis DLBL Hydroavacciniforme-like lymphoma	<5–15% (Geng and Wang, 2015)
	Lymphocyte-depleted classical HL	95%(Geng and Wang, 2015)
	Mixed cellularity classical HL	70%(Geng and Wang, 2015)
	Nodular sclerosis classical HL	10–40%(Geng and Wang, 2015)
T-cell associated	Extranodal NK/T-cell lymphoma, nasal type	84.8%(Wang et al., 2014)
	Angioimmunoblastic T-cell lymphoma	72.7%(Wang et al., 2014)
	Systemic EBV-positive T-cell lymphoproliferative disease of childhood	
	Peripheral T-cell lymphoma	40.0%(Wang et al., 2014)

cerebellar ataxia, development of occulocutaneous telangiectasias, increased susceptibility to cancer, particularly lymphoma and leukemia, and evidence of immunodeficiency.

The immunologic defects in AT affect both the humoral and cellular systems, including decreased naive CD4+ and CD8+ T cells, effector memory CD4+ cells, naïve and switched B cells, despite a marked increase in NK cells, active CD8+ T cells and non-switched B cells (Celiksoy et al., 2014; Schubert et al., 2002). Patients also exhibit impaired Ig gene rearrangement (Fig. 3), which manifests as increased IgM monomers and decreased IgA, IgE and IgG subclasses (Mohammadinejad et al., 2015). The *ATM* gene product has a diverse array of functions, but the exact mechanism of oncogenicity and immunodeficiencies induced by mutated ATM are not completely understood. What has become clear is that the AT immune phenotype results from limited lymphocyte output and impaired gene rearrangement in T and B cells, manifesting as restricted antigen receptor repertoires and abnormal Ig class-switching, respectively (Staples et al., 2008).

Many studies have illustrated the high prevalence of malignancy in AT, including a recent report of acute leukemia, HL, non-Hodgkin lymphpoma (NHL), T cell prolymphocytic leukemia and carcinoma in AT patients, out of whom EBV was found in HL and B cell NHL cases (Suarez et al., 2015). The first reported case with EBV-associated LPD was a 16 year old male with extra-nodal marginal zone MALT lymphoma, who experienced 3 years of remission after anti CD-20 Ab therapy (Bennett and Bayerl, 2015). The second patient was a 14-year old with nodular sclerosing HL, who was completely treated with brentuximab vedotin therapy along with complementary COPP and rituximab regimen (Meister et al., 2015). Recently, Beier et al., reported a 13 year old patient who developed NHL and had undergone HSCT after successful chemotherapy with Dexamethasone, Vincristine, Cyclophosphamide, Doxorubicin, Etoposide, Cytarabine and Methotrexate (Beier et al., 2016). The latter was the first long-term surviving NHL and AT patient receiving HSCT. Although the correlation between increased EBV-associated LPD and AT disease is not well recognized, studies on ATM-deficient murine models reveal that generation of an MHV68-specific immune response is altered, suggesting a role for this protein in controlling gamma-herpes virus latency by development of a specific repertoire of antiviral $CD8^+$ T cells (Kulinski et al., 2012) (Table 3).

2.2. ITK deficiency

Interleukin-2 inducible T cell kinase (ITK) deficiency is an autosomal recessive immunodeficiency disease, which is well documented as progressing to EBV- associated B cell lymphoproliferation, notably HL.

The first report of ITK deficient patients described two girls from a consanguineous Turkish family, both with a homozygous R335W mutation in the SH2 domain of the *ITK* gene (Huck et al., 2009). Remarkably, both sisters developed HL. The older sister died despite receiving chemotherapy due to progressive T cell loss leading to respiratory failure from pneumocystis pneumonia. The younger sister was treated with haploidentical peripheral blood stem cell transplantation, but died from adverse consequences of aplasia. Later, three patients from a Palestinian family, all harboring a homozygous nonsense mutation Y588X were reported to develop EBV-associated HL (Stepensky et al., 2011). All three received chemotherapy. One responded well to chemotherapy, one underwent a successful allogeneic bone marrow transplant and the other died of severe hemophagocytic lymphohistiocytosis (HLH). In another study, three other unrelated individuals were reported to present with EBV-associated B cell lymphoproliferation (Linka et al., 2012; Mansouri et al., 2012). The first, from Morocco with an R29H mutation, died at the age of 26. The second, from India, with aS499SfsX4 mutation, died after stem cell transplantation, and the third, an Iranian patient with a P156PfsX109 mutation, died 2 years after diagnosis. Later, two studies reported two individual EBV-positive HL, who went on complete remission after pre-conditioned HSCT (Alme et al., 2015; Shamriz et al., 2014). Another study reported a NHL and a HL in a sibling with ITK deficiency, one of whom died during R-CHOP chemotherapy due to severe infections. The last and the largest study, analysed 7 patients, 4 with HL or HL-like LPDs and 3 with Polymorphic B-LPDs. 3 patients had undergone HSCT, out of whom only one patient survived. Also one HL patient went on remission after chemotherapy (Table 3).

The age distribution of patients is 3–14 years, mostly 4–6 years. 13 out of 20 patients with EBV-LPDs developed HL, one developed NHL, one manifested with Large B cell lymphoma and lymphomatoid granulomatosis and the remainder developed undifferentiated B-LPDs. This fact can propose the association of ITK deficiency with development of HL. 8 patients had received transplantation, out of whom 4 patients died because of the complications. Since patients treated with chemotherapy had gained similar results, the efficiency of HSCT in increasing the survival of EBV-LPD developed ITK defeicient patients still needs to be studied. In this regard, the use of reduced intensity conditioning regimens have been showed to result in more successful engraftments. (Shamriz et al., 2014; Stepensky et al., 2011)

The immunologic profile of patients with ITK deficiency includes lymphopenia with a severe decline in invariant natural killer T (iNKT) cells and CD4+ T cells, especially naive CD45RA + CD4 + T cells. CD8 + T cell and B cell counts in the majority of patients are normal. Serum immunoglobulin (Ig) levels are normal to decreased (Ghosh et al., 2014).The common cell lost or reduced in many immunodeficient patients, which may play a role in EBV progression, is the NKT cell. ITK, in conjunction with IL-15, GATA-3 and T-box transcription factor, T-bet, are required for terminal maturation, development of effector function, and long-term survival of NKT cells (Felices and Berg, 2008). Therefore, ITK deficient patients exhibit decreased NKT cell counts and impaired NKT cell

Table 2
PIDs with reported cases of EBV-LPDs. (Autosomal recessive AR, X-linked XL, Autosomal dominant AD).

N	PID	WHO classification (Al-Herz et al., 2014; Picard et al., 2015)	Gene	loci	Mode of inheritance	Defected immune pathway
1	Ataxia-Telangiectasia	Combined immunodeficiencies (with DNA repair defects)	ATM	11q22-q23	AR	Restricted antigen receptor repertoires and abnormal Ig class-switching
2	ITK deficiency	Combined immunodeficiencies AND Immune dysregulation (lymphoproliferative syndrome)	ITK	5q31-q32	AR	Impaired survival of NKT cells and NK cell cytotoxicity, defected thymic selection and T cell differentiation leading to increased innate CD4 and CD8 cells
3	X-linked lymphoproliferative disease type 1 (SAP deficiency)	Combined immunodeficiencies AND Immune dysregulation (lymphoproliferative syndrome)	SH2D1A	Xq25	XL	Impaired TCR-induced cytokine production, defective 2B4 and NTB-A induced cytotoxicity of NK cells and CD8T cells, impaired NKT cell development, impaired contact of Tfh and B cells required for long-term humoral immunity
4	Wiskott-Aldrich syndrome	Combined immunodeficiencies (with congenital thrombocytopenia)	WAS	Xp11.4-p11.21	XL	Defective hematopoietic cell growth and functions especially CTL and NK cytotoxicity, due to impaired actin polarization
5	CD27 deficiency	Combined immunodeficiencies AND Immune dysregulation (lymphoproliferative syndrome)	CD27	12p13	AR	Decreased production of Th1-type cytokines, defected naïve T cell expansion, impaired activation of tumor-antigen specific T cells and NKT-dependent activation of CD8+ T cells, Defects in B cell proliferation and differentiation to CD38 + CD20- plasmablasts and antibody production
6	XMEN disease (MAGT1 deficiency)	Combined immunodeficiencies	MAGT1	Xq21.1	XL	Impaired T cell proliferation and activation due to reduced activation of phospholipase Cγ1, defective NK and CD8T cell cytotoxicity because of decreased expression of NKG2D receptor
7	Coronin1A deficiency	Combined immunodeficiencies (T^-B^+ SCID)	CORO1A	16p11.2	AR	Impaired NK cell lytic granule secretion, defected T cell locomotion, Defected thymic egression leading to decreased naïve T cells, impaired development of NKT and MAIT cells
8	ALPS-FAS	Immune dysregulation (lymphoproliferative syndrome)	TNFRSF6	10q24.1	AD-AR	Impaired lymphocyte homeostasis due to defected FAS-mediated apoptosis
9	MST1 deficiency (STK4 mutation)	Combined immunodeficiencies	STK4	20q11.2-q13.2	AR	Defects in Naïve T cell survival, Treg development, homing of CD8+ cells to secondary organs, and increased T cell apoptosis
10	Artemiss hypomorphic mutation	Combined immunodeficiencies (T^-B^+ SCID) – DNA recombination defects	DCLRE1C	10p13		Impaired B and T cell development due to defects in chromosomal rearrangement during V(D)J recombination
11	DNA ligase IV hypomorphic mutation	Combined immunodeficiencies (T^-B^- SCID)	LIG4	13q33-q34		Impaired B and T cell development due to impaired repair of double strand breaks in V(D)J recombination
12	RAG1 hypomorphic mutation	Combined immunodeficiencies (T^-B^- SCID)	RAG1	11p13		B cell, CD4+ and CD8+ T cell lymphopenia despite increase in γδT cells
13	DiGeorge syndrome	Combined immunodeficiencies (with thymic defects)	TBX1	22q11.21	AD (or De novo)	Defected AIRE gene expression and impaired T cell development
14	Activated PI3K-δ	Combined immunodeficiencies AND Predominantly antibody deficiency (Isotype or light chain deficiency with normal B-cells)	PIK3CD, PI3K-d	1p36.2	AD (Autosomal dominant)	Higher sensitivity of CD4+ and CD8+ T cells to AICD and reduced T cell cytokine production, suppressed Ig class switching, low serum IgG2 levels and high serum IgM levels
15	WHIM syndrome	Predominantly antibody deficiency (Severe reduction in at least 2 Ig isotopes with low or normal B-cells)	CXCR4	2q21	AD	Myelokathexis, impaired thymopoiesis and B cell development
16	CTPS1 deficiency	Combined immunodeficiency	CTPS1	1p34.1	AR	Lymphopenia due to the impaired antigen-induced proliferation of B and T cells
17	MCM4 deficiency	Combined immunodeficiencies (with DNA repair defects)	MCM4	8q11.2	AR	Decreased active circulating NK cells
18	ZAP70 deficiency	Combined immunodeficiency	ZAP70	2q12	AR	Decreased functionally active CD4T cells due to the impaired TCR pathway and CD8 lymphopenia due to impaired CD8 development
19	NF-κB1 haploinsufficiency	Common variable immunodeficiency	NF-κB1	4q24	–	Impaired function of B and T cells, impaired differentiation and T cell- independent Ig class switching of B cells

cytokine secretion. ITK also plays positive and negative regulatory roles in NK cell cytotoxicity, mediated via distinct NK-activating receptors (Fig. 1). It primarily increases cytotoxicity by stimulating ITAM-containing FcR, while negatively affecting NKG2D-initiated cytotoxicity (Khurana et al., 2007).

ITK is a non-receptor tyrosine kinase, which consists of a pleckstrin homology (PH) domain at the N-terminus, a Tec homology (TH) domain; a Src homology 3 (SH3) domain; a Src homology 2 (SH2) domain and a catalytic kinase domain at the C-terminus. ITK is autophosphorylated when it is recruited to the cell membrane

in response to TCR activation. Activated ITK induces phospholipase C-γ to hydrolyze phosphatidylinositol-4,5-biphosphate and produce inositol-1,4,5-triphosphate (IP3). The latter causes calcium to release from the endoplasmic reticulum and together with calmoldulin, activates the serine/threonine phosphatase calcineurin. Calcineurin dephosphorylates nuclear factor of activated T cells (NFAT), triggering NFAT nuclear localization and subsequent regulation of gene transcription. NFAT is the major regulator of T cell lymphokine gene transcription (Fig. 2-B).

ITK has a predominant role in thymic selection and T cell differentiation and also TCR-dependent activation of mature T cells. As a result, the majority of CD8+ and CD4+ T cells in ITK deficient mouse models show features of innate T cells, such as the up-regulation of CD44 and CD122 (Nayar et al., 2012) (Fig. 2-A). These mature CD4+ or CD8+ thymocytes express high levels of a transcription factor, eomesodermin and are dependent on IL-4 signaling for their development, indicating that they have been converted to an innate-like phenotype (Prince et al., 2014).

2.3. X-linked lymphoproliferative disease type 1 (SAP deficiency)

X-linked lymphoproliferative disease (XLP1) was first described in 1975 as a fatal immunodeficiency affecting six males from the Duncan family, which led to the original naming of this condition as Duncan's disease (Purtilo et al., 1975). XLP1 is caused by loss-of function mutations in *SH2D1A*, which encodes the intracellular adaptor molecule SAP (signaling lymphocyte activation molecule (SLAM) associated protein). The clinical background is usually a male patient presenting with the triad of fulminant infectious mononucleosis (also known as EBV-induced hemophagocytic lymphohistiocytosis), dysgammaglobulinaemia and/or lymphoma (Rezaei et al., 2011b).

SAP is an adaptor protein that is expressed in all T cells, NK cells, NKT cells, and in a minority of bone marrow B cells (Rezaei et al., 2011b). SAP interacts with the cytoplasmic domain of the SLAM family receptors via tyrosine-based switch motifs called ITSM (immunoreceptor tyrosine-based switch motif) that reside within the SLAM receptor tails. SAP exhibits dual modes of function. First, it acts as a competitor that inhibits the binding of other SH2-domain containing proteins, such as the SHP2 phosphatase, to the SLAM receptors (Sayos et al., 1998). Second, it acts as an adaptor to bind to and recruit the Fyn tyrosine kinase to the SLAM receptors, in so doing, SAP facilitates phosphorylation of the SLAM receptors and stimulates downstream signaling (Bloch-Queyrat et al., 2005; Chan et al., 2003).

SLAM activated pathways have important roles during regulation of antigen-specific proliferation and Th2-type cytokine production by CD4+ T cells (Cocks et al., 1995) (Fig. 2-B). As a result, SAP deficiency, like SLAM deficiency, results in dysregulated patterns of TCR-induced cytokine production with preferential production of IFN-γ and diminished IL-4 production (Czar et al., 2001).

SAP-deficient NK cells exhibit impaired cytolytic activity, which along with reduced CD8+ T cell killing, likely contributes to the increased susceptibility of affected individuals to EBV infection as these cells are critical for anti-viral defense (Orange, 2013). 2B4 is a surface molecule that functions through SAP-induced signaling pathways. Its ligand, CD48 is highly expressed on EBV-infected B cells. The outcome of activation via the 2B4 pathway is increased cytotoxicity of NK cells that likely plays a role in defending against EBV infection (Parolini et al., 2000). NTB-A is also a SAP-associated SLAM family receptor functions in a manner similar to 2B4 molecule, except that like other SLAM-related receptors it is a homotypic receptor that binds to like molecules on adjacent cells (Bottino et al., 2001). The loss of functional SAP in XLP patient cells results in defective 2B4 and NTB-A induced cytotoxicity (Fig. 1). In a murine model of Sap deficiency, it was determined that presence of Sap allows for 2B4 phosphorylation (Bloch-Queyrat et al., 2005), and later, it was learned that loss of SAP expression impairs the interaction between Fyn and phosphorylated SLAM receptors, leading to impaired signal transduction (Meinke and Watzl, 2013). Further studies showed that SAP deficiency not only impairs the delivery of activating signals by the SLAM-related receptors, but it also lessens signaling function by allowing inhibitory phosphatases such as SHIP or SHP2 to bind to the SLAM receptors (Dong et al., 2012; Eissmann et al., 2005; Parolini et al., 2000; Watzl and Claus, 2014).

As with NK cells, SLAM receptor functions are also impaired in SAP deficient CD8+ T cells (Palendira et al., 2011). SAP deficient CD8+ cells sustain their effector activity, but their activity is dependent on the APC cell line (Hislop et al., 2010). They show poor response to antigen presenting B cells. This loss of response was overcome by blocking 2B4 and NTB-A receptors in SAP deficient patients (Palendira et al., 2011).

Another prominent immune cell defect in XLP1 patients is lack of NKT cells. Studies in mice illustrate that NKT cell and thymocyte-selected CD4+ cell development requires signaling via a SAP-Fyn-PKCθ pathway which is activated by engagement of the Slamf1 (SLAM) and Slamf6 (Ly108) receptor (Griewank et al., 2007; Li et al., 2007) (Fig. 2-A). Based on the fact that NKT cells are likely to be involved in defense against malignancies and autoimmunity, it is proposed that impaired NKT development can generate the appropriate immunological environment in which malignant cells and dysregulated immune cells can proliferate and function (Orange, 2013). It has been proposed that an intact SAP pathway is essential for development, cytokine secretion and cytotoxicity of type II NKT cells more than type I (Weng et al., 2014). A recent *in vitro* study on SAP deficient mice revealed that SAP pathway is crucial for IL4 secretion by iNKT cells and the reduced IL4 secretion is due to absence of iNKT cells type II (Michel et al., 2016).

Because the impaired SLAM receptor related pathways observed in SAP deficient patients are those that facilitate T/NK cell interactions with B cells, and EBV has great affinity to infect B cells, it is believed that these defects may explain why XLP1 patients are severely and uniquely susceptible to EBV infection but not to other viral infections.

The defects in humoral immunity observed in XLP patients are associated with reduced memory B cell count, poor germinal centre formation and diminished Ig switching. Sustained contact between a subset of helper T cells called T Follicular helper cells (Tfh) and B cells is required for long-term humoral immunity. SAP is essential for the delivery of Tfh cell help to B cells (Fig. 3) (Hu et al., 2013).

Thirty percent of patients with SAP develop lymphoma, out of whom the majority were of the Burkitt (Rezaei et al., 2008, 2011b) and non-Hodgkin's type (Filipovich et al., 1993), even though, diverse cases of lymphoma like immunoblastic or extranodal lymphomas account for few other cases (Table 3).

Previously, it was believed that most of the manifestations ofSAP deficiency were solely due to EBV infection. With increased use of genetic testing, it is now clear that with the exception of fulminant infectious mononucleosis, XLP patients can develop lymphoma and hypogammalgobulinemia even in the absence of prior EBV infection (Koochakzadeh et al., 2015; Sumegi et al., 2000). Although historic references reveal that up to 96 percent of XLP patients used to die as the result of EBV (Seemayer et al., 1995). Early diagnosis and management have led to decreased mortality rates. Currently, reduced intensity conditioning hematopoietic cell transplantation remains the most effective curative treatment for SAP deficient patients (Marsh et al., 2014; Shamriz et al., 2014).

2.4. Wiskott-Aldrich syndrome

Wiskott-Aldrich syndrome (WAS) is one of the most studied diseases that has been reported to have correlations with EBV associated LPDs since 1986 (Ilowite et al., 1986). Mutations in the *WAS* gene located in Xp11.22-23 results in defective WASP function as a scaffold for actin polymerization. This leads to impaired hematopoietic cell growth and functions; esp. signal transduction in immune system cells (Rezaei et al., 2008). Clinical presentations of WAS include recurrent infections, thrombocytopenia, eczema and increased susceptibility to develop tumors and autoimmunity (Bosticardo et al., 2009). EBV-induced LPDs observed in patients with WAS include lymphomatoid granulomatosis (Sebire et al., 2003), NHL (Du et al., 2011; Yoshida et al., 1997), LMP1 + HL (Du et al., 2011; Sasahara et al., 2001), LMP1 +, EBNA2 + lymphoma (Gulley et al., 1993), and other LPDs (Nakanishi et al., 1993) (Table 3).

Studies reveal that reduced CTL cytotoxicity may play the main role in defective immunity against infections and B cell malignancies in WAS patients (De Meester et al., 2010). The regulation of actin dynamics and organization is vital for efficient CTL and NK cell cytotoxicity. Considering the normal levels of lytic effector molecules in WAS CTLs, the reduced CTL killing likely results from defective polarization and secretion of lytic granules as the result of impaired activation of the ARP2/3 complex (Mace et al., 2010) (Fig. 1).

Another important cell defect in WAS patients relates to impaired NK cell crosstalk (Catucci et al., 2014; Romagnani and Babic, 2014) followed by NK cell cytotoxicity defects. NK cells are involved in two different synapses; one with dendritic cells (DCs) called the regulatory synapse (which polarizes DC cytokine release for NK cell activation) and another with target cells called lytic synapse (which facilitates target cell killing). NK cells require F-actin accumulation not only to establish polarized contact with target cells but also to provide a structural synapse to propagate activation signals (Gismondi et al., 2004). WASP is localized to the lytic synapse together with F-actin. Thereby, NK cells from WAS patients fail to accumulate F-actin and perforin at the synapse and have impaired cytolytic function. Also, DCs from *Wasp−/−* mice fail to induce NK cells. However the exact mechanism involved in impaired NK/DC crosstalk is not understood. Although, defects in NK/DC crosstalk and NK cell cytotoxicity are shown to correlate with impaired antitumoral activity; even impaired NK cell activation and function directly relates to high prevalence of LPDs or not remains to be studied.

2.5. CD27 deficiency

CD27 deficiency is an autosomal recessive immunodeficiency disorder characterized by mutations in the *CD27* gene, which encodes a TNF-R (Tumor necrosis factor receptor) superfamily member that is present on the B cell membrane and required for activating T cells and long-term maintenance of T cell immunity. Specific immunologic features ascribed to this disorder include lack of memory B cells (no CD27+ cells), normal T cell count, low NKT cells and hypogammaglobulinemia (Al-Herz et al., 2014).

CD27 deficiency was identified in ten patients from four different families, eight of whom harbored a germline homozygous missense mutation (C53Y) in a motif within the ligand-binding domain of CD27 (Salzer et al., 2013). The two other individuals harbored a homozoygous nonsense mutation in CD27 gene (W8X). Of the ten affected individuals, five presented with EBV-driven LPD at diagnosis or later during the course of disease, and the remainder had positive laboratory evidence of prior EBV infection, but no sign of lymphoproliferation. Three individuals with EBV-LPD were treated with rituximab, one of whom exhibited recurrent LPD that progressed to T cell lymphoma and was treated with chemotherapy and unrelated cord blood transplantation. The other two patients died of suspected lymphoma (Salzer et al., 2013; van Montfrans et al., 2012). Later, Alkhairy et al. studied 17 patients of various origins and reported 4 patients with EBV-related LPDs and two suspected EBV-driven diffuse large B cell lymphomas (DLBL) (Alkhairy et al., 2015). Except the patient with extranodal B cell LPD of orbit that harbored a heterozygous nonsense mutation (c. C30A, p. C10X), the remainder harbored a common homozygous missense mutation (c. G158A, p. C53Y). Two patients responded well to Rituximab treatment and two others, who had undergone HSCT, were alive at the end of study (Table 3).

CD27 activity is dependent on the interaction with CD70. The CD27-CD70 interaction is crucial for regulation of T, B, and NK cell activity (Nolte et al., 2009). Furthermore, some studies revealed that the CD27-CD70 interaction is crucial for naive T-cell expansion and production of Th1-type cytokines (Kawamura et al., 2011) (Fig. 2-B), and together with CD28/CD80 and 4-1BB/4-1BBL interactions is critical for activation of tumor-antigen specific T cells (Zeng et al., 2014), These data support the notion that CD27 deficiency can increase susceptibility to hematologic malignancies. Interestingly, it was reported that the survival of cancer patients increases following treatment with soluble CD27, which increases T cell activation and proliferation (Huang et al., 2013). In another study, it was proposed that this interaction also leads to NKT-dependent activation of CD8+ T cells (Taraban et al., 2008) and formation of memory CD8+ T cell clones that can protect against pathogens (van Gisbergen et al., 2011). Defects in these CD27-dependent processes may explain why CD27 deficient patients develop recurrent viral infections. CD70 dependant CD27 signaling is required for B cell proliferation and differentiation to CD38 + CD20- plasmablasts and antibody production (Sammicheli et al., 2012) (Fig. 3). Impairments in this function likely underlie the poor antibody production that is observed in CD27-deficient patients. Moreover, reduced iNKT cells in severe forms of CD27 deficient patients proposed the idea that CD27-CD70 is also essential for development of iNKT cells (Salzer et al., 2013).

2.6. XMEN disease (MAGT1 deficiency)

X-linked immunodeficiency with magnesium defect, EBV infection and neoplasia (Li et al., 2014) is a novel hereditary immunodeficiency caused by loss-of-function mutations in the *MAGT1* gene, which encodes a critical magnesium transporter. As a consequence of the germline mutations, T cells from patients with XMEN exhibit impaired magnesium influx following TCR engagement leading to reduced activation of phospholipase Cγ1 and subsequent T cell proliferation and activation (Li et al., 2011b; Ravell et al., 2014). These defects can be rescued by treatment of cells with phorbol 12-myristate 13-acetate (PMA) and ionomycin, further supporting the notion that loss of MAGT1 leads to a defect in proximal TCR signaling, prior to the induction of Ca2+ flux (Li et al., 2011b). Interestingly, the decline in intracellular magnesium level also affects expression of the NKG2D receptor, which lead to defective NK and CD8T cell cytotoxicity (Chaigne-Delalande et al., 2013) (Fig. 1). B cell activation in patients with XMEN is normal, leading to the proposal that MAGT1 is more important in T cell signaling in comparison to B cell signaling (Li et al., 2011b).

Patients with XMEN exhibit CD4+ T cell lymphopenia, inverted CD4:CD8 ratios, splenomegaly and dysgammaglobulinemia (Li et al., 2014, 2011b). Studies have demonstrated absent proliferative T cell response to EBV stimulation despite normal responses to other common viruses such as VZV and CMV (Dhalla et al., 2015). Remarkably, provision of magnesium supplementation to MAGT1 deficient patients restores NKG2D expression and reduces the number of EBV-infected B cells in vivo, revealing the key role of MAGT1

in NK and CD8+ cells during normal host immunity to EBV infection (Chaigne-Delalande et al., 2013) (Fig. 1).

Chronic EBV infection and associated LPDs are common findings in these patients, which are often associated with a poor prognosis despite various treatment modalities (Li et al., 2014). There are 5 reported cases of definite EBV-associated LPDs in literature. Li et al., studied 7 XMEN patients, out of whom 4 developed EBV-LPDs. Two patients with HL and polymorphic B cell LPD underwent unrelated HSCT but they died of the transplant complications. Another post-mortem study was done in a 45-year old patient who died of chronic EBV-driven lymphoma. Later, a LMP1+ HL with atypical Reed-Sternberg cells was reported in a 52-year old patient. The patient went on a remission after treatment with R-CHOP regimen (Table 3).

2.7. Coronin 1A deficiency

Coronin 1A deficiency is an autosomal recessive genetic disorder associated with mutations affecting the *CORO1A* gene.

Investigations involving three siblings from a Moroccan family who presented with EBV associated B cell lymphoproliferation revealed a homozygous missense V134M mutation in the *CORO1A* gene, which was predicted to affect the β-propeller domain of Coronin-1 (Moshous et al., 2013). One sibling went into complete remission after treatment, while the other two died after induction therapy and HSCT (Hematopoietic stem cell transplantation), respectively. In addition to the 3 Moroccan siblings discussed, two other Coro1a deficiency patients developed DLBL. The first one was a 15 year old female with a compound heterozygous mutation (p.P83RfsX10 and p.Q360RfsX44), who developed DLBL during the induction chemotherapy for an existing high grade EBV-positive HL. Another 14 month old child with a hemizygous p.R12L mutation developed DLBL affecting CNS, GI, lung and thymus. Both patients died of lymphoma complications. All of the reported patients developed aggressive DLBL. The age of lymphoma development was low in comparison with other PIDs except the one who developed DLBL during the chemotherapy for HL (Table 3).

Coronin 1 is an accessory protein associated with filamentous (F)-actin and the actin-related protein 2/3 complex (ARP2/3 complex). As a consequence, it acts in membrane interactions (Foger et al., 2006). In macrophages, it is a component of the phagosome wall that is released before fusion with lysosomes. In murine models, Coronin 1 is required for calcium-calcineurin signaling (Moshous and de Villartay, 2014). Recently, it was shown that Coronin 1A is crucial for NK cell lytic granule secretion through F-actin disassembly and is thus essential for NK cell cytotoxicity (Mace and Orange, 2014) (Fig. 1). Despite normal NK cell counts, Coronin 1A deficient patients exhibit severe T cell lymphopenia with reduced number of CD4+ and CD8+ naive T cells (Moshous et al., 2013). The finding of a normal sized thymus in affected individuals has prompted the idea that the severe decline in naive T cells results from defects in thymus egression and defective T cell locomotion (Moshous and de Villartay, 2014; Shiow et al., 2008) (Fig. 2-A). Later, it was shown that during T cell maturation, Coronin 1 also works as a regulatory factor of pro-apoptotic and pro-survival signals and F-actin accumulation does not correlate with apoptosis induction in naïve T cells (Mueller et al., 2011). Normal B cells and normal total serum Ig with low specific Igs have been seen in affected individuals. Decreased NKT and MAIT (Mucosal-associated invariant T cells) cell numbers were observed in one patient, suggesting a role for Coronin 1 role in the development and/or survival of these nonconventional T cells (Moshous et al., 2013).

2.8. Autoimmune lymphoproliferative syndrome (ALPS)

ALPS consists of a group of immune dysregulatory disorders with different patterns of inheritance, in which apoptosis pathway defects leads to impaired lymphocyte homeostasis (Fig. 2-A). The most prevalent form of ALPS is ALPS-FAS with a heterozygous mutation in *TNFRSF6*, an intracellular domain of FAS (Pace and Vinh, 2013).

Due to the similar clinical and immunological manifestations, ALPS may be misdiagnosed as chronic active EBV infection (CAEBV) (Nomura et al., 2011). These presentations are hepatosplenomegaly, lymphadenopathy, EBV infection cytopenia, hypergammaglobulinemia and increased IL10 level. In comparison, patients with ALPS have elevated double negative (DN) α/β T cells and soluble Fas-L. The risk of malignancy in ALPS is high but development of malignancy requires a triggering factor like EBV.

In a study of 10 ALPS patients, 2 patients developed EBV-positive HL and 1 patient developed EBV-positive BL (Straus et al., 2001). One of the patients with HL died of HSCT complications and the patient with BL was treated with chemotherapy. Moreover, EBV-LPD was reported in a 33-year old who developed a composite lymphoma of FL, DLBL and cHL (Pace and Vinh, 2013). He was treated with R-CHOP chemotherapy regimen (Table 3).

2.9. MST1 *mutation (STK4 deficiency)*

MST1 (macrophage stimulating 1) deficiency is a novel autosomal recessive PID with bi-allelic inactivating mutation in *MST1*, which encode STK4 (serine/threonine protein kinase), a factor that regulates Treg and naïve T cell migration, homeostasis and tolerance acting through Foxo proteins (Ouyang and Li, 2011). Foxo1 acts by regulating expression of L-selectin, CCR7, *Il7ra* in naïve T cells (Kerdiles et al., 2009) and *Foxp3* in regulatory T cells (Luo and Li, 2013). Recent studies have revealed that STK4 regulates Foxo1/3 stability through phosphorylation in lymphoid T cells and STK4 deficiency brings about excessive degradation of Foxo proteins, which impairs Foxp3 induction and Treg development (Du et al., 2014). Thereby, STK4 deficiency results in a naive T-cell survival defect and also impairs homing of CD8+ cells to secondary lymphoid organs, due to non-functional expression of the homing receptors CCR7 and CD62L (Nehme et al., 2012) (Fig. 2-A). In addition, MST1 deficient T cells have impaired survival due to defective IL-7R/Bcl2 pathway and increased Fas expression. In combination, the immune cell developmental defects and increase in transitional B cells and hypergammaglobulinemia (which lead to increased titers of autoantibodies), lead to autoimmunity, EBV viremia and recurrent sinopulmonary and mucocutaneous infections mostly associated with herpes viruses, but also other viral (mulloscum contagiosum), fungal (candidiasis) and bacterial (Staphylococcal) infections. (Abdollahpour et al., 2012; Crequer et al., 2012; Nehme et al., 2012).

To date, 12 patients with STK deficiency of different origin have been reported (Abdollahpour et al., 2012; Dang et al., 2016; Halacli et al., 2015; Nehme et al., 2012) out of whom, 4 patients had developed EBV-LPD during the course of their disease. The first patient with EBV associated B cell LPD was a girl from a family with 3 affected children who developed GVHD and severe infections after HSCT. Another EBV-LPD was reported in a patient with lymphoplasmacytic lymphoma with κ-light chain restriction, and monoclonal immunoglobulin gene rearrangement. Moreover, a recent study reported 2 siblings with homozygous nonsense mutation in STK4 (c.442C > T, p.Arg148X) that both developed EBV-LPD. One died shortly after HSCT because of cerebrovascular accident and the other is still alive (Table 3).

2.10. Omenn syndrome

According to the latest WHO classification of PIDs (Al-Herz et al., 2014; Picard et al., 2015), Omen syndrome is comprised of a series of diseases that harbor distinct hypomorphic mutations affecting the *RAG1, RAG2, DCLRE1C, IL7RA, RMRP, ADA,LIG4, IL-2RG, AK2*, or it is associated with DiGeorge syndrome. Some cases of Omenn syndrome still have no known gene mutation. Unlike patients with null mutations in these genes, patients with hypomorphic mutations present a T-B- SCID (severe combined immunodeficiency) but still retain some recombination activity and develop a rudimentary degree of specific immunity (Villa et al., 1998). Here we discuss some of the different genetic subtypes of Omenn syndrome, which are associated with development of EBV-LPDs.

2.10.1. Artemis

The Artemis protein, which is encoded by the *DCLRE1C* gene, is a metallo-β-lactamase that acts in the non-homologous end joining (NHEJ) pathway (Moshous et al., 2001). It gains its endonuclease activity by forming a complex with DNA-PKcs (DNA-dependent protein kinase catalytic subunit) in order to open the hairpin structures formed during RAG1/RAG2-mediated V(D)J recombination in T and B lymphocytes. Hypomorphic mutations in *DCLRE1C*, lead to defective chromosomal rearrangement in lymphocytes, manifesting as T−B− radiosensitive SCID, which may underlie the increased rate of lymphoid malignancies in these patients (Jacobs et al., 2011).

Fourteen patients with hypomorphic *DCLRE1C* gene defects have been studied to date, three of whom developed EBV associated LPD (Lee et al., 2013). In patients with EBV-LPD, severe T and B lymphocytopenia were evident. Of these three patients, two affected siblings from the same family harbored compound heterozygous mutations (exon1–3 deletion and D451KfsX11) (Moshous et al., 2003). Cytogenic analysis revealed chromosome 9 trisomy and a translocation involving chromosomes 7 and 14 in lymphoma cell lines. These two siblings presented with lymphoproliferation of large CD20+ Ki67+ cells and rare small lymphocytes. EBV markers, including EBER and LMP1 were positive in both patients. Both children died despite treatment.

The third patient from unrelated kindred harbored a homozygous p.P171R mutation presented with reduced CD4, CD4 + CD45RA+ and CD8T cell counts (Woodbine et al., 2010). This individual first developed HL at age 7, but 2 years after successfully achieving remission, developed EBV-LPD and underwent successful mismatched family donor PBSCT (peripheral blood stem cell transplantation) (Table 3).

2.10.2. DNA ligase IV

DNA ligase IV deficiency is an autosomal recessive T-B-NK+ SCID that is characterized by chromosomal instability, immunodeficiency, developmental defects and growth delay. Like Artemis, DNA ligase IV is a component of the NHEJ pathway that repairs the double strand breaks occurring during V(D)J recombination. Thus, its deficiency leads to impaired lymphocyte development and generates the common T-B-NK+ SCID phenotype.

The clinical manifestations of *LIG4* mutations comprise a wide range from severe pancytopenia, microcephaly and growth retardation to SCID phenotype patients without any developmental defects (Rezaei et al., 2008). From all the cases studied up to now, three have suffered from EBV-associated LPDs, one of whom presented the lymphoma after HSCT (Buck et al., 2006). A second German individual developed an LMP-1 positive, monoclonal DLBL and died of pulmonary aspergillosis during preparative therapy for allogeneic stem cell transplantation (Enders et al., 2006). The last patient was a 14 year old Japanese girl with a gingival tumor diagnosed as EBV-related type III latency, CD20+ CD79a+ DLBL, who died of pulmonary aspergillosis during treatment for her lymphoma (Toita et al., 2007) (Table 3).

2.10.3. RAG1

In 2005, a new form of SCID caused by a unique hypomorphic mutation in *RAG1* (R561H) was reported that showed different features from previously described hypomorphic *RAG1* mutations (Ehl et al., 2005). This individual presented with lymphopenia affecting the B, CD4+ and CD8+ T cell lines, but there was a profound increase in γδT cells, normal Ig levels, and specific Ab production. The patient developed lymphoproliferation in the lungs and a sterile mastoiditis, which was composed of medium- to large-sized CD20+ cells with scattered CD15- CD30+ Reed-Sternberg-like cells that responded well to anti-CD20 therapy. Lack of CD4+ T cells was more prominent than CD8+ T cells. It is not yet understood whether the γδT cells excess occurs as a consequence of or a preliminary cause for the immune dysregulation observed in this individual.

The only reported case of EBV-LPD in hypomorphic RAG1 mutation cases was a 5.7-year old who developed EBV+ DLBL and was partially treated with rituximab (Schuetz et al., 2008). The patient underwent HSCT and was out of lymphoma during the 3-year follow-up (Table 3).

2.11. DiGeorge syndrome

DiGeorge syndrome (DGS) is a severe genetic defect that in most cases leads to perinatal death as the result of cardiac anomalies and recurrent infections. Patients carry monoallelic deletions at chromosomal locus22q11.2 that lead to deletion of genes required for normal migration of facial neural crest cells to pharyngeal pouches. This defect then leads to the classic triad of clinical features: congenital cardiac defects affecting the outflow tract, partial to severe combined immunodeficiency (T-B+ NK +) and hypocalcemia, which are caused by developmental defects affecting conotruncal region, and thymus and parathyroid gland hypoplasia, respectively. Dysmorphic facial features, renal and gastrointestinal defects may also be observed (Rezaei et al., 2008). Patients exhibit normal, decreased or increased antibody levels, but B cell counts are usually normal (Gennery, 2012).

Thymic hypoplasia in partial DGS or complete aplasia in classic DGS is the major factor generating the T cell immunological defects. Beside severe age-specific T cell lymphopenia through infancy (Chinen et al., 2003), the most intriguing defects are a decline in functional CD4+ CD25+ regulatory T cell count and decreased expression of the *AIRE* gene (Rezaei et al., 2008). Considering the role of these immunoregulatory cells and impaired central tolerance, DGS patients are prone to develop autoimmunity and malignancy. Interestingly, the low-for-age T cell levels improve gradually despite their impaired proliferative response to mitogens, which suggests homeostatic expansion of the T cell reservoir (Maggadottir and Sullivan, 2013). This is done by accelerated conversion of naive to memory cells through expression of advanced maturation markers on T cells, development of shorter telomeres and fewer T-cell receptor excision circles (Piliero et al., 2004). While this compensatory mechanism acts to preserve T cell immunity, it leads to decreased diversity of T cell specificity and brings about oligoclonality (Pierdominici et al., 2003; Piliero et al., 2004), which may increase the patient's susceptibility to infections and their adverse consequences.

The first DGS patient, reported to develop EBV-associated lymphoproliferation, was a girl diagnosed to have immunoblastic B cell NHL at 19 months of age who was left untreated and died one month later (Ramos et al., 1999). Another patient was a 14 year-old girl who developed B cell lymphoma and was treated by thymus transplantation (Hong et al., 2001).Another patient that developed EBV-associated lymphoproliferation, died 12 h after admission and

Table 3
A literature review on reported cases of PIDs with EBV-LPDs. (Patients Pts, Immunohistochemistry IHC, HSCT Hematopoietic stem cell transplantation, Cord blood transplantation CBT, classic Hodgkin lymphoma cHL, Burkitt lymphoma BL, Hodgkin lymphoma HL, non-Hodgkin lymphoma NHL, Diffuse large B cell lymphoma DLBL, Lymphomatoid granulomatosis LG, Mixed cellularity MC, Nodular sclerosing NS Lymphadenopathy LAP, Intracranial hypertension ICH, Cyclophosphamide CPM, Oncovin ONC, Procarbazine PRC, Prednisone PRD, Methylprednisolone M-PRD, Doxorubicin DOX, Dexamethasone DXM, Cytarabine ARA-C, Gemcitabine GMC, Etoposide ETO, Vincrystine VCR, Ifosfamide IFS, Vinorelbine VNR, Rituximab RTX, Fludarabine FLD, Melphalan MLP, Anti-thyroglobuline ATG, Adriamycine ADM, Gancyclovir GNC, Vinblastine VIN, Dacarbazine DCB, Cyclosporine CYC).

PID	Associated LPD	Pathology and IHC	Number of pts	Age distribution	LPD diagnostic clinical manifestations	Treatment	Outcome	Reference
Ataxia-Telangiectasia	HL NHL	–	12 HL 19 NHL	10.6y (median) 9.7y (median)	–	–	–	(Suarez et al., 2015)
	Extra-nodal marginal zone MALT lymphoma	–	1	16y	Chronic lymphadenitis, Cervical, celiac, para-aortic LAP	Anti CD20 Ab	CR	(Bennett and Bayerl, 2015)
	cHL (NS)	–	1	14y	Cervical, auxillary and mediastinal LAP	Anti CD30 Ab, COPP (CPM, ONC, PRC, PRD)	CR (despite significant weight loss)	(Meister et al., 2015)
	NHL	–	1	13y	Mental and growth retardation, spreading LAP in Waldeyer's ring, intrapulmonary, abdominal and auricular lymph nodes	Anti CD20 Ab, Chemotherapy (DOX, DXM, ARA-C, CPM, ETO, VCR) and HSCT	Alive	(Beier et al., 2016)
ITK deficiency	cHL (MC)	–	1	5y	Cervical and inguinal LAP	Chemotherapy (IFS, VNR, ETO, ARA-C, GMC) Radiotherapy, HSCT	CR	(Alme et al., 2015)
	P1:Polymorphic blast rich B-LPD, cHL (MC) P2: HL-like B-LPD P3-P5: cHL (MC) P6-P7: Polymorphic B-LPD	P1: EBER+, CD20,30+, LMP+ HL P2: CD20,30+, LMP+ P3: EBER+, PAX5+, CD30+, LMP+ P4: PAX5+, CD30+, LMP+ P5: EBER+, PAX5+, CD20,30+, LMP+ P6: CD20,30+, EBER+ P7: CD20,30+, EBER+	7	P1: 5y P2: 6y P3: 4y P4: 5y P5: 3y P6: 6y P7: 13y	P1:Generalized LAP and hepatosplenomegaly, lung involvement P2: Retroperitoneal and abdominal LAP and hepatosplenomegaly P3: Generalized LAP, hepatosplenomegaly and BM involvement P4: Cervical LAP, lung involvement P5: Cervical LAP, lung, parotid, kidney and liver involvement P6: Generalized LAP, lung involvement P7: Hilar LAP, hepatosplenomegaly, lung involvement	P2: HSCT P4: Chemotherapy P5: HSCT P6: HSCT	P1: Died of lymphoma P2: Died of HSCT complications P3: Died of lymphoma P4: CR P5: Alive P6: Died of HSCT complications P7: Died of lymphoma	(Bienemann et al., 2015)
	P1: NHL P2: HL		2	P1: 6y P2: 2.5y	P1: Cervical and occipital LAP P2: –	P1: CHOP and anti CD20 Ab P2: Chemotherapy	P1: Died of infection P2: –	(Cipe et al., 2015)
	HL (Stage IIIB)	–	1	3.9y	Lung and kidney involvement	HSCT with pre-conditioning (RTX, FLD, MLP, ATG)	CR	(Shamriz et al., 2014)
	P1: B- LPD P2: B-LPD, DLBL and LG	–	2	P1: 11y P2: 6y	P1: LAP, kidney involvement P2: LAP, lung and kidney involvement	P1: – P2: HSCT	P1: Died at 26y P2: Died from severe GVHD	(Linka et al., 2012)
	B cell proliferation	–	1	14y	Pulmonary infiltration, Mediastinal LAP	Anti CD20 Ab	CR	(Mansouri et al., 2012)
	cHL	CD30+, LMP+	3	P1: 4y P2: 5y P3: 3y	P1: LAP and Hepatosplenomegaly P2: Lymphadenopathy P3: LAP and Hepatosplenomegaly	P1: Chemotherapy (RTX, VP-16, VNR, GMC) P2: Chemotherapy P3: HSCT with precondition-ing (FLD, MLP, ATG, RTX)	P1: Died of respiratory failure due to lymphoma P2: CR P3: Alive	(Stepensky et al., 2011)

Table 3 (*Continued*)

PID	Associated LPD	Pathology and IHC	Number of pts	Age distribution	LPD diagnostic clinical manifestations	Treatment	Outcome	Reference
	P1: Polymorphic B-LPD and HL P2: HL	P1: B-LPD: CD20,22,30+, LMP1+ HL: CD30+, LMP1+ P2: CD20+, LMP1+	2	P1: 6y-8y P2: 5y	P1: Generalized LAP, Hepatosplenomegaly – HL: Nasal concha tumor P2: Retroperitoneal and abdominal LAP, Hepatosplenomegaly	P1: Chemotherapy (PRD, PRC, VCR, CPM, ADM) + Anti CD20 Ab P2: Chemotherapy (GNC, Steroid, RTX), HSCT	P1: Died of respiratory failure due to lymphoma P2: Died of ischemic brain injury	(Huck et al., 2009)
SAP deficiency	P1: BL P2: HL (stage IVA)		2	P1: 7.5y P2: 11.6y	P1: Rectal lymphoma P2: Cervical, submandibular, para-aortic LAP, lung involvement, Hepatosplenomegaly	P1-P2: HSCT with precondi-tioning (FLD, Busulfex, Thiotepa)	P1-P2: CR	(Shamriz et al., 2014)
	HL (NS)		1	17y	Mediastinal LAP, lung involvement	Chemotherapy and Radiotherapy	CR	(Sperl et al., 2012)
	BL	–	6	2-40y	–	–	Most of them were alive after lymphoma treatment, at the end of the study	(Pachlopnik Schmid et al., 2011)
	BL	CD20,79a+, Ki67+, LMP1+	1	4y	LAP, Hepatosplenomegaly, Cerebellum tumor	ETO, DXM, CPM	Partial remission, died of ICH	(Hugle et al., 2007)
	BL	–	1	3y	–	Chemotherapy	CR	(Sumazaki et al., 2001)
Wiskott Aldrich	DLBL	Non-germinal centre, CD19,20,22,45,79a+ LCA+,PAX5+, MUM1+	1	14y	Cervical adenitis, nurological symptoms with brain lesion	Anti CD20 Ab	Died of active disease	(Du et al., 2011)
	–	–	2	P1: 2 m (age at WAS diagnosis)	–	–	P1: alive at the end of study P2: died in 2.5y of age	(Lee et al., 2010)
	BL	CD20,79a+, c-myc, LMP+	1	12y	Recurrent colicky abdominal pain and bloody stools	Anti CD20 Ab, CHOP	CR	(Pasic et al., 2006)
	DLBL	B cell marker +	1	15y	Progressive respiratory distress, profuse night sweats	CPM, ONC, PRD, Radiotherapy, Laser surgery	Died of lung infection	(Palenzuela et al., 2003)
	LG	CD3,5,20,79a +	1	15y	Non-healing lesion in left thigh	Anti CD20 Ab	CR	(Sebire et al., 2003)
	HL	Lymphocyte depletion type, CD30+, LMP1+	1	8y	Pulmonary hilar LN	ABVD (DOX, Bleomycin, VIN, DCB)	CR	(Sasahara et al., 2001)
	DLBL	–	1	20m	Systemic LAP, Macroamylasemia	–	–	(Yoshida et al., 1997)
	NHL	L26+	1	14y	LAP, CNS, gastric wall and pulmonary lesions	Acyclovir, Adenosine arabinoside	Died of sepsis	(Nakanishi et al., 1993)
	Large cell immunoblastic lymphoma	CD19+, κ light chain, LMP1+, EBNA2+	1	11y	Rectosigmoid tumor	Chemotherapy, Excision, L-Asparaginase therapy	Died of colon perforation	(Gulley et al., 1993)
CD27 deficiency	P3: T cell lymphoma P4: Extranodal B-LPD	–	4	P1: 1y P2: 4y P3: 15y P4: 4y	P1: recurrent LPD P2: HLH P4: orbital mass	P1: Anti CD20 Ab P2: Anti CD20 Ab, HLH2004, CBT P3: R-CHOP, CBT P4: Anti CD20 Ab	P1: Alive P2: Alive P3: Alive P4: CR	(Alkhairy et al., 2015)
	P3: late T cell lymphoma	–	3	P1: 15m P2: 18m P3: 15y	P1: Recurrent EBV-LPD and SIRS P2: HLH	P1: Anti CD20 Ab and steroids P2: HLH2004 (DXM, ETO, CYC, RTX), CBT P3: R-CHOP, unrelated CBT	P1: CR P2: Alive P3: Alive	(Salzer et al., 2013)

Table 3 (*Continued*)

PID	Associated LPD	Pathology and IHC	Number of pts	Age distribution	LPD diagnostic clinical manifestations	Treatment	Outcome	Reference
XMEN disease	HL	CD20+, LMP1+	1	52y	LAP, hepatosplenomegaly, B-symptoms	Anti CD20 Ab, R-CHOP	PR	(Dhalla et al., 2015)
	P1: B-LPD P2: BL P3: HL P4: Polymorphic B-LPD	P2: (2 lymphomas) λ light chain − κ light chain P3: 2 lymphomas	4	P1: 12y P2: 7–14y P3: 17–22y P4: 45y	P1: autoimmune cytopenia, respiratory infections, LPD in CNS	P3: Campath, FLD, MLP and unrelated HSCT P4: unrelated HSCT	P3: died of infection and haemorrhagic shock P4: died of transplant complications	(Chaigne-Delalande et al., 2013; Li et al., 2014)
	Chronic lymphoma	–	1	–	–	–	Died of lymphoma	(Li et al., 2011a)
Coronin1a deficiency	DLBL	CD20+, PAX5+, BCL2+, EBER+, LMP1+, EBNA2+	1	14m	Cervical LAP, CNS, GI, lung and thymus involvement	Acyclovir, IVIG, anti CD20 Ab, Chemotherapy	Died of respiratory failure due to lymphoma	(Punwani et al., 2015)
	HL and DLBL	HL: CD20+ DLBL: CD38+	1	15y	HL: Cervical and mediastinal LAP DLBL: Conjunctival and liver mass	Chemotherapy for HL	Died of DLBL	(Stray-Pedersen et al., 2014)
	P1: DLBL P2: DLBL P3: B cell lymphoma	P1-P3: CD20+, EBER+	3	P1: 12m P2: 7.5m P3: 14m	P1: left orbit mass P2: Cervicothoracoabdominal LAP and cerebal lesion P3: Cervicothoracoabdominal LAP and medullary lesion	P1: Chemotherapy P2: Chemotherapy P3: anti CD20 Ab, chemotherapy and HSCT	P1: CR P2: Died during induction therapy P3: Died from HSCT complications	(Moshous et al., 2013)
ALPS-FAS	P1: cHL (MC) P2: HL P3: BL	–	3	P1: 8y P2: 11y P3: 50y	–	P1: Chemotherapy, HSCT P2: Chemotherapy P3: Chemotherapy	P1: Died of pulmonary hemorrhage after transplant P3: CR	(Straus et al., 2001)
	T cell lymphoma	–	1	–	–	Chemotherapy	CR	(Neven et al., 2011)
	FL, DLBL, cHL	–	1	33y	LAP	R-CHOP	CR	(Pace and Vinh, 2013)
STK4 deficiency	B cell LPD	–	1	9y	Neutropenia	Anti CD20 Ab prior to HSCT	Died of GVHD	(Nehme et al., 2012)
	Lymphoplasmacytic lymphoma		1	4y	EBV-associated lymphadenopathy, Cardiac anomalies, cutaneous mulloscum contagiosum and HPV infections	–	–	(Abdollahpour et al., 2012)
	–	–	2	P1: 3y P2: –	Recurrent cryptosporidiosis and HSV infections, Persistent EBV viremia	–	P1: Died of CVA P2: Alive	(Dang et al., 2016)
DCLRE1C mutation	HL	–	1	9y	Cervical and mediastinal LAP	Chemotherapy, HSCT	CR	(Woodbine et al., 2010)
	B cell lymphoma	CD20+, Ki67+, LMP1+	2	P1: 9m P2: 5y	Liver, lung, lymph node and skeletal muscle involvement	Anti B cell specific Ab	Died of lymphoma	(Moshous et al., 2003)
DNA ligase IV mutation	DLBL	LMP1+	1	2y	High fever, cervical LAP, hepatomegaly, necrotizing mucositis.	Chemotherapy	Died of aspergillosis	(Enders et al., 2006)
	DLBL	Type III latency, CD20,79a+	1	14y	Left upper gingival tumor	VCR, CPM, PRD	Died of respiratory aspergillosis	(Toita et al., 2007)
RAG1 mutation	DLBL	CD20,30,79a+	1	5.7y	Tumor of right tonsil	anti CD20 Ab, HSCT	CR (during 3y F/U)	(Schuetz et al., 2008)
DiGeorge syndrome	T cell lymphoma (CD8)	CD45,2,3,5,7,8+, TIA1 and Granzyme B	1	25y	Hepatosplenomegaly, ascites, mediastinal and para-aortic LAP	Untreated	Died of DIC before treatment	(Itoh et al., 2011)
	Large B cell lymphoma	κ-chain monotypy	1	14y	Fever, generalized LAP and pleural effusion	Modified LMB 89 (CPM, VCR, PRD, DOX, MTX) Thymus Transplant	Recurred once during the 2-year follow-up	(Hong et al., 2001)

Table 3 (*Continued*)

PID	Associated LPD	Pathology and IHC	Number of pts	Age distribution	LPD diagnostic clinical manifestations	Treatment	Outcome	Reference
	Immunoblastic B cell NHL		1	19m	Hemiparesis due to cerebral mass, Mediastinal LAP, liver and kidney involvement	Untreated	Died 1 month later	(Ramos et al., 1999)
Activated PI3K-δ	DLBL		1	15y	EBV viremia, LAP	–	–	(Lucas et al., 2014)
	HL (NS)		1	17y	EBV viremia, LAP	–	–	(Lucas et al., 2014)
WHIM syndrome	B cell lymphoma		1	30y	Right-sided facial nodules	CHOP	CR	(Chae et al., 2001)
	T-LPD (CD8) B-LPD		1	26y	Persistent high fever, epiglottitis, pleural effusion, ascites, cervical and para-aortic LAP, splenomegaly	PRD for T-LPD, CHOP for B-LPD	T-LPD regressed, but died of CHOP complications	(Imashuku et al., 2002)
CTPS1 deficiency	NHL		2	P1: 6y P2: 1y	P1: CNS involvement P2: CNS involvement	P1: HSCT P2: HSCT	P1: died of lymphoma P2: Alive	(Martin et al., 2014)
MCM4 deficiency	B-LPD	CD20+, LMP+	1	2.9y	Small bowel tumor	Surgically removed	CR	(Eidenschenk et al., 2006)
ZAP70 deficiency	DLBL	CD19,22,79a, 10,20+	1	11m	Generalized LAP	Chemotherapy (VCR, CPM, and M-PRD)	Died of lymphoma complications	(Newell et al., 2011)
NF-κB1 insuffi-ciency	–	–	1	18y	Hepatosplenomegaly, Generalized LAP	Steroids, anti CD20 Ab	PR	(Boztug et al., 2016)

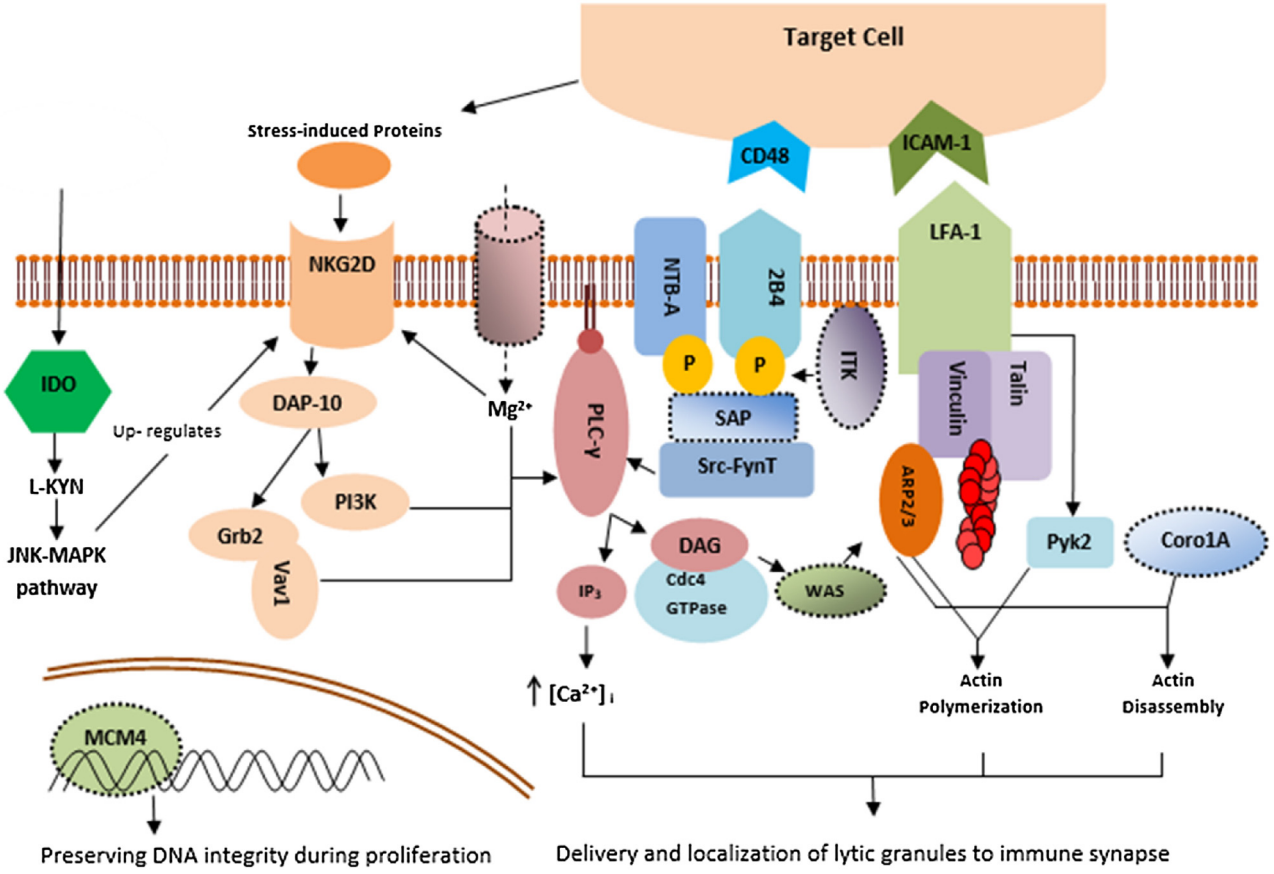


Fig. 1. Mediators involved in NK cytotoxicity. Note the 6 main factors bordered by dots, which are deficient in diseases discussed. Mg^{2+}-induced NKG2D expression is impaired in XMEN disease. Suppression of JNK pathway by EBV-induced IDO activity results in defected NKG2D up-regulation. ITK and SAP deficiency affect the ITSM-mediated pathways, WASP and coronin1a deficiency impair actin remodelling for localized granule secretion. MCM4 is crucial for preserving the DNA integrity during the proliferation of NK cells.

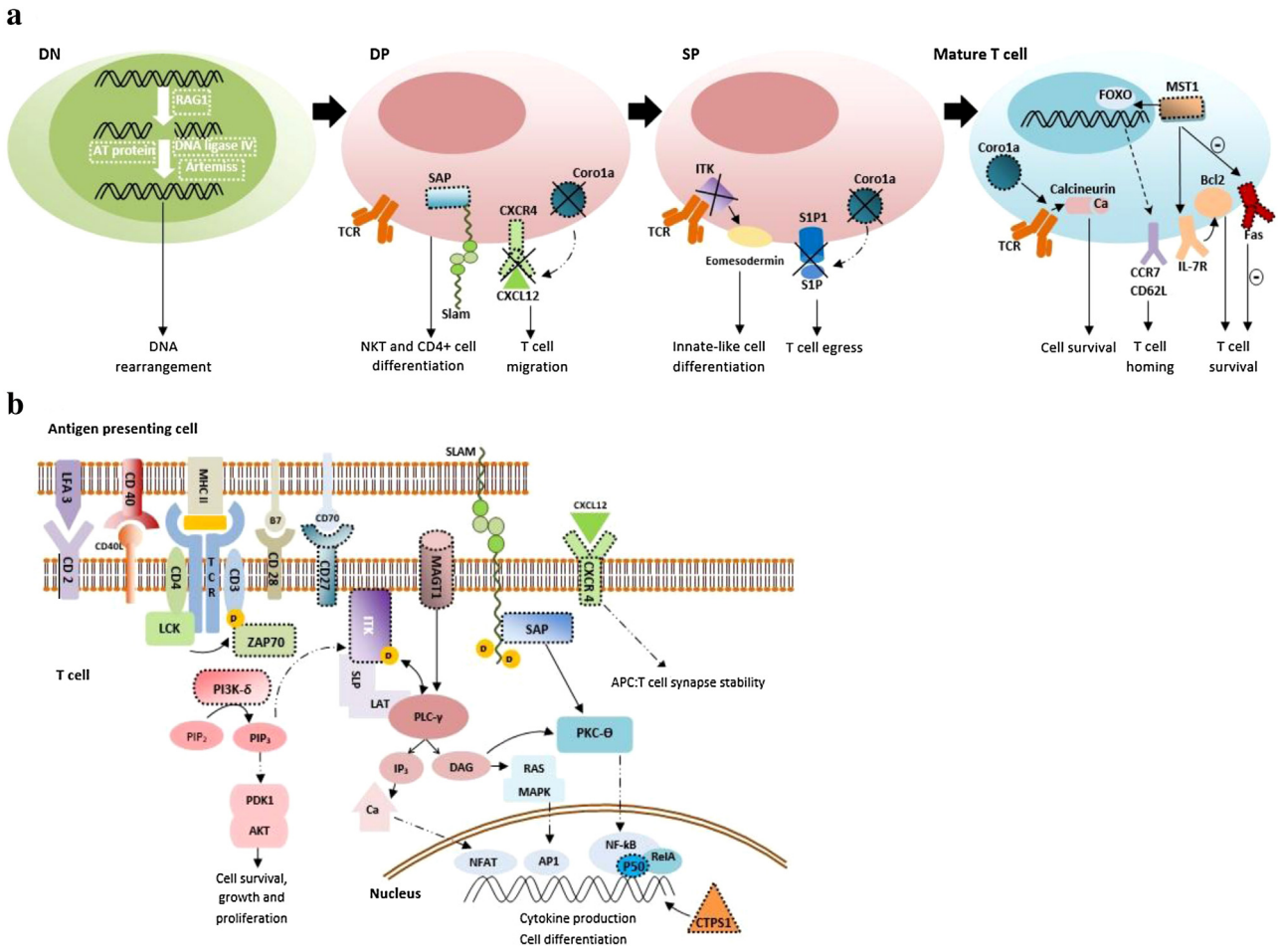


Fig. 2. PIDs with known defects in T cell development or activation. A. T cell development. RAG1, ATM, DNA ligase IV and Artemis are involved in DNA breakage and NHEJ during TCR DNA rearrangement. SLAM/SAP signaling is required for NKT cell development. CXCR4/CXCL12 association that leads to cell migration is suppressed by mutant CORO1A. Coronin 1 is also required for generation of prosurvival signals upon TCR induced Ca-Calcineurin signaling. ITK deficient cells express eomesodermin, differentiating to innate-like cells. MST1 enhances expression of receptors required for cell homing and increases cell survival. Fas deficiency in ALPS-FAS results in impaired lymphocyte homeostasis. (Double negative DN, Double positive DP, Single positive SP) B. T cell activation. CD27 is crucial for T cell activation. ITK and SAP act in pathways leading to activation of NF-Kb, AP1 and NFAT transcription factors. SAP also plays an important role in bridging activated T cells to B cells as shown in Fig. 3. ZAP70 is a mediator of TCR pathway which phosphorylates downstream adaptor proteins. P50 is member of NF-κB family, which is essential for triggering transcription of cytokines. CTPS1 is a key enzyme in replication and transcription. Activated PI3K-δ dominantly acts in the AKT pathway which is a major mechanism of oncogenesis.

was analysed post-mortem (Itoh et al., 2011). Histological studies revealed EBV+ neoplastic cells positive for CD45, CD2, CD3, CD5, and CD7, proposing a T-cell lymphoma comprised mostly of cytotoxic CD8+ T cells and few CD4+ T cells (Table 3).

2.12. Activated PI3K-δ

APDS, activated phosphoinositide3-kinase delta (PI3K-δ) syndrome, is a novel PID caused by an autosomal dominant germline gain of function mutation E1021K in the PIK3CD gene that encodes p110δ. P110δ is the catalytic subunit of the lipid kinase PI3K-δ that generates the second messenger IP_3 (Inositol-3-phosphate) by degradation of PIP_2 (phosphatidylinositol 4,5-biphosphate). The level of IP_3 production by mutant PI3K-δ is around 6 times higher than wild type PI3K-δ because of its stronger binding affinity to membrane lipids and suppressed binding to other inhibitory molecules (Angulo et al., 2013). Higher IP_3 concentrations result in increased levels of active downstream molecules, like phosphorylated AKT protein (Fig. 2-B).

The immunological profile of patients with APDS is notable for decreased circulating T cells (total CD3 +) and/or CD4+ and/or CD8+ T cells in 71% of cases studied (Angulo et al., 2013). Moreover, increased PI3K-δ activity leads to higher sensitivity of CD4+ and CD8+ T cells to activation-induced cell death and reduced T cell cytokine production (Angulo et al., 2013). Patients also exhibit low serum IgG2 levels despite high serum IgM levels, and increased transitional (CD19 + CD38 + IgM +) yet decreased class switched memory B cells (CD19 + CD27 + IgD−) (Angulo et al., 2013). Studies have shown that PI3K-δ pathway activity suppresses Ig class switching (Janas et al., 2008) (Fig. 3), which might explain these defects. The humoral defects are believed to cause the high rate of bacterial and especially recurrent respiratory infections in APDS patients. It is not yet known whether or how these defects contribute to the development of the few EBV-induced LPD cases reported.

It has been elucidated that PI3K-δ harbours the ability to transform cells and initiate tumor formation through Akt signaling pathways (Kang et al., 2006). Of the APDS cases studied so far, many presented with lymphoma (Angulo et al., 2013; Kracker et al., 2014; Lucas et al., 2014), one of which had EBV+ DLBL (Lucas et al., 2014), another with EBV+ nodular sclerosing HL (Lucas et al., 2014), and the remainder with EBV-negative lymphomas or lymphomas that were not examined for their EBV status (Table 3).

2.13. WHIM syndrome

Warts, Hypogammaglobulinemia, Immunodeficiency, Myelokathexis (WHIM) syndrome is an autosomal dominant genetic disorder characterized by warts, hypogammaglobulinemia, infections and myelokathexis (Gorlin et al., 2000; Rezaei et al., 2009). The latter refers to the inability of neutrophils to be released from the bone marrow, despite bone marrow myeloid hyperplasia, which affects other hematopoietic cell line differentiation as well and manifests as B and T cell lymphopenia and panhypogammaglobulinemia (Al-Herz et al., 2014). As a consequence, patients often present with recurrent infections and malignancies (Rezaei et al., 2011a).

Presentation with EBV-LPD was first reported in a man with WHIM syndrome who developed EBV+ B lymphoma (Chae et al., 2001). Later a female patient with the rare association of EBV+ T-LPD and B–LPD was reported who developed EBV+ B lymphoma, right after resolution of T-LPD (Imashuku et al., 2002). Both of them, appeared to develop LPD in their late twenties, a higher age distribution in comparison with other PIDs. The first patient developed T cell lymphoma, a rare association of LPD with PIDs (Table 3).

WHIM syndrome results from gain-of-function mutations in *CXCR4*, the receptor for CXCL12, which is critical for regulating the release of neutrophils from the marrow during inflammation and maintaining circulating neutrophil homeostasis (Suratt et al., 2004). The WHIM syndrome-associated *CXCR4* mutations cause impaired receptor internalization leading to increased signaling (Bachelerie, 2010; Balabanian et al., 2005; Dotta et al., 2011). Consequently, treatment with plerixafor, a CXCR4 antagonist, increases neutrophil counts in patients with WHIM syndrome (McDermott et al., 2011). Interestingly, murine studies reveal that CXCR4 desensitization is also vital for thymopoiesis, B-cell development (Balabanian et al., 2012) and formation of stable T-APC interactions (Kallikourdis et al., 2013). This latter observation may provide clues as to why patients with WHIM syndrome develop EBV-LPD.

2.14. CTPS1 deficiency

CTP synthase 1 deficiency is another combined immunodeficiency caused by defected *de novo* pyrimidine synthesis pathway due to the lack of CTPS1 enzyme. CTPS1 is essential for proliferation of lymphocytes especially T cells, following activation by antigens (Fig. 2-B, 3). CTPS2 acting via salvage pathway partially activates pyrimidine synthesis in lymphocytes, but the activity of CTPS2 is not sufficient for recompensing lack of CTPS1 (Martin et al., 2014). As a result, patients with CTPS1 deficiency have low T cell and low to normal B cell counts.

The development of EBV-associated NHL has been reported in 2 patients from distinct families, who received HSCT when they were 6-years old and 1-year old, respectively. One patient died from lymphoma recurrence and the other was alive at the end of 1-year follow-up (Table 3).

2.15. MCM4 deficiency

MCM4 deficiency is an autosomal recessive disorder manifested with short stature, adrenal failure, decreased NK cells and predisposition to viral infections. MCM4 is a member of MCM complex which acts in maintenance of DNA integrity during DNA replication (Fig. 1). The immunologic defect in MCM4 deficient patients is lack of transition of $CD56^{bright}$ NK cells to $CD56^{dim}$ NK cells, which account for about 90% of circulating NK cells. The $CD56^{bright}$ NK cells in these patients do not proliferate in response to IL-2 or IL-15. Other immune cell lines are normal in number and function.

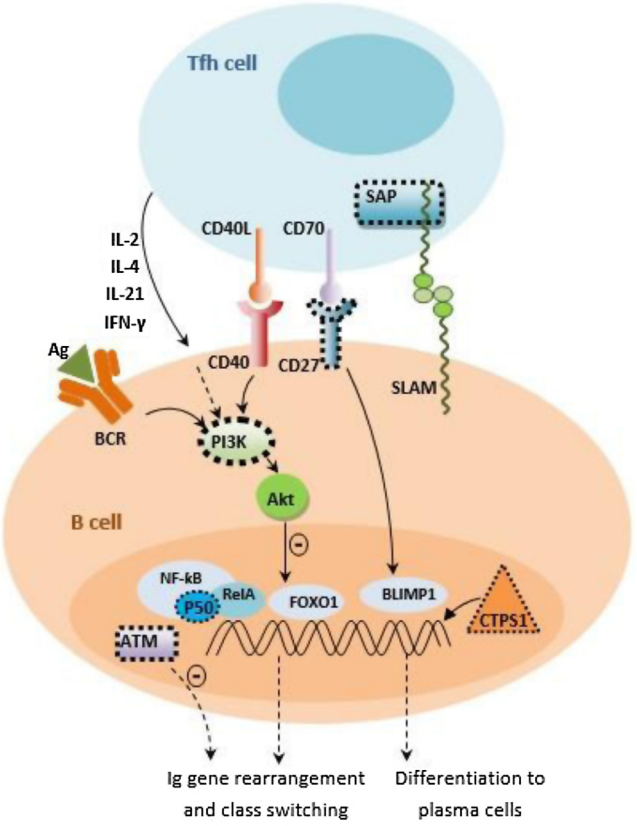


Fig. 3. Association between PIDs with known B cell activation defects. SAP is essential for bringing T follicular helper (Tfh) cells to B cells. CD27 molecule associated with CD70 enhances expression of Blimp1 transcription factor and results in B cell differentiation to plasma cells. Combined contribution of BCR, CD40 and interleukin receptors activates PI3 K. Mutated activated PI3 K overactivates AKT pathway. Activated AKT suppresses Foxo transcription factor which regulates class switching recombination. CTPS1 is a key enzyme in replication and transcription. P50 is member of NF-κB family, which is essential for Ig class switching. (Antigen Ag, Immunoglobulin Ig).

Out of the patients with *MCM4* deficiency reported to date, one had developed EBV-associated B-LPD in the small bowel which was surgically removed (Eidenschenk et al., 2006) (Table 3).

2.16. ZAP70 deficiency

ZAP70 deficiency is a combined immunodeficiency disorder with the profound presentation of CD8 lymphopenia. Although the count of CD4T cells in patients with *ZAP70* deficiency appears to be normal, these peripheral T cells are functionally unable to activate the TCR pathway (Fig. 2-B) (Au-Yeung et al., 2009). The ZAP70 is crucial for differentiation of DP T cells to SP CD8T cells. Moreover ZAP70 is one of the essential mediators of TCR pathway. It binds to the CD3ζ-chain of TCR and phosphorylates downstream adaptor proteins LAP and SLP76, leading to proper lymphokine production, cell differentiation and proliferation (Poliani et al., 2013).

The only presentation of EBV-LPD in patients with ZAP70 deficiency has been reported in a 11-months old girl with a homozygous mutation (c.836-837 delAT), who died of lymphoma complications despite being treated with chemotherapy (Newell et al., 2011) (Table 3).

2.17. NF-κB1 haploinsufficiency

This common variable immunodeficiency is a recently discovered disease which is not available in the IUIS 2015 PID list yet.

NF-κB1 insufficiency predominantly affects maturation, survival, differentiation and T cell- independent Ig class switching of B cells, but it can also lead to impaired T cell function (Fig. 2-B, 3). *NF-κB1* encodes a member of NF-κB transcription factor family, called p50. In order to trigger transcription, P50 is heterodimerized with RelA, another member of NF-κB family. This complex activates the transcription of inflammatory cytokines' genes and immune response genes, through the canonical pathway.

The only patient reported to have EBV-associated LPD harbored a novel heterozygous mutation in *NF-κB1* gene (c.491delG; p.G165AfsX31) (Boztug et al., 2016). She had developed EBV-LPD at the age of 18. Treatment with four courses of Rituximab for two times, led to a partial remission and she was a candidate of HSCT (Table 3).

3. Conclusions

In our study, we have reviewed the reported PID patients who have been reported to develop EBV-LPDs. A minority of patients have developed LPDs associated with T cells, who are among patients with CD27 deficiency, DiGeorge syndrome, WHIM syndrome or ALPS. The common defected pathway among them is T cell development from defected initial immune tolerance to defected apoptosis, proposing the idea that improper naïve T cell expansion and T cell differentiation is a weak point of immune defense against development of EBV-associated T cell LPDs. The patients with T-LPD have developed the lymphoma at 15–26 years of age and have undergone a remission when treated either by chemotherapy or additional CBT. The higher age involvement and the well response to treatment may indict the better prognosis of the T-LPDs in comparison with other LPDs.

Almost about one third of reported EBV+ B-LPDs are HLs. They have developed HL at 2.5-52 years of age with a mean of 11 years of age. The remission rate is about 60% with an inconsiderable difference among patients who have undergone HSCT and those who have been solely treated by chemotherapy. The distribution of HL in the majority of PIDs and the high prevalence of HL, are two main points to be considered in further studies on therapeutic strategies for EBV-associated HL.

The most severe form of EBV+ B-LPD is DLBL, which have occurred in about 10% of PID patients. Two third of patients have developed DLBL before 2 years of age. Among 8 patients who were treated with chemotherapy, only one patients survived. Although it is not as prevalent as HL, but the early involvement and the poor outcome of reported patients proposes the need for a better follow-up and screening of patients with associated PIDs, esp. Coronin1A deficiency and WAS patients. Both diseases are associated with defects in NK and CTL cytotoxicity that may be essential in immune defense against development of EBV-associated DLBL.

In addition, there is a high prevalence of EBV-associated BL development among SAP deficient patients. Most of them have undergone remission after chemotherapy. There are other reports of BL in WAS, XMEN disease and ALPS patients that have also had a well outcome after chemotherapy.

Although the typical diagnostic presentation of EBV-LPDs is generalized lymphadenopathies, there have been several extranodal or atypical presentation of LPDs e.g. CNS lesions, orbital and conjunctival masses, tumors invading gastrointestinal and upper respiratory mucosa, cutaneous and skeletal muscle masses and tumors in tonsils. The atypical presentation of the disease is more frequently observed in patients with DLBL and BL development. This confusing presentations further indicts the importance of early diagnosis of LPDs in patients with PID esp. those with a higher risk of developing DLBL and BL, which are SAP deficiency, WAS and coronin1a deficiency.

The development of EBV-induced LPDs in individuals with PIDs highlights several critical immune pathways needed to protect against virus infection and virus-induced oncogenicity. Although the exact mechanisms by which these pathways protect against the virus are yet to be clarified, studying these pathways may give us hints to better understand the oncogenic properties of EBV and how to best combat against the virus. Nonetheless, several common themes have emerged.

There are a few humoral immunity defects in PIDs associated with EBV-driven LPDs (Fig. 3), but consistent with the fact that cellular immunity plays the major role in defense against viral pathogens; most PIDs associated with susceptibility to EBV involve defects in T and/or NK cells. CTL and NK cell cytotoxicity are of utmost importance in providing protection against most viral infections and malignancies (Trinchieri, 2003). Fig. 1 depicts a schematic model of the receptors and downstream pathways involved in NK cell cytotoxicity, which partly resemble those involved in CTL killing. Defective proteins in ITK deficiency, XLP type 1, Coronin1A deficiency, WAS and XMEN disease have a direct effect on killer cell function. There are supporting ideas that point to the effect of EBV infection on impaired cytotoxicity through increased IDO metabolites (Song et al., 2011). EBV infection increases expression of IDO metabolites by B cells. These metabolites reduce NKG2D expression by NK cells, inhibiting NKG2D-mediated cytotoxicity (Salzer et al., 2013).

Even though most of the discussed PIDs contain diverse cell line defects, T cells seem to be affected in the majority of cases. These defects affect various steps in T cell development and activation, ranging from impaired TCR rearrangement and thymic egress to poor long-term maintenance of cellular immunity and reduced cell activation. Diseases associated with relative loss of effective T cells (including NKT cells) in the circulation, whether by defective development or impaired egress from the thymus (Omenn syndrome, coronin1a deficiency, XLP type 1, ITK deficiency, WHIM syndrome, Ataxia-Telangiectasia, and MST1 mutation), are presented in Fig. 2-A. Fig. 2-B represents diseases associated with defective T cell activation pathways (CD27 deficiency, XLP type 1, activated PI3K-δ, DGS, WHIM syndrome, XMEN disease and ITK deficiency) that can also contribute to EBV-LPDs. The absence of iNKT cells in 3 major PIDs with the high prevalence of EBV-LPD, ITK deficiency, XLP1 and CD27 deficiency, prompted to the idea that this subtype of NKT cells is essential for suppressing the progression of EBV-LPDs (Salzer et al., 2013).

Moreover, there are PIDs like activated PI3K-δ, characterized by immortal B cells, the main targets of EBV infection. They can impair the negative selection of B cells either by suppressing autoinhibition or through breaking the tolerance. The result is overproliferation of B cells and emerging B cell lymphoproliferation. PI3K-δ, a mediator which also acts in B cell activation, in company with PKC-Θ and PLC-γ are limiting steps through which cell activation and differentiation is programmed. Activated PI3K-δ triggers oncogenesis by overactivating Akt pathway, developing immortal monoclonal transitional B cells.

The balance between EBV oncogenicity and the immune system is obviously complex. Further study of the pathogenesis of these PIDs, will help us realize the underlying mechanisms increasing the susceptibility to EBV-related LPDs and providing a background for developing novel therapeutic strategies in order to lessen the high burden of morbidity and mortality rates.

Conflicts of interest

The authors declare no conflicts of interest.

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