Epstein–Barr virus infection in primary immunodeficiency

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ABSTRACT

Primary immunodeficiency (PID) is a group of genetic disorders which affects immune cell development, differentiation, and function. The affected individuals are highly susceptible to infection by a diverse array of pathogens. Epstein–Barr virus (EBV) infection is ubiquitous in humans and usually involves an asymptomatic or self-limiting clinical course. In rare cases, EBV can cause not only an acute infection but also a severe exaggerated immune response and lymphoproliferative disease.

Furthermore, EBV infection in patients with PID can lead to immune dysregulation and increased risk of malignancies, in addition to the severe course of the acute infection. Recognition of the different genetic defects and their effect on immunological pathways provide us with fundamental insights into the pathophysiology of EBV infection and associated disease, and may lead to developing better targeted therapies in the future. Here, we review all of PIDs with an abnormal response to EBV disease.

Statement of novelty: Here we provide a review of the current knowledge of all PIDs reported to be associated with abnormal response to EBV infection and associated disease, such as hemophagocytic lymphohistiocytosis.

Epstein–Barr virus (EBV) is 1 of 8 human herpesviruses that establish lifelong persistent infection in humans (Tangye et al. 2017). It is estimated that more than 90% of the global population are seropositive to EBV (Tangye et al. 2017). EBV belongs to the gamma-1 herpesvirus genus, whose members are distinguished by their restriction to primate hosts, B lymphoid tropism, and ability to drive B cell growth through expression of a unique set of latent cycle genes (Palendira and Rickinson 2015; Taylor et al. 2015).

EBV infection can manifest as either a lytic infection or a latent infection with expression of a very limited number of viral proteins (Cohen 2015). The initial EBV infection is acquired orally through the saliva (Palendira and Rickinson 2015; Tangye et al. 2017). It replicates as a lytic infection through the oropharynx with high levels of viral shedding in the throat (Palendira and Rickinson 2015; Taylor et al. 2015). It is thought that oral epithelial cells and possibly some infiltrating B cells at mucosal surfaces are the sites for viral replication during the lytic phase (Palendira and Rickinson 2015; Tangye et al. 2017). The mode of viral entry into B cells remains unclear (Tangye et al. 2017). The replicative cycle that follows viral entry results in sequential expression of lytic proteins involved in producing new viral particles and immune evasion (Tangye et al. 2017). Among these are proteins that interfere with antigen processing and presentation to CD8+ T cells, those that down regulate MHC class II, as well as a few that reduce expression of ligands for NK cell-activating receptors (Tangye et al. 2017).

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Following the spread of EBV infection through B cells, it then enters into the memory B cell pool where it can stay as a latent infection and recirculate between the blood and pharyngeal lymphoid tissue (Taylor et al. 2015).

Primary immunodeficiency (PID) is a heterogeneous group of hereditary diseases that are associated with compromised immune responses that reduce the ability of immune system to combat infectious pathogens, as well as the presence of malignant cells, and autoimmune state (Notarangelo 2010). In immunocompromised individuals, reactivation of EBV and persistence of proliferating latent growth-transforming EBV infected B cells are associated with severe pathologies that can have fatal outcome. These include hemophagocytic lymphohistiocytosis (HLH, also termed virus-associated hemophagocytic syndrome), non-malignant B cell lymphoproliferative diseases (LPDs), B cell lymphomas including Hodgkin's lymphomas, as well as non-Hodgkin's lymphomas such as Burkitt's lymphoma and diffuse large B cell lymphoma (DLBCL) (Kuehn et al. 2017).

In this review, we describe the PIDs associated with EBV-infection and disease. Identification of proteins important for control of EBV may help to identify new targets for immunosuppressive therapies.

Lymphoproliferative conditions and susceptibility to EBV

XLP-1: mutations in SH2D1A

X-linked lymphoproliferative disease (XLP-1) was first described in 1975 as a fatal immunodeficiency affecting 6 males from the Duncan family, which led to the original naming of this condition as Duncan's disease (Purtilo et al. 1975; Shabani et al. 2016). XLP-1 is caused by mutations in *SH2D1A*, encoding signaling lymphocytic activation molecule (SLAM)–associated protein (SAP). SAP is an SH2 domain containing intracellular adaptor protein that regulates signaling downstream of the SLAM family of surface receptors expressed on T cells, NK and NKT cells (Coffey et al. 1998; Nichols et al. 1998; Sayos et al. 1998; Rezaei et al. 2011). The most common clinical features of XLP-1 are EBV-induced fulminant HLH (~45%–70%), B cell lymphoma (~25%) out of whom the majority are Burkitt (Rezaei et al. 2011) and non-Hodgkin's type (Rezaei et al. 2011), and hypogammaglobulinemia (~50%) (Tangye et al. 2017).

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). As a result, SAP deficiency results in dysregulated patterns of TCR-induced cytokine production with preferential production of interferon (IFN)-γ and diminished interleukin (IL)-4 production (Cocks et al. 1995). SAP-deficient NK cells exhibit impaired cytolytic activity. As with NK cells, SLAM receptor functions are also impaired in SAP deficient CD8+ T cells (Palendira et al. 2011). SAP deficient CD8+ cells demonstrate poor response to antigen presenting B cells (Hislop et al. 2010). The impaired NK cytolytic activity along with reduced CD8+ T cell killing likely contributes to the increased susceptibility of affected individuals to EBV infection (Cocks et al. 1995).

It is thought that susceptibility to EBV infection, but not other viral infections, in XLP-1 patients is due to the affinity of EBV to B cells, while the T and NK cell interaction with B cells is impaired due to a defect in the SLAM receptor related pathway. Defects in humoral immunity observed in XLP patients are associated with reduced memory B cell count, poor germinal centre formation, and diminished immunoglobulin switching (Shabani et al. 2016).

The most recently published survival rate in XLP-1 is 71.4%, which is a marked improvement compared to the 25% survival rate reported in the 1980s (Booth et al. 2011; Schmid et al. 2011*a*). Early diagnosis and management have led to decreased mortality rates. Currently, hematopoietic stem cell transplantation (HSCT) remains the most effective curative treatment for SAP deficient patients (Marsh et al. 2014; Shamriz et al. 2014).

XLP-2: mutations in XIAP

In 2006, Rigaud et al. reported 12 males presenting with XLP-like syndrome (Nakanishi et al. 1993). These individuals had inactivating mutations in *BIRC4*, located on chromosome Xq25, which encodes the X-linked inhibitor of apoptosis (IAP) protein, XIAP (Nakanishi et al. 1993). Although initially described as XLP-2 due to similarities in clinical presentation to boys with SAP deficiency, it is now recognised as a more complex disorder of immune dysregulation with a wide spectrum of clinical manifestations (Worth et al. 2016). The main clinical features are HLH, splenomegaly, colitis, and periodic fevers (Schmid et al. 2011*b*;

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Yang et al. 2012; Speckmann et al. 2013; Aguilar and Latour 2015). Unlike XLP-1, B lymphoma rarely occurs in XIAP deficiency, and when hypogammaglobulinemia is noted in XLP-2, it is usually transient (Filipovich et al. 2010; Marsh et al. 2010; Schmid et al. 2011*b*; Speckmann et al. 2013; Aguilar and Latour 2015). XIAP protein is 1 of 8 members of the IAP family and acts mainly as a potent inhibitor of caspases 3, 7, and 9; however, it is also involved in a variety of other signaling pathways, including nuclear factor kappa B (NF-κB) and c-Jun N-terminal kinase activation (Obexer and Ausserlechner 2014). It is not yet clear how the deficient protein leads to the clinical phenotype. A recent study of 1 XIAP kindred has identified individuals with persistent CD8 lymphocytosis and unusually large expansion of EBV-specific CD4+ and CD8+ T cells in the blood many years after symptomatic primary EBV infection. This supports the idea that hyperexpansion of the EBV-induced T cell response could underlie some of the cases of XIAP-associated HLH (Worth et al. 2016).

The mortality caused by XIAP deficiency is ~40%, with approximately one third of deaths resulting from HLH (Marsh et al. 2010; Schmid et al. 2011*b*). More recent report suggests a much lower mortality rate (Speckmann et al. 2013), indicating that, like XLP-1, survival has greatly improved since the discovery of the molecular lesion causing this condition (Tangye et al. 2017).

CD27 deficiency

CD27 deficiency is caused by homozygous mutations in the *CD27* gene, which encodes a tumor necrosis factor (TNF) receptor superfamily member that is present on the B cell membrane. CD27 is required for activating T cells as well as long-term maintenance of T cell immunity. The reported clinical presentation of these patients was symptomatic primary EBV infection/lymphadenopathy early in life, while some presented with chronic EBV viremia. About 50% of patients developed malignancy. Some patients had a history of severe infections with other viral etiologies including influenza virus, and herpesviruses such as varicella-zoster virus (VZV) or cytomegalovirus (CMV) (van Montfrans et al. 2012; Salzer et al. 2013; Alkhairy et al. 2015). The immunologic features in this disorder include lack of memory B cells (no CD27+ cells), normal T cell count, low NKT cells, and hypogammaglobulinemia (Alkhairy et al. 2015).

CD27 activity is dependent on its 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 required for naïve T cell expansion and production of Th1-type cytokines (Kawamura et al. 2011), 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). Impairment in this function likely underlies the poor antibody production that is observed in CD27-deficient patients.

CTPS1 deficiency

CTP synthase 1 (CTPS1) deficiency is an autosomal recessive disease caused by a defect in 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. CTPS1 activity is induced following T cell receptor (TCR) activation, and deficiency results in a T cell proliferative defect despite normal TCR activation signaling. As a result, patients with CTPS1 deficiency have low T cell and low to normal B cell counts. Clinically, these patients present before 2 years of age with severe viral infections and encapsulated bacterial infection, suggesting both a functional defect of T cell cytotoxicity and T cell-independent B cell immunity. All 8 patients reported developed chronic EBV viremia, 50% (4/8) of patients developed severe infectious mononucleosis, and almost one third of them (3/8) developed CNS LPD. Six patients received an HSCT, and 4 remained alive, well and free of symptoms (Worth et al. 2016).

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RASGRP1 deficiency

RASGRP1 encodes for a diacylglycerol (DAG)-regulated guanidine exchange factor (GEF) preferentially expressed in T and NK cells (Hogquist 2001; Kortum et al. 2013). RASGRP1 is a specific activator of the small G protein RAS that in turn activates the cascade of Raf-MEK-ERK kinases (also termed as the MAP kinases/MAPK cascade). TCR-mediated RAS-to-ERK activation is mainly dependent on RASGRP1 in human primary T cells (Roose et al. 2005; Warnecke et al. 2012). The clinical presentation of RASGRP1-deficient patients include recurrent infections, hepatosplenomegaly, lymphadenopathy, EBV-associated lymphoproliferation and B cell lymphoma, as well as autoimmune features including autoimmune hemolytic anemia, thrombocytopenia, and uveitis (Salzer et al. 2016; Platt et al. 2017; Mao et al. 2018; Somekh et al. 2018; Winter et al. 2018).

RASGRP1-deficient T cells exhibit defective MAPK activation and impaired proliferation, as well as decreased CD27-dependent proliferation towards CD70-expressing EBV-transformed B cells, a crucial pathway required for expansion of antigen-specific T cells during anti-EBV immunity (Winter et al. 2018).

CD70 deficiency

To date, 6 individuals from 4 unrelated families with homozygous mutations in CD70 were reported, affecting either expression of CD70 or its ability to bind CD27 (Abolhassani et al. 2017; Izawa et al. 2017; Caorsi et al. 2018). CD70 is the counter structure of CD27 (Lens et al. 1998; Borst et al. 2005). It is largely absent from naïve or resting leukocytes but is rapidly induced after activation of B cells, myeloid cells, and to a lesser extent T cells (Hintzen et al. 1994; Tesselaar et al. 1997, 2003; Lens et al. 1998; Borst et al. 2005; Izawa et al. 2017). Thus, CD70 is predominantly expressed by activated antigen presenting cells, with highest levels on B cells.

The clinical features of CD70 deficiency resemble those of CD27 deficiency, with all patients experiencing EBV viremia and most developing EBV-associated lymphoproliferation or B cell malignancy, hypogammaglobulinemia, and impaired specific antibody responses; infection with other herpesviruses also occurred in a few patients. However, unlike CD27 deficiency, all patients with CD70 deficiency are currently alive (Abolhassani et al. 2017; Izawa et al. 2017), suggesting mutations in CD27 cause more severe disease than those in CD70 (Tangye et al. 2017).

CARMIL2 (RLTPR) deficiency

Mutations in CARMIL2 (also known as RLTPR) have been recently reported by 4 independent groups to cause a novel autosomal recessive, primary immunodeficiency disorder with variable phenotypic presentations. CARMIL2 is a regulator of actin capping protein which is a critical component of cell motility. It is part of the human CARMIL family, of which at least the first 2 members have distinct cell migration functions that are nonredundant. CARMIL2 orchestrates cell polarity by modulating microtubules and intermediate filaments (Wang et al. 2016; Schober et al. 2017).

Currently, 21 patients with CARMIL2 deficiency have been reported, and the most common clinical presentations across all studies are dermatitis (80%), recurrent chest infections (80%), and skin abscesses (62%). Persistent uncontrolled viral infections such as warts, molluscum contagiosum, and EBV are also common (Sorte et al. 2016; Wang et al. 2016; Schober et al. 2017; Alazami et al. 2018). Defects in CARMIL2 is also a predisposing factor to severe mucocutaneous candidiasis and mycobactrial infections.

ITK deficiency

IL-2–inducible T cell kinase gene *(ITK)*, is a member of the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family of nonreceptor kinases that is expressed by hematopoietic cells involved in proximal TCR signaling. By regulating PLCγ1 phosphorylation, ITK coordinates T cell activation and function (Readinger et al. 2009). Homozygous mutations in ITK were first recognized through its high prevalence of EBV-associated disease. The expression of ITK is restricted to T cells, NK cells, iNKT cells, and mast cells. In T cells, it is induced upon TCR activation or IL-2 stimulation and is thought to play a critical role in downstream signaling. Altogether, 13 patients from 8 families have been identified with loss-of-function biallelic mutations in ITK (Huck et al. 2009; Stepensky et al. 2011; Linka et al. 2012; Mansouri et al. 2012; Serwas et al. 2014; Cipe et al. 2015; Çağdaş et al. 2017). Most patients presented with EBV viremia, EBV-induced lymphoproliferation that frequently developed into lymphoma, CD4+ T cell lymphopenia, hepatosplenomegaly, and progressive hypogammaglobulinemia (Huck et al. 2009; Stepensky et al. 2011; Linka et al. 2012;

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Mansouri et al. 2012; Ghosh et al. 2014; Bienemann et al. 2015; Cipe et al. 2015; Çağdaş et al. 2017). Several instances of severe VZV and CMV infections were also recorded among the above mentioned patients, thus the overall picture of viral susceptibility associated with ITK mutation remains unclear (Palendira and Rickinson 2015). Of the 13 reported ITK-deficient patients, 8 died, whereas 2 of 3 survived HSCT (Huck et al. 2009; Stepensky et al. 2011).

MAGT1 deficiency

MAGT1 deficiency was recently identified through its impairment of EBV control. It is caused by loss of the X-chromosome–encoded Mg2+ ion transporter MAGT1, hence its definition as X-linked immunodeficiency with Mg2+ defect, EBV infection, and neoplasia (XMEN). The patients reported all had high EBV genome loads in the blood, and haematological malignancy is reported in all post-pubertal patients described, with many experiencing LPD early in life. These patients also have a history of recurrent respiratory infections, viral pneumonia, and severe pox virus (molluscum contagiosum) or herpesvirus (VZV and herpes simplex virus, HSV) infections (Chaigne-Delalande et al. 2013; Li et al. 2014). *MAGT1* encodes a ubiquitously expressed transmembrane Mg2+ transporter involved in the maintenance of free basal intracellular Mg2+ pools. However, MAGT1 also associates with the *N*-oligosaccharyl transferase complex and therefore may have a role in protein N-glycosylation (Cherepanova et al. 2016). In T cells, MAGT1 mediates the Mg2+ influx induced by TCR stimulation and, through downstream Mg2+ pathway signaling, also optimizes Ca2+ influx. MAGT1-deficient patients have low CD4+ T cell numbers, likely due to poor thymic output, whereas NK cell and CD8+ T cell (including EBV-specific CD8+ T cell) numbers appear normal (Li et al. 2014). However, both NK and CD8+ T cell cytotoxicity were partially impaired. That led to the finding that free Mg ions regulate these cells' expression of NKG2D, a membrane protein that engages its ligand, NKG2DL, on the target cell surface. As the name implies, NKG2D was first identified as an NK activating receptor but it also now appears to be required for optimal cytotoxicity by NKG2D-expressing CD8+ T cells. (Palendira and Rickinson 2015). Importantly, magnesium supplementation treatment *in vivo* and *in vitro* restored basal intracellular Mg2+ concentration, NKG2D expression, cell cytotoxicity, and immunity to EBV in MAGT1-deficient patients (Chaigne-Delalande et al. 2013).

Primary immunodeficiencies associated with EBV disease

Coronin 1A

Deficiency in the actin regulator coronin 1A (*CORO1A*) has been reported in 9 patients to date (Shiow et al. 2008, 2009; Moshous et al. 2013; Stray-Pedersen et al. 2014; Punwani et al. 2015; Yee et al. 2016). It was originally described as a thymic egress defect causing T- B+ NK+ severe combined immunodeficiency (SCID) (Shiow et al. 2008). Like other immunodeficiencies caused by actin cytoskeletal defects, coronin 1A deficiency impacts a wide range of lymphocyte processes, including development, survival, TCR signaling, immune synapse formation and migration (Föger et al. 2006; Mugnier et al. 2008; Mace and Orange 2014; Punwani et al. 2015). Impaired calcium flux and f-actin accumulation at the immune synapse result in increased T cell apoptosis and CD4 + lymphopenia. Patients with coronin 1A deficiency presented with severe infections, and 5 developed EBV-driven B cell lymphoma. Four patients had severe mucocutaneous immunodeficiency manifestations including epidermodysplasia verruciformis-human papilloma virus (EV-HPV). No patients have developed HLH or severe infectious mononucleosis (Shiow et al. 2008; Moshous et al. 2013; Punwani et al. 2015). Patients have an immunophenotype of absent or low naïve T-cells, severely impaired T proliferative responses, normal levels of total immunoglobulins, and impaired vaccine responses. Three patients were reported with neurological abnormalities including autism-like symptoms, which are likely explained by the role of coronin 1A in neurodevelopment reported in mice (Jayachandran et al. 2014).

STK4 deficiency

Serine threonine kinase 4 (STK4) deficiency, also known as mammalian sterile 20-like protein (MST1) deficiency, is an autosomal recessive combined immunodeficiency characterised by progressive CD4+ lymphopenia (Abdollahpour et al. 2012; Nehme et al. 2012). STK4 is a factor that regulates Treg and naïve T cell migration, homeostasis, and tolerance acting through Foxo proteins (Ouyang and Li 2011). STK4 regulates the stability of Foxo1/3 in lymphoid T cells, which are involved in FOXP3 induction, and therefore a deficiency in STK4 leads to impaired Treg development (Du et al. 2014). STK4 deficiency results in a naïve T cell survival defect and

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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). Overall, the immune abnormalities lead to autoimmunity, EBV viremia, recurrent sinopulmonary and mucocutaneous infections mostly associated with herpesviruses as well as other viral (mulloscum contagiosum), fungal (candidiasis) and bacterial (Staphylococcal) infections (Abdollahpour et al. 2012; Nehme et al. 2012).

To date, 12 patients with STK deficiency of different origin have been reported, out of whom, 4 patients had developed EBV-lymphoproliferative disease during their disease (Abdollahpour et al. 2012; Nehme et al. 2012; Halacli et al. 2015; Dang et al. 2016).

APDS

Activated phosphatidylinositide 3-kinase delta (PI3Kδ) syndrome (APDS) is an inherited immune disorder caused by heterozygous gain-of-function mutations in the genes encoding the phosphoinositide 3-kinase delta (PI3Kδ) subunits p110δ or p85δ. Affected individuals develop combined immunodeficiency of variable clinical severity, characterised by recurrent sinopulmonary infections, increased susceptibility to viral infections, lymphoproliferation, bronchiectasis and an autosomal dominance inheritance pattern (Angulo et al. 2013; Deau et al. 2014; Lucas et al. 2014; Carpier and Lucas 2017). P110δ is the catalytic subunit of the lipid kinase PI3K-δ that generates the second messenger IP3 (inositol-3-phosphate) by degradation of PIP2 (phosphatidylinositol 4,5-biphosphate). PI3Kd is involved in downstream signaling from T and B cell antigen receptors, costimulatory receptors, cytokine receptors and some Toll like receptors (Okkenhaug 2013). Unregulated activity results in hyperactivation of the Akt-mTOR pathway, inducing excessive terminal differentiation of effector lymphocytes, impaired cytokine production and impaired immunoglobulin class switching in B cells (Angulo et al. 2013; Lucas et al. 2014). EBV infection is found in 30% of APDS patients and represents an important risk factor for the development of B cell lymphoma (occurring in 20% of EBV-infected APDS patients) (Carpier and Lucas 2017).

PRKCD deficiency

One patient with homozygous loss-of-function mutation in *PRKCD* (PKCδ) has been reported to date, and initially presented with recurrent otitis media and sinusitis, generalized lymphadenopathy, hepatosplenomegaly, B cell lymphocytosis, and persistent EBV viremia (Kuehn et al. 2013). The patient's serum had autoantibodies to several cellular proteins, and his NK cells had diminished cytotoxicity (Kuehn et al. 2013).

LPS-Responsive Beige-Like Anchor (LRBA) deficiency

LRBA deficiency is a PID caused by biallelic loss-of-function mutations in the *LRBA* gene. Affected individuals present with a variety of clinical symptoms including early onset hypogammaglobulinemia, recurrent infections, autoimmunity, and chronic diarrhea (Alkhairy et al. 2016; Gámez-Díaz et al. 2016). The main features of LRBA are typically a common variable immunodeficiency (CVID)-like phenotype, autoimmunity, and inflammatory bowel disease. The immunologic abnormalities in LRBA-deficient patients include decreased IgG antibody production, defect in specific antibody response, deficient T cell activation and proliferation, increased apoptosis, and decreased autophagy in B lymphocytes. The majority of LRBA-deficient patients have also low B-cell subset counts, mainly in switched memory B cells and plasmablasts (Lopez-Herrera et al. 2012; Azizi et al. 2017). Therefore, LRBA deficiency is a clinically variable syndrome with a wide spectrum of clinical and immunologic manifestations. LRBA deficiency is an autosomal recessive disease characterized by a CVID phenotype, autoimmunity with inflammatory bowel disease (Alangari et al. 2012; Alkhairy et al. 2016). One patient presented with EBV lymphoproliferative disease, elevated EBV DNA in the blood, and autoimmune pancytopenia (Alangari et al. 2012).

ALPS

Autoimmune lymphoproliferative syndrome (ALPS) consists of a group of immune dysregulatory disorders with different patterns of inheritance, and is caused by mutations that impair lymphocyte responses to apoptosis triggered by the Fas pathway, leading to impaired lymphocyte homeostasis. The most prevalent form of ALPS is ALPS-FAS with a heterozygous mutation in TNFRSF6, an intracellular domain of FAS (Pace and Vinh 2013). ALPS patients often present with hepatosplenomegaly, lymphadenopathy, EBV infection, cytopenia, and hypergammaglobulinemia. They demonstrate elevated double negative T cells and soluble

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Fas-Ligand. The risk of developing lymphoma increases significantly with age, and at 30 years 15% of patients have developed lymphoma (Price et al. 2014). Estimates of the fraction of ALPS lymphomas that are EBV associated vary from 15% to 40% in independent surveys (Straus et al. 2001; Pace and Vinh 2013; Price et al. 2014). Two patients have also developed HLH (Bode et al. 2015). How deficiency in the Fas-mediated apoptosis pathway could increase the risk of EBV-associated lymphomas is unknown. However, 1 possibility is that during long-term virus carriage, one of the immune controls governing EBV in the B cell system involves Fas-mediated cell killing (Palendira and Rickinson 2015).

Familial HLH

Familial HLH (FHL) is a group of diseases associated with impaired cytolytic activity of CD8+ T cells and NK cells. These diseases are caused by gene defects in the perforin gene and the components of lytic granule exocytosis machinery (Sepulveda and de Saint Basile 2017). Four genes have been identified in which mutations cause FHL: *PRF1, UNC13D, STX11*, and *STXBP2*, which are responsible for FHL2, FHL3, FHL4, and FHL5, respectively.

Perforin is encoded by *PRF1* and is expressed in cytotoxic granules of cytotoxic T cells and NK cells. Mutations in perforin result in an autosomal recessive disorder known as FHL2. Perforin mutations result in impaired killing of target cells by cytotoxic T cells and NK cells. EBV-positive infectious mononucleosis followed by persistent splenomegaly and lymphadenopathy and chronic active EBV disease and HLH was reported in a boy with perforin mutation (Katano et al. 2003; Cohen et al. 2011).

UNC13D encodes munc13-4 which interacts with syntaxin-11 to change the conformation of syntaxin from a closed to an open conformation. The change allows priming of cytotoxic granules and ultimately results in fusion of the granules with the membrane of the cell, followed by exocytosis of granules. Mutations in munc13-4 result in an autosomal recessive disease referred to as FHL3 with impaired NK and T cell cytotoxicity. Mutations in munc13-4 were reported in 1 patient with chronic EBV viremia who had cerebral vasculitis, hypogammaglobulinemia, chronic hepatitis, splenomegaly, and recurrent respiratory infections (Rohr et al. 2010).

STXBP2 encodes munc18-2 which forms a bridge assisting in the docking of cytotoxic granules to the plasma membrane of cytotoxic T cells or NK cells. Mutations in munc18-2 result in an autosomal recessive disease referred to as FHL5. Deficiency in munc18-2 results in impaired binding of munc18-2 to syntaxin-11 reduced stability of both proteins, and impaired exocytosis of cytotoxic granules from cytotoxic T cells or NK cells (Côte et al. 2009; zur Stadt et al. 2009). Mutations in munc18-2 were reported in 4 patients with chronic active EBV disease, and 2 of them developed HLH after primary EBV infection (Rohr et al. 2010).

ZAP70

ZAP70 deficiency is a combined immunodeficiency disorder with a profound presentation of CD8 lymphopenia. Although the count of CD4 T cells in patients with ZAP70 deficiency appears to be normal, they function abnormally due to impaired TCR signaling (Au-Yeung et al. 2009). The B cell and NK cell compartments seem unaffected (Turul et al. 2009). ZAP70 is a nonreceptor tyrosine kinase that is a key component of the TCR signal transduction pathway. Upon TCR stimulation, ZAP70 is recruited to the CD3ζ chain where, after its phosphorylation by Lck, it phosphorylates a number of downstream targets to initiate the signaling cascade (Turul et al. 2009). Although the clinical presentations of patients with ZAP70 deficiency have been heterogeneous, generally, they show increased susceptibility to recurrent bacterial, fungal, or viral infections in the first 2 years of life and a failure to thrive. Of the viral infections, HSV, molluscum contagiosum, and HPV are the most pathogenic. The EBV status of many patients was often not determined. However, 1 infant with normal numbers of B cells and CD4+ T cells, but a near absence of CD8+ T cells, developed an aggressive EBV-positive diffuse large B cell lymphoma (Newell et al. 2011).

TYK2

Tyrosine kinase 2 (TYK2), is a Janus kinase associated with the receptors of type I interferons, IL-6, IL-10, IL-12, and IL-23, and plays a central role in the signal transduction of these cytokines (Nemoto et al. 2018). TYK2 deficiency presents with symptoms of hyper-IgE syndrome (HIES) with susceptibility to various pathogens, including *Staphylococcus*, mycobacteria and HSV (Nemoto et al. 2018). Recently, 2 siblings with TYK2 deficiency were described, who presented with T cell lymphopenia characterized by low naïve

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CD4+ T cell counts and who developed EBV-associated B cell lymphoma (Nemoto et al. 2018).

Non-homologous DNA end-joining deficiencies (radiosensitive SCID)

Defects of the non-homologous DNA end-joining mechanism result in T- B- NK+ SCID, but the clinical severity of defects in this pathway are heterogeneous as several patients have been described with a hypomorphic phenotype. Hypomorphic DNA ligase IV (*LIG4*) and Artemis (*DCLRE1C*) gene mutations demonstrate susceptibility for EBV-driven LPD or diffuse large B cell lymphoma. However, HLH has not been reported (Moshous et al. 2003; Enders et al. 2006; Toita et al. 2007; Woodbine et al. 2014). Although there are a low number of affected individuals described for each of these conditions, the incidence of EBV LPD seems to be between 20% and 50% of described patients (Worth et al. 2016).

NF-κB1 and NF-κB2

NF-κB1 insufficiency predominantly affects maturation, survival, differentiation, and T cell-independent immunoglobulin class switching of B cells, but can also lead to impaired T cell function. NF-κB1 is a member of NF-κB transcription factor family, called p50. It triggers transcription of inflammatory cytokines and immune response genes through the canonical pathway by creating a heterodimer with RelA, another member of NF-κB family. EBV-driven LPD and recurrent EBV infection have been reported in patients with heterozygous mutations in the NF-κB1 gene (Boztug et al. 2016; Schipp et al. 2016; Lougaris et al. 2017).

A recent report describes a patient with a heterozygous NF-κB2 precursor-skipping mutation that resulted in a constitutive presence of p52. The mutation was shown to cause CID with severe EBV infection (Kuehn et al. 2017).

CARD11 gain-of-function mutations

Patients with gain-of-function mutations in CARD11 present with B cell lymphocytosis, splenomegaly, lymphadenopathy with florid follicular hyperplasia, recurrent sinusitis, and otitis media (Snow et al. 2012). Some patients have chronic EBV infection. The disorder is also referred to as B cell expansion with NF-κB and T cell anergy (BENTA) (Outinen et al. 2016). CARD11 is a scaffold protein that is essential in the activation of the canonical NF-κB pathway in B and T cells (Cohen 2015). It is not yet understood whether the EBV infection is a contributor to the lymphocytosis or a result of the immune abnormality observed in this entity.

NK cell abnormalities and EBV

There are currently three genetically defined conditions with selective loss of NK cell function. All three are associated with increased susceptibility to various pathogens, including herpesviruses such as HSV-1 and VZV; however, EBV is also implicated on occasion (Rickinson et al. 2014).

The most NK-specific deficiency involves patients with a homozygous missense mutation in Fc-γ receptor 3A (CD16), the NK cell activating receptor for antibody-dependent cell cytotoxicity (ADCC). Interestingly, the mutation does not affect NK cell development or ADCC function but does impair spontaneous NK-mediated cytolysis (Rickinson et al. 2014). Although only three patients have been described with homozygous mutations in the gene coding for CD16, two developed EBV-related severe complications, prolonged infectious mononucleosis (de Vries et al. 1996), and EBV-associated lymphadenopathy (Grier et al. 2012). Patients with CD16 deficiency have normal numbers of NK cells but impaired NK cell cytotoxicity. Affected patients suffered from severe viral infections, particularly VZV and HPV in addition to EBV (Cohen 2015).

Another condition affecting NK cell development arises from homozygous mutation of the gene encoding minichromosome maintenance 4 (MCM4), a helicase component of the DNA replication complex (Eidenschenk et al. 2006; Hughes et al. 2012). Patients with mutations in MCM4 present with adrenal insufficiency, growth retardation, low numbers of NK cells, and absent CD56dim NK cells (Gineau et al. 2012). Among the few MCM4-deficient kindreds studied to date, one child developed EBV-positive B cell lymphoproliferative disease. Notably, this child was the only one of four siblings who also failed to mount a T cell dependent EBNA1 antibody response to EBV infection (Rickinson et al. 2014).

Patients with mutations in GATA binding protein 2 (GATA2) can have various signs and symptoms including acute myeloid leukemia, myelodysplastic

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syndrome, autoimmune disease, pulmonary alveolar proteinosis, and primary lymphedema. Patients with GATA2 mutations have presented with chronic active EBV disease, and persistent EBV viremia (Hsu et al. 2011; Spinner et al. 2014). Two of those patients had an EBV-associated disease, and both involved unusual EBV-positive malignancies of mesenchymal cells. One was of spindle cell origin, whereas the other was a leiomyosarcoma (Spinner et al. 2014). In addition to EBV, these patients also are susceptible to other severe herpesvirus infections as well as severe HPV, fungal, and non-tuberculous mycobacterial infections. *GATA2* encodes a transcription factor important for hematopoiesis; accordingly, patients with mutations in GATA2 often have low numbers of B cells, CD4 T cells, NK cells, dendritic cells, red blood cells, neutrophils, monocytes, and platelets (Cohen 2015).

Syndromes with CID and severe EBV infection

Wiskott–Aldrich syndrome (WAS)

Wiskott–Aldrich syndrome (WAS) is an X-linked immunodeficiency caused by mutations in the gene encoding the WAS protein. Mutations in the *WAS* gene located at Xp11.22-23 results in defective WASP function, which acts as a scaffold for actin polymerization, leading to impaired hematopoietic cell growth and functions (Thrasher and Burns 2010). More than 300 mutations have been identified with different effects on WAS expression or function (Massaad et al. 2013). However, the classical syndrome, associated with complete absence of WAS protein, is characterized by small platelets, thrombocytopenia, and increased susceptibility to bacterial, viral, and fungal infections. Among several immune defects are a progressive T cell lymphopenia, near absent iNKT cell numbers, and impaired NK and T cell effector function due to defective immune synapse formation. About 13% of WAS patients develop malignancies, mainly B cell lymphomas, with an average age of onset of 9.5 years (Sullivan et al. 1994). EBV infection appears to increase the lymphoma risk. EBV-induced LPDs observed in patients with WAS include lymphomatoid granulomatosis (Sebire et al. 2003), non-Hodgkin's lymphoma (Gulley et al. 1993; Yoshida et al. 1997; Du et al. 2011), Hodgkin's lymphoma (Sasahara et al. 2001; Du et al. 2011) and other LPDs (Nakanishi et al. 1993).

Ataxia telangiectasia (AT)

AT is an autosomal recessively inherited syndrome characterised by progressive cerebellar ataxia, oculomotor dyspraxia, oculocutaneous telangiectasia, immunodeficiency and susceptibility to malignancy. It is caused by mutations in the ATM protein, which plays an integral role in DNA repair and cell cycle checkpoint control (Paull 2015). Immune defects vary between patients, but typically present as mild impairment of both humoral and cell-mediated immunity. Low levels of serum antibodies and reduced numbers of B cells are common features, whereas NK cell numbers appear normal. CD4+ T cell lymphopenia has been reported in some patients, but T cell function remains broadly intact. Patients are particularly susceptible to bacterial sinopulmonary infections early in life, and many develop chronic lung disease (Chopra et al. 2014). A recently published French registry study demonstrated a 19.1% incidence of lymphoma in patients with AT by 20 years of age. Approximately one-third of these lymphomas were Hodgkin's lymphomas (all tested were EBV-related), and the remaining two-thirds were non-Hodgkin's lymphomas (50% EBV positive) (Suarez et al. 2015). HLH, severe infectious mononucleosis or chronic EBV viraemia has not been described in AT.

WHIM

Warts, Hypogammaglobulinaemia, Immunodeficiency, and Myelocathexis (WHIM) syndrome is characterised by a susceptibility to severe papilloma virus and herpesvirus infections (Gorlin et al. 2000). 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 (Gorlin et al. 2000). The WHIM syndrome-associated CXCR4 mutations cause impaired receptor internalization leading to increased signaling (Balabanian et al. 2005; Bachelerie 2010; Dotta et al. 2011). Two cases of EBV-associated LPD (fatal in 1 case) have been described (Chae et al. 2001; Imashuku et al. 2002).

Chediak–Higashi syndrome

Chediak–Higashi syndrome (CHS) is an autosomal recessive disorder, caused by a defect of *LYST*, a gene that encodes a regulator of lysosomal trafficking. Mutations affect the size, structure, and function of

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lysosomes and other secretory granules, resulting in abnormally large organelles in virtually all granulated cells (Kaplan et al. 2008). The most important features of the immunodeficiency are neutropenia and NK cell dysfunction. Patients suffer recurrent life-threatening bacterial and viral infections.

Furthermore, without HSCT, almost 85% of affected children will progress to an accelerated disease with lymphoproliferative infiltration of major organs and HLH (Kaplan et al. 2008). Although there has been no detailed analysis, EBV infection has been postulated as a trigger. In one early report, 6 of 9 unrelated patients were EBV seropositive, and 3 of these were reported to have signs of chronic active EBV infection post-infectious mononucleosis (Merino et al. 1986). Another more recent report has shown a clearer association between primary EBV infection and CHS acceleration (Ogimi et al. 2011).

22q11.2 deletion syndrome (Di George)

22q11.2 deletion syndrome (22q11.2DS), also known as Di George syndrome (DGS), is the most common chromosomal microdeletion disorder. It was initially described as a clinical triad of immunodeficiency, hypoparathyroidism, and congenital heart disease. The syndrome is now known to have a heterogeneous presentation that includes multiple additional congenital anomalies and later-onset conditions, such as palatal, gastrointestinal and renal abnormalities, autoimmune disease, variable cognitive delays, behavioural phenotypes, and psychiatric illness (McDonald-McGinn et al. 2015). Thymic hypoplasia in partial DGS or complete aplasia in classic DGS is the major factor generating the T cell immunological defects. Besides severe age-specific T cell lymphopenia through infancy, there is additionally a decline in functional CD4+ CD25+ regulatory T cell counts and decreased expression of the AIRE gene (Shabani et al. 2016). EBV-associated lymphoproliferation was reported to date in 3 patients with 22q11.2 deletion syndrome (Shabani et al. 2016).

Conclusion

EBV infection can manifest in a variety of ways: asymptomatic/mild infection, infectious mononucleosis, HLH, or a variety of malignancies. These clinical features are most prominent in immunocompromised individuals resulting from coincident infections, iatrogenic therapies, or gene mutations. Our understanding of the host-virus interaction in EBV infection and better characterised the pathophysiology of severe and aberrant EBV infection has increased significantly over the past 2 decades. By identifying new genes associated with immunodeficiency and predisposition to EBV viremia and associated disease, the underling cellular, biochemical, and molecular mechanism involved in the immunity to EBV are starting to unravel. This understanding will hopefully allow identification of targeted biological, cellular, or small molecule therapies for managing these patients effectively and safely in the future.

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