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Primary Immunodeficiencies Associated with EBV Disease

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Abstract

Epstein-Barr virus (EBV) infects nearly all humans and usually is asymptomatic, or in the case of adolescents and young adults can result in infectious mononucleosis. EBV-infected B cells are controlled primarily by NK cells, CD4 T cells, and CD8 T cells. While mutations in proteins important for B cell function can affect EBV infection of these cells, these mutations do not result in severe EBV infection. Some genetic disorders affecting T and NK cell function result in failure to control EBV infection, but do not result in increased susceptibility to other virus infections. These include mutations in *SH2D1A, BIRC4, ITK, CD27, MAGT1, CORO1A,* and *LRBA.* Since EBV is the only virus that induces proliferation of B cells, the study of these diseases have helped to identify proteins critical for interactions of T and/or NK cells with B cells. Mutations in three genes associated with hemophagocytic lymphohistocytosis, *PRF1, STXBP2, and UNC13D*, can also predispose to severe chronic active EBV disease. Severe EBV infection can be associated with immunodeficiencies that also predispose to other viral infections and in some cases other bacterial and fungal infections. These include diseases due to mutations in *PIK3CD, CTPS1, STK4, GATA2, MCM4, FCGR3A, CARD11, ATM, and WAS*. In addition, patients with severe combined immunodeficiency, which can be due to mutations in a number of different genes, are at high risk for various infections as well as EBV B cell lymphomas. Identification of proteins important for control of EBV may help to identify new targets for immunosuppressive therapies.

1. Introduction

Epstein-Barr virus (EBV) infects 95% of the human population and most individuals are infected asymptomatically and are unaware that they shed virus from the oropharynx throughout their life. Infection of adolescents and young adults often results in infectious mononucleosis with fever, sore throat, lymphadenopathy, and splenomegaly. EBV infection of B cells can result in a lytic infection with death of the cells. More often virus infection of B cells results in in a latent infection and with expression of a very limited number of viral proteins. Certain B cell abnormalities affect the interaction of EBV with the host. Patients with Bruton's agammaglobulinemia lack mature B cells and thus their B cells cannot be infected with EBV (Faulkner et al. 1999). Patients with the hyperIgM syndrome have mutations in CD40L and their cells are impaired for transformation by EBV in vitro (Imadome et al. 2003). B cells from patients with mutations in STAT3 have impaired proliferation in response to virus infection (Koganti et al. 2014). However, no B cell defects have been described to date that result in more severe EBV infection.

Control of EBV-infected cells is mediated by natural killer (NK cells), invariant NKT (iNKT) cells, CD4 T cells and CD8 T cells (Chung et al. 2013; Hislop et al. 2007). Impairment in the function of these cell types can result in failure to adequately control EBV infection. This can lead to persistent EBV viremia, lymphoproliferation, and ultimately EBV lymphomas.

Surprisingly, many of the genes important for controlling EBV infection are not critical for controlling other pathogens including other members of the herpesvirus family. This indicates a unique characteristic of EBV relative to other pathogens. EBV is the only human virus that induces growth proliferation of B cells. Therefore, host cell proteins important for interactions of T or NK cells with B cells are often critical for control of EBV. Identification of cellular gene mutations associated with severe EBV infection helps us to identify proteins important for the B cell-T cell or B cell-NK cell immunologic synapse. These cellular proteins may also serve as targets for new immunosuppressive medications.

2. Immunodeficiencies Specific for EBV Disease (Tables 1, 2)

2.1 X-linked lymphoproliferative disease 1 (XLP1)

The first genetic disorder linked with severe and often fatal EBV disease was XLP1, also known as Duncan's disease. Purtillo and colleagues described an X-linked lymphoproliferative disease (XLP) in boys that often presented with fulminant infectious mononucleosis with lymphocytic and histiocytic infiltration of the bone marrow, central nervous system, and other organs (Purtillo et al. 1975). Female carriers are not affected. If untreated, patients often die from bone marrow failure with bleeding and infection, or liver failure. Subsequent studies showed that the disease has a variety of phenotypes including fatal infectious mononucleosis, aplastic anemia or hypogammaglobulinemia after primary EBV infection, immunoblastic B cell lymphoma, Burkitt lymphoma, or plasmacytoma, and that the underlying cause is an abnormal immune response to infection with EBV (Purtillo 1976; Purtillo et al. 1977). More recent studies show that the presenting symptoms of XLP1 include hemophagocytic lymphohistiocytosis (HLH) in 31.9 % of persons, dysgammaglobulinema in 22%, a family history of XLP1 alone in 16.5%, lymphoma in 14.3 %, fulminant infectious mononucleosis in 7.7%, and other symptoms in 7.7% (Booth et al. 2011). These other symptoms include aplastic anemia, lymphomatoid granulomatosis, and vasculitis. Patients have impaired antibody responses to vaccination. Most lymphomas are EBV-positive non-Hodgkin B lymphomas, although T cell lymphomas and EBV-negative B cell lymphomas have also been reported. In most cases, there is not a clear correlation between specific mutations and clinical phenotype (Booth et al. 2011; Filipovich et al. 2010). Within families, different members can have different severity of presentation despite the same mutation.

The gene responsible for XLP1 was identified in 1988 and is referred to as *SH2D1A* (Coffey et al. 1998), *DSHP* (Nichols et al. 1998), and *SAP* (Sayos et al. 1998) and is expressed on T, NK, and iNKT cells. Mutations in SAP account for 60–70% of cases of XLP. The protein encoded by the gene, SAP (SLAM-associated protein), is an adapter molecule that is expressed on T, NK, and iNKT cells. SAP consists of a single Src homology 2 (SH2) domain and interacts with several proteins including SLAM, 2B4, NTB-A, CD84, Ly108,

and Ly9 (Cannon et al. 2010). The interaction of SAP with SLAM reduces production of IFN-γ (Latour et al. 2001) and T cell killing of virus infected cells (Dupre et al. 2005). The interaction of SAP with 2B4 (Parolini et al. 2000) and NTB-A (Bottino et al 2001) increases NK cell cytotoxicity. SAP deficient cells are impaired for formation of immunologic synapses and killing of B cells, but not dendritic cells (Qi et al. 2008; Zhao et al. 2012). This results in inefficient recruitment and retention of T cells to germinal centers. CD84 and Ly108 are critical for T and B cell contacts and CD84 is required for germinal center formation; in the absence of SAP, germinal centers are defective (Cannons et al. 2010). SAP is also important for control of T cell proliferation and apoptosis during antigen stimulation; in the absence of SAP T cells are resistant to apoptosis mediated by T cell receptor restimulation (Snow et al. 2009). Taken together, these effects result in impaired T and NK cell cytotoxicity, with massive proliferation of T and NK cells, excessive cytokine production, and HLH.

XLP1 patients have impaired controlled of EBV, but not other virus infections or bacteria. These patients lack class-switched memory B cells (Chiganti et al. 2008). SAP knockout mice lack virus-specific memory B cells and long-lived plasma cells, due to a defect in CD4 T cells (Crotty et al.2003). Patients who survived EBV infection were found to have impaired recognition of SLAM-ligand EBV transformed B cells expressing EBV protein, but were able to recognize SLAM-ligand negative EBV-infected B cells (Hislop et al. 2010). Somatic reversion of SAP mutated cells in patients who survived XLP1 occurred solely in memory CD8 T cells and these T cells proliferated and were cytotoxic for EBV-infected B cells (Palendira et al. 2012). A study of female XLP carriers (who have SAP^+/SAP^- alleles) showed that memory CD8 T cells specific for influenza and CMV were present in both SAP^+ and SAP^- cells; however, EBV-specific T cells were only present in SAP^+ cells (Palendira et al. 2011). These differences are due to the failure of SAP^- cells to respond to antigens presented by B cells, and since EBV is the only human virus that latently infects B cells, these results help to explain why XLP1 is a disease confined to EBV and does not predispose to infections by other pathogens. Blocking NTB-A and 2B4, both of which bind to SAP, restores the ability of SAP^- T cells to respond to antigen presentation in the B cells. While patients with XLP1 have normal numbers of T and B cells, they lack iNKT cells (Nichols et al. 2005) which are critical for T cell receptor-induced cellular cytotoxicity (Das et al. 2013). These patients also have impaired T cell production of IL-10 (Ma et al. 2005). Thus, patients with XLP1 have impaired recognition of antigens presented by B cells, absent iNKT cells, impaired T cell cytotoxicity, and reduced expression of IL-10 by T cells.

While intravenous immunoglobulin, which contains neutralizing antibody to EBV, has been used to try to prevent EBV infection in patients with XLP1, breakthrough infections have occurred resulting in death. Rituximab, an anti-CD20 monoclonal antibody, was reported to reverse fulminant infectious mononucleosis in two patients with XLP1 (Milone et al. 2005). Reduced intensity conditioning hematopoietic stem cell transplantation (HSCT) resulted in an 80% one year survival rate in patients presenting with XLP1, regardless of whether they had a history of HLH (Marsh et al. 2014). In the future, genetic therapy correcting the SAP gene directly may be possible, and this has been demonstrated using retrovirus-mediated gene transfer in a mouse model of XLP1 (Rivat et al. Blood 2013).

2.2 X-linked lymphoproliferative disease 2 (XLP2)

XLP2, due to a mutation in *BIRC4* which encodes the X-linked inhibitor of apoptosis (XIAP) was initially described in patients from three families who presented with HLH often, but not always, associated with EBV, splenomegaly, hypogammaglobulinemia, and colitis (Rigaud et al. 2006). XIAP is expressed in B, T, NK, and dendritic cells as well as non-hematopoietic cells. Mutations in XIAP account for about 20–30% of cases of XLP. While the initial paper reported that patients had low numbers of iNKT cells, a later report indicated that patients had normal numbers of these cells (Marsh et al. 2009). These patients have normal numbers of B, T, and NK cells. A review of 25 cases of XLP2 found that only 8 presented with HLH; other patients presented with colitis, severe infectious mononucleosis, or splenomegaly; iNKT cells were not reduced (Speckmann et al 2013). There was no clear correlation of specific mutations with the severity of disease (Filipovich et al. 2010; Speckmann et al. 2013). Patients who underwent reduced conditioning HSCT had a better long term survival rate (55%) than those who had ablative conditioning (14%) (Marsh et al 2013).

Mutations in XIAP result in enhanced T cell apoptosis in response to stimulation with anti-Fas antibody, anti-CD3 antibody, and trimeric TRAIL (Rigaud et al. 2006); however, a subsequent report did not find enhanced apoptosis with anti-Fas antibody (Marsh et al. 2010). T cells from patients with XIAP have enhanced T cell reactivation-induced cell death. XIAP is also important for NOD2-mediated signaling (Krieg et al 2009) as well as activation of NF-κB. Thus, patients with XLP2 have enhanced T cell apoptosis to various stimulation including T cell receptor restimulation.

A comparison of patients with XLP1 and XLP2 found that HLH was more common in XLP2 (76%) versus XLP1 (55%), but was more likely to be fatal in patients with XLP1 (61%) versus XLP2 (23%) (Pachlopnik Schmid et al. 2011). Infection with EBV triggered the onset of HLH in 92% of persons with XLP1 and 83% with XLP2. Significantly more patients with XLP1 had hypogammaglobulinemia (67%) and lymphoma (30%), than those with XLP2 (33% and 0% respectively). In contrast, significantly more patients with XLP2 had cytopenias (52%) and splenomegaly (87%) in the absence of HLH, and hemorrhagic colitis (17%) than XLP1 (12%, 7%, 0% respectively). The large number of differences between XLP1 and XLP2 has led some authors to propose that XLP2 should be reclassified instead as an X-linked familial HLH disorder (Filipovich et al. 2010).

2.3 IL-2 inducible T cell kinase (ITK)

IL-2 inducible T cell kinase (ITK) deficiency was first reported in two girls with homozygous mutations who died with B cell proliferation due to EBV (Huck et al. 2009). The disease has been called EBV-associated autosomal lymphoproliferative syndrome. ITK is a member of the TEC family of kinases, and has a critical role in T cell receptor signaling. It is important for T cell proliferation and differentiation. Both girls had high levels eomesodermin in CD8 T cells, and iNKT cells were absent from the one girl who was tested. A review of seven patients (four girls and three boys) with ITK deficiency from 4 families found that all patients presented with fever, lymphadenopathy, and all of whom were tested had markedly elevated EBV DNA in the peripheral blood (Linka et al.2012).

Most had hepatosplenomegaly, pulmonary disease, hypogammaglobulinemia, leukopenia, and CD4 lymphopenia. Pathology showed Hodgkin lymphoma in four patients, B cell lymphoproliferative disease in two patients, and both large B cell lymphoma and lymphomatoid granulomatosis in one. Two patients underwent HSCT, one survived and the other died of complications associated with graft-versus-host disease. All patients that were tested had low numbers of iNKT cells and an impaired calcium flux in T cells after stimulation of the T cell receptor with anti-CD3 antibody.

2.4 CD27

Two brothers were reported with homozygous mutations in CD27 with persistent EBV viremia; one had aplastic anemia and the other had hypogammaglobulinemia (van Montfrans et al 2012). Both patients had undetectable CD27 on all lymphocytes, but normal numbers of lymphocyte subsets. T cell proliferative responses to CD27-dependent mitogens (CD2 and pokeweed mitogen) were reduced and T cell-dependent B cell responses to vaccines were impaired. CD27 is a member of the tumor necrosis-receptor family and binds to its ligand, CD70, and providing costimulatory signaling to activate B, T, and NK cells. CD27 is a marker for memory B cells, and enhances B cell differentiation, and T and NK cell function.

Eight patients in three additional families with CD27 deficiency were subsequently reported; three patients had asymptomatic deficiencies in memory B cells, three had EBV HLH and lymphoproliferative disease, and two had lymphoma (Salzer et al. 2013). Three patients developed hypogammaglobulinemia after primary EBV infection. Two with severe disease had reduced NK cell function and diminished numbers of iNKT cells. One patient received repeated courses of rituximab and two underwent HSCT.

2.5 Magnesium Transporter 1 (MagT1) protein

MAGT1 encodes a magnesium transporter protein located in the plasma cell membrane. MagT1 protein allows an influx of magnesium into cells after stimulation of the T cell receptor which results in activation of T cells (Li et al. 2011). The influx of magnesium results in increased calcium signaling, activation of PLC (phospholipase C)-γ1, PKC (protein kinase C)-θ, and NF-κB. Thus, magnesium, like calcium, can act as an intracellular second messenger to couple events on the cell surface with changes in the cytoplasm and nucleus.

Seven patients have been reported with mutations in *MAGT1* who had markedly elevated levels of EBV DNA in the blood; these patients ranged in age from 3 to 45 years old with a mean age of 16 years (Chaigne-Delalande et al. 2013). Four patients had B lymphomas, three of which were tested for EBV and were positive. Stimulation of the T cell receptor in PBMCs from the patients resulted in impaired calcium signaling, and reduced activation of PLC γ1, PKC-θ, and NF-κB.

Patients with mutations in *MAGT1* often have low CD4 cell counts with an inverted CD4:CD8 ratio, reduced NKG2D (an NK cell activating receptor) on NK cells and cytotoxic T lymphocytes (CTLs), and impaired T cell activation. Their CTLs showed reduced killing of autologous EBV-transformed B cells and their NK cells were impaired for killing of other target cells. In addition to elevated levels of EBV in the blood, some patients had

hypogammaglobulinemia, sinusitis, and chronic diarrhea. Two patients had autoimmune cytopenias. All patients had splenomegaly; one had hemophagocytosis. Two patients underwent HSCT and both died of complications related to the transplant. The disease has been termed XMEN (X-linked immunodeficiency with magnesium defect, EBV infection, and neoplasia).

Patients with mutations in *MAGT1* had lower levels of intracellular magnesium, which suggested that supplemental magnesium might improve their immune responses. In vitro supplemental magnesium of PBMCs from patients resulted in increased levels of intracellular magnesium, NKG2D and improved NK cell and CTL cytotoxicity. Treatment of two patients with magnesium supplementation resulted in increased levels of intracellular magnesium, increased expression of NKG2D on CTLs, improved CTL activity against autologous EBV-transformed B cells, and a reduction in the percentage of EBV-infected cells in the blood.

2.6 Coronin actin binding protein 1A

Three siblings in one family that presented with EBV B cell lymphoproliferative disease in early childhood were found to have homozygous mutations in *CORO1A* which encodes coronin actin binding protein 1A (Moshous et al. 2013). One patient had an EBV-positive lymphoproliferative process and two had EBV lymphomas. Two of the patients in whom EBV DNA levels in the blood were measured had elevated levels. All three patients had recurrent ear, nose, and throat as well as upper respiratory tract infections. Two of the patients died; one in preparation for HSCT and one from graft-versus-host disease after HSCT. Coronin actin binding protein 1A binds to actin-related protein 2/3 and is important for T cell synapse formation and T cell receptor signaling. The patients had reduced numbers of CD4, CD8, CD19, and naïve T cells, a reduced T cell repertoire, and low or no iNKT cells and few mucosal-associated invariant T cells.

2.7 LPS-responsive beige-like anchor (LRBA) protein

Patients with mutations in *LRBA* present with inflammatory bowel disease, chronic diarrhea, and autoimmune cytopenias (Alangari et al. 2012). One patient presented with EBV lymphoproliferative disease, elevated EBV DNA in the blood, and autoimmune pancytopenia. The LRBA protein has domains that are conserved with the Chediak-Higashi syndrome protein and is important for endocytosis of ligand-activated receptors; however, its role in immunity is not well understood.

3.0 Proteins Associated with EBV Disease and Familial Hemophagocytic Lymphohistiocytosis (FHL) (Tables 1, 2)

3.1 Perforin

Familial hemophagocytic lymphohistiocytosis (FHL) is a group of diseases due to mutations in proteins important for maturation or release of cytotoxic granules from CTLs and NK cells, or for entry of cytotoxic proteins from these granules into target cells. Four genes have been identified in which mutations cause FLH- *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 CTLs and NK cells. When foreign antigens are expressed on antigen-presenting cells, CTLs become activated and granules containing perforin and granzymes dock on the plasma membrane and are released. Perforin oligomerizes to forms pores in target cells which allows entry of granzymes into these cells resulting in activation of caspases and death of the cells. Mutations in perforin result in an autosomal recessive disorder known as FHL2. Perforin mutations result in impaired killing of target cells by CTLs and NK cells.

We described a boy who presented with EBV-positive infectious mononucleosis followed by persistent splenomegaly and lymphadenopathy and was diagnosed with chronic active EBV disease (CAEBV) and HLH (Katano et al. 2004; Cohen et al. 2011). The patient had different mutations in the two alleles of perforin which resulted in reduced expression of the native form of the protein. The patient only expressed the immature form of perforin, since the perforin was not cleaved at the carboxyl terminus to yield the active form of the protein. Accordingly, his T cells were impaired for killing target cells.

3.2 Munc 13–4

Munc 13–4 is encoded by *UNC13D*. Munc 13–4 interacts syntaxin 11 to change syntaxin's conformation from a closed to an open conformation; a soluble NSF attachment protein receptor (SNARE) complex is formed between v-SNARE on cytotoxic granules and the target membrane t-SNARE syntaxin 11. This allows priming of cytotoxic granules and ultimately results in fusion of the granules with the membrane of the cell with 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 one patient with CAEBV who had cerebral vasculitis, hypogammaglobulinemia, chronic hepatitis, splenomegaly, and recurrent respiratory infections (Rohr et al. 2010). The patient was a compound heterozygote for munc13–4 mutations. The patient was initially EBV seropositive and then developed CAEBV with a high viral load and HLH, and died of the disease.

3.3 Munc 18–2

Munc18–2 is encoded by *STXBP2*, a member of the sec1/munc18 (SM) family of proteins that are important for SNARE-mediated membrane fusion. Munc18–2 binds to syntaxin11, on the plasma membrane of NK cells, and to v-SNARE on cytotoxic granules. Thus, munc-18–2 forms a bridge assisting in the docking of cytotoxic granules to the plasma membrane of CTLs 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 CTLs or NK cells (Cote et al. 2009; zur Stadt et al. 2009). Mutations in 18–2 are associated with a disease termed FHL5. Mutations in munc18–2 affect folding of the protein which impair its binding activity (Hackmann et al. 2013). These patients have impaired NK and T cell killing of target cells.

Mutations in munc18–2 were reported in four patients with CABEV (Rohr et al. 2010). Three patients had homozygous mutations and one was a compound heterozygote. Two

patients developed HLH after primary EBV infection; one presented with HLH-like symptoms and then severe HLH after primary EBV infection, and one was initially EBV seropositive and then developed CAEBV with a high viral load and HLH. All four patients had hypogammaglobulinemia, three had persistent splenomegaly, two had recurrent infections, and one had Hodgkin lymphoma. Three underwent HSCT at ages 6, 16 and 16 and one survived; the fourth patient with lymphoma had a HSCT and remains alive and well.

4.0 Genes Associated EBV and other Infections (Tables 1, 2)

4.1 Phosphatidylinositol-3-OH kinase (PI3K) catalytic subunit p110δ

4.1.1 PI3K p110δ gain of function mutations—Thirty-one patients with gain-of-function mutations in the p110δ catalytic subunit of phosphatidylinositol-3-OH kinase (PI3K) have been reported who had impaired control of EBV (Lucas et al. 2013; Angulo et al. 2013). PI3K is activated in T cells after ligand binding to the T cell receptor (Okkenhaug and Vanhaesebroeck 2003). This results in binding of the p85 regulatory domain of PI3K to phosphorylated tyrosine residues on proteins and its dissociation from the p110 catalytic subunit of PI3K. p110δ is found exclusively in lymphocytes. Free p110δ is then recruited to the plasma membrane and it phosphorylates PIP2 (phosphatidylinositol-(4,5)-biphosphate) to PIP3 (phosphatidylinositol-(3,4,5)-triphosphate). This results in phosphorylation of Akt (also known as protein kinase B) which phosphorylates mammalian target of rapamycin (mTOR). The mTOR complex (composed on mTOR, raptor, and GβL) phosphorylates 4E-BP1 (a protein translation initiation inhibitor) and p70S6 kinase (which promotes protein translation). Phosphorylation of the former inhibits its ability to block eukaryotic translation initiation factor eiF4E, while phosphorylation of the latter activates the S6 ribosomal protein to increase protein translation. This results in increased protein synthesis, cell growth, proliferation, differentiation, and survival.

Heterozygous mutations (N334K, E525K, and E1021K) in p110δ result in gain of function mutations (Lucas et al. 2013; Angulo et al. 2013). These likely block the interaction of p110δ with p85 (to allow unbridled activity of p110δ) or promoter the association of p110δ with the cell membrane. This results in increased activation (phosphorylation) of PI3K either in the presence or absence of T cell receptor stimulation. Stimulation of their peripheral blood mononuclear cells with antibody to CD3 and CD28 results in reduced IL-2 secretion and decreased proliferation compared with controls. Surprisingly, these patients have increased numbers of EBV-specific T cell based on tetramer staining and increased EBV-specific effector memory cells. Patients with mutations in p110δ have reduced memory CD8 T cells, reduced naive CD4 T cells, increased senescent effector CD8 T cells, reduced class switched IgG and IgA cells, and increased activation-induced cell death.

Patients present early in childhood with sinus and pulmonary infections, persistent EBV and/or CMV viremia, lymphoproliferative disease with lymphoid nodules in mucosa that can obstruct the lungs and gastrointestinal tract, and autoimmune cytopenias. Patients have normal or elevated IgM, variable levels of IgG, reduced IgA, and impaired antibody production after vaccination. Patients have decreased CD4 cells and increased CD8 cells with an inverted CD4/CD8 ratio, and a progressive B and T cell immunodeficiency. Two patients developed EBV-positive B cell lymphomas and one patient had a marginal zone

lymphoma. The impaired ability to control EBV may be due to the low numbers of CD4 cells and/or the reduction in memory CD8 T cells.

This disease has been termed PASLI (p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immune deficiency) (Lucas et al 2013) or APDS (activated PI3Kδ syndrome) (Angulo et al. 2013). Treatment of one patient with rapamycin, an mTOR inhibitor, resulted in reduced CD8 T cell numbers, increased IL-2 secretion, and increased T cell proliferation after stimulation with anti-CD3 and anti-CD28 antibody in vitro (Lucas et al 2013). The patient had a reduction in the size of his lymph nodes, liver, and spleen. Treatment of cells in vitro from patients with mutations in p110δ with specific inhibitors of p110δ reduced the activity of the protein (Angulo et al. 2013).

4.1.2. PI3K p110δ loss of function mutation—

One patient has been reported who 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,

4.2 Cytidine 5' triphosphate synthase 1 (CTPS1)

Eight patients from 5 families were reported with mutations in cytidine 5' triphosphate synthase (CTPS1). Four patients presented with severe infectious mononucleosis (three of which had chronic EBV viremia), three with lymphoproliferative disease involving the central nervous system (two of whom had EBV-positive non-Hodgkin lymphoma), and one with asymptomatic chronic EBV viremia (Martin et al al. 2014). All of the patients had other severe herpesvirus infections during childhood and infections with encapsulated bacteria. One had Streptococcal pneumonia sepsis and meningitis, and one had Neisseria meningitidis meningitis. Six of the eight underwent HSCT and four survived; one died of graft-versus-host disease and one from disseminated varicella-zoster virus.

Most patients with CTPS1 had lymphopenia with low CD4:CD8 ratios during infections. One patient who was studied more intensively had low numbers of naïve CD4 T cells, increased effector memory T cells, low numbers of CD27 memory B cells, and absent iNKT cells. Proliferation and DNA synthesis of T cells in response to anti-CD3 antibody and proliferation of B cells in response to anti-B cell receptor and CpG were impaired. Reduced levels of CTP were present in stimulated T and B cells from the patients. CTPS1 expression is normally increased with T cell activation; therefore, deficiency of the protein presumably limits the ability of T cells to proliferate and control virus and bacterial infections.

4.3 Serine/threonine kinase 4 (STK4)

Three patients from two families with mutations in serine/threonine kinase 4 (STK4) were reported with high levels of EBV DNA in the blood. One patient developed an EBV-positive Hodgkin lymphoma and survived, a second patient developed disseminated EBV B-cell lymphoproliferative lesions and died after HSCT from graft-versus host disease and infectious complications, and a third patient with autoimmune hemolytic anemia underwent HSCT and also died from graft-versus host disease and infection (Nehme et al. 2011). The

patients had a history of recurrent bacterial and viral infections, dermatitis, CD4 lymphopenia, reductions in the numbers of naïve T cells, impaired T cell proliferative responses to phytohemagglutinin and to anti-CD3 antibody, reduced T cell receptor repertoires, and increased levels of IgG. Increased Fas expression was present on the surface of the cells, which showed increased sensitivity to Fas-induced apoptosis.

Another study reported three patients from one family with STK4 mutations; one patient with generalized lymphadenopathy had a biopsy which showed a monoclonal EBV lymphoproliferative process that was reported to resemble a lymphoplasmacytic lymphoma (Abdollahpour et al. 2012). These patients had bacterial and viral infections (including extensive warts and molluscum contagiosum), mucocutaneous candidiasis, neutropenia, CD4 lymphopenia, B cell lymphopenia, and most had elevated levels of IgG. STK4 is also referred to as mammalian sterile 20-like protein (MST1) and is involved in signaling pathways important for cell proliferation and apoptosis; STK4 is cleaved by caspases and is thought to be a pro-apoptotic protein.

4.4 GATA Binding Protein 2 (GATA2)

Patients with mutations in GATA binding protein 2 (GATA2) can have various signs and symptoms including acute myeloid leukemia, myelodysplastic syndrome, autoimmune disease, pulmonary alveolar proteinosis, and primary lymphedema. Patients with GATA2 mutations have presented with chronic active EBV disease, EBV-positive smooth muscle tumors, and persistent EBV viremia (Hsu et al. 2011; Spinner et al. 2014). In addition, these patients also are susceptible to other severe herpesvirus infections as well as severe human papillomavirus, 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.

4.5 Minichromosome maintenance complex component 4 (MCM4)

Patients with mutations in minichromosome maintenance complex component 4 (MCM4) present with adrenal insufficiency, growth retardation, low numbers of NK cells, and absent $CD56^{dim}$ NK cells (Gienau et al. 2012). These latter cells are cytotoxic and produce cytokines after recognition of target cells. One patient developed an EBV lymphoma (Eidenschenk et al. 2006). MCM4 is a DNA helicase that is important for DNA replication.

4.6. Fcγ receptor 3A (CD16a)

Two patients with mutations Fcγ receptor 3A (CD16) were described with EBV diseases; one patient had a prolonged illness with fever and malaise associated with EBV infection (deVries et al. 1996) and the second was reported to have recurrent lymphadenopathy due to EBV-positive Castleman's disease (Grier et al. 2012). The former patient also had severe infections with Bacille Calmette-Guerin and varicella-zoster virus, while the latter patient also had severe HPV infections and deficient NK cell cytotoxicity. Fcγ receptor 3A is expressed on NK cells and neutrophils; mutations in this receptor are responsible for classical NK cell deficiency.

4.7. Caspase recruitment domain-containing protein 11 (CARD11): gain of function mutations

Patients with germline 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). One patient presented with persistently elevated EBV DNA in the blood as well as splenomegaly, lymphadenopathy, bronchiectasis, recurrent otitis media, and molluscum contagiosum. The CARD11 protein is required for activation of NF-κB by antigen receptor in B and T cells. Somatic gain-of-function mutations of CARD11 are present in many diffuse large B cell lymphomas.

4.8 Other immunodeficiencies associated with multiple infections

Other primary immunodeficiency diseases associated with multiple infections can present with EBV lymphoproliferative disease or lymphomas. Ataxia telangiectasia is an autosomal recessive disease due to a mutation in *ATM* which encodes a serine/threonine kinase that is important for DNA repair. In addition to neurologic and skin disease, these patients often develop sinopulmonary infections, interstitial lung disease, and are at increased risk for malignancies. These patients often have increased levels of EBV DNA in the blood and can develop EBV lymphomas.

Wiskott-Aldrich syndrome is an X-linked disorder due to mutations in *WAS*. The Wiskott-Aldrich syndrome protein is important for forming the immunologic synapse which is the site of interaction between antigen presenting cells and T cells. In addition to increased propensity of infections, these patients have thrombocytopenia, eczema, and autoimmune disease. Patients may develop EBV lymphomas.

Patients with severe combined immunodeficiency (SCID) can have mutations in a number of different genes; these result in impaired B cell and T cell immunity. In addition to increased infections these patients often have chronic diarrhea and failure to thrive. These patients are susceptible to EBV-positive B cell lymphomas.

Abbreviations

APDS	Activated PI3Kδ syndrome
CAEBV	Chronic active EBV disease
CARD11	Caspase recruitment domain family, member 11
CTL	Cytotoxic T lymphocyte
CTPS1	Cytidine 5’ triphosphate synthase
EBV	Epstein-Barr virus
FHL	Familial hemophagocytic lymphohistiocytosis
GATA2	GATA binding protein 2
HLH	Hemophagocytic lymphohistiocytosis

HPV	human papillomavirus
HSCT	Hematopoietic stem cell transplantation
iNKT	Invariant NKT
ITK	IL-2 inducible T cell kinase
LRBA	LPS-responsive beige-like anchor
MagT1	Magnesium transporter 1
MCM4	Minichromosome maintenance complex component 4
MST1	Mammalian sterile 20-like protein
MTOR	Mammalian target of rapamycin
NK	Natural killer
PASLI	p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immune deficiency
PI3K	Phosphatidylinositol-3-OH kinase
PIP2	Phosphatidylinositol-(4,5)-biphosphate
PIP3	Phosphatidylinositol-(3,4,5)-triphosphate
PKC	Protein kinase C
PLC	Phospholipase C
PML	Progressive multifocal leukoencephalopathy
SAP	SLAM-associated protein
SCID	Severe combined immunodeficiency
SH2	Src homology 2
SM	Sec1/munc18
SNARE	Soluble NSF attachment protein receptor
STK4	Serine/threonine kinase 4
XIAP	X-linked inhibitor of apoptosis
XLP	X-linked lymphoproliferative disease
XMEN	X-linked immunodeficiency with magnesium defect, EBV infection, and neoplasia

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Table 1.

Clinical Features of Immunodeficiencies Predisposing to EBV Disease

Protein	Gene	Name of Syndrome	Transmission	EBV-associated symptoms	Non-infectious diseases in the absence of EBV infection
SLAM-associated protein	*SH2D1A*	XLP1	X-linked	Fulminant infectious mononucleosis, B cell lymphoma, HLH, lymphomatoid granulomatosis	EBV-negative B cell lymphoma, aplastic anemia, vasculitis
X-linked inhibitor of apoptosis	*BIRC4*	XLP2	X-linked	Fulminant infectious mononucleosis, HLH, splenomegaly, cytopenias	Colitis, HLH, inflammatory bowel disease
IL-2 inducible T cell kinase	*ITK*	EBV-associated autosomal lymphoproliferative syndrome	Autosomal recessive	Lymphoproliferation, Hodgkin lymphoma, HLH. hepatosplenomegaly, lung disease, lymphomatoid granulomatosis	Autoimmune kidney disease
CD27	*CD27*	CD27 deficiency	Autosomal recessive	Lymphoproliferative disease, HLH, lymphoma, aplastic anemia	none
Magnesium transporter 1 protein	*MAGT1*	XMEN	X linked	B cell lymphoma	Autoimmune cytopenias
Coronin actin binding protein 1A	*CORO1A*	Coronin 1A deficiency	Autosomal recessive	B cell lymphoma, lymphoproliferative disease	Neurocognitive impairment
LPS-responsive beige-like anchor protein	LRBA		Autosomal recessive	B cell lymphoproliferative disease, EBV viremia	Inflammatory bowel disease, chronic diarrhea, autoimmune cytopenias
Perforin	*PRF1*	FHL2	Autosomal recessive	HLH, CAEBV, splenomegaly	HLH
Munc13–4	*UNC13D*	FHL3	Autosomal recessive	CAEBV, vasculitis, hepatitis, splenomegaly,	HLH
Munc18–2	*STXBP2*	FHL5	Autosomal recessive	CABEV, lymphoma, splenomegaly	HLH, colitis, bleeding
PI3K catalytic subunit 110δ: gain of function mutations	*PIK3CD*	PASLI, APDS	Autosomal dominant	Lymphoma	Lymphoid nodules in upper airway and gastrointestinal tract, autoimmune cytopenias
PI3K catalytic subunit 110δ: loss of function mutation	*PIK3CD*		Autosomal recessive	EBV viremia	Lymphadenopathy, hepatosplenomegaly, autoantibodies
CTP synthase 1	*CTPS1*	CTP synthase 1 deficiency	Autosomal recessive	Severe infectious mononucleosis; lymphoproliferative disease, lymphoma	none
Serine threonine kinase 4	*STK4*	STK4 deficiency	Autosomal recessive	B cell lymphoma, lymphoproliferative disease, autoimmune hemolytic anemia	Dermatitis, autoimmune cytopenias
GATA binding protein 2	*GATA2*	MonoMac	Autosomal dominant	Severe infectious mononucleosis, EBV-positive smooth muscle tumors, CAEBV, HLH	Myeloid malignancies, myelodysplastic syndrome, autoimmune disease, pulmonary alveolar proteinosis, primary lymphedema.
Minichromosome maintenance complex component 4	*MCM4*	Classical NK cell deficiency type 2	Autosomal recessive	EBV lymphproliferative disease, lymphoma	Adrenal insufficiency, growth retardation

Protein	Gene	Name of Syndrome	Transmission	EBV-associated symptoms	Non-infectious diseases in the absence of EBV infection
Fcγ receptor 3A (CD16a)	*FCGR3A*		Autosomal recessive	EBV-positive Castleman disease	none
Caspase recruitment domain-containing protein 11: gain of function mutations	*CARD11*		Autosomal dominant	EBV viremia	Autoimmune neutropenia

Abbreviations: XLP: X linked lymphoproliferative disease; HLH, hemophagocytotic lymphohistiocytosis; XMEN, X-linked immunodeficiency with magnesium defect, EBV infection, and neoplasia; CAEBV, chronic active EBV disease; FHL, familial hemophagocytic lymphohistiocytosis; PI3K, phosphoinositide 3' kinase; PASLI, p110δ –activating mutation causing senescent T cells, lymphadenopathy, and immune deficiency; APDS, activated PI3K6 syndrome; CTP, cytidine 5' triphosphate.

Table 2.

Immunologic and Infectious Features of Immunodeficiencies Predisposing to EBV Disease

Protein	Humoral Immune Findings	Cellular Immune Findings	Chronic EBV viremia	Other Infections	Reference
SLAM associated protein	Low IgG, increased IgA, increased IgM, reduced antibody response to vaccinations and infections	Absent iNKT cells, normal numbers of B, T cells; reduced memory B cells; impaired T and NK cell killing	no	none	Coffey et al. 1998; Nichols et al. 1998; Sayos et al 1998
X-linked inhibitor of apoptosis	Low IgG	Normal or low numbers of iNKT cells, normal numbers of B, T, NK cells	no	none	Rigaud et al. 2006; Speckmann et al 2013
IL-2 inducible T cell kinase	Low or normal IgG	Absent iNKT cells, low numbers of WBC, CD4 T cells; normal numbers of B cells	yes	none	Huck et al. 2009; Linka et al. 2012
CD27	Low or normal IgG	Normal or reduced iNKT and memory B cells	yes	none	van Montfrans et al 2012; Salzer et al. 2013
Magnesium transporter 1 protein	Low or normal IgG	Low numbers of CD4 cells, normal numbers of iNKT cells; reduced levels of NKG2D on NK and T cells, impaired T cell killing of EBV transformed B cells, impaired NK cell function	yes	Bacterial sinusitis, chronic diarrhea	Li et al. 2011; Li et al. 2014
Coronin actin binding protein 1A	Normal or low normal IgG, normal or low IgM	Reduced numbers of CD4 T, CD8 T, naïve T cells, and B cells; low or absent iNKT cells	yes	Recurrent ear, nose, throat and upper respiratory tract infections	Moshous et al. 2013
LPS-responsive beige-like anchor protein	Normal or low IgG	Normal or low B cell numbers; normal T, NK cell numbers	yes	Usually none, may have recurrent otitis media and pneumonia	Alangari et al. 2012
Perforin	Normal IgG	Low numbers of B cells, CD4 cells, and neutrophils; impaired NK cell and CTL killing	no	none	Katano et al. 2004
Munc13–4	Low IgG	Low numbers of neutrophils, impaired NK cell and CTL killing	no	Recurrent upper airway infections	Rohr et al. 2010
Munc18–2	Low IgG	Low numbers of neutrophils, impaired NK cell and CTL killing	yes	Recurrent upper airway infections	Rohr et al. 2010
PI3K catalytic subunit 110δ: gain of function mutations	Low, normal, or high IgG	Low numbers of CD4 cells, memory T cells, and naïve CD4 T cells; increased CD8 cells and senescent effector CD8 T cells	yes	Sinus and pulmonary infections, CMV viremia	Lucas et al. 2013; Angulo et al. 2013
PI3K catalytic subunit 110δ: loss of function mutation	High IgG and IgM	Increased numbers of B cells, reduced memory B cell and diminished NK cell killing	yes	Recurrent otitis media and sinusitis	Kuehn et al. 2013

Protein	Humoral Immune Findings	Cellular Immune Findings	Chronic EBV viremia	Other Infections	Reference
CTP synthase 1	Normal or increased IgG	Lymphopenia, low CD4/CD8 ratios, low naïve CD4 T cells, low CD27 memory B cells; absent iNKT cells; increased effector memory T cells	yes	Herpesviruses, encapsulated bacteria	Martin et al. 2014
Serine threonine kinase 4	High IgG	Low numbers of CD4 cells, naïve T cells, B cells, and neutrophils	yes	Severe HPV and molluscum contagiosum infection, candida, recurrent bacterial and virus infections	Nehme et al. 2011; Abdollahpour et al. 2012
GATA binding protein 2	Normal IgG	Low numbers of B cells, CD4 T cells, NK cells, dendritic cells, and monocytes	yes	Severe HSV, VZV, CMV, HPV, non-tuberculous mycobacteria, fungal infections	Spinner et al. 2014
Minichromosome maintenance complex component 4	Normal IgG	Low numbers of NK cells, absent $CD56^{dim}$ NK cells	unknown	Respiratory infections, recurrent herpesvirus infections	Gineau et al. 2012; Eidenschenk et al. 2006
Fcγ receptor 3A	Normal IgG	Variable numbers of NK cells, but impaired function	unknown	Respiratory infections, severe H herpesvirus infections	deVries et al. 1996; Grier et al. 2012
Caspase recruitment domain-containing protein 11: gain of function mutations	Normal or slightly increased IgG, low IgM, reduced antibody response to polysaccharide-based vaccines	B cell lymphocytosis, normal T cell numbers	yes	Respiratory infections, sinusitis, otitis media, molluscum contagaiosum,	Snow et al. 2012

Abbreviations: iNKT, invariant NKT; HPV, human papillomavirus; PML, progressive multifocal leukoencephalopathy; CTL, cytotoxic T lymphocyte; CTP, cytidine 5’ triphosphate.

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