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Review Article

REVIEW ARTICLE

Immunodeficiencies that predispose to pathologies by human oncogenic γ-herpesviruses

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One sentence summary: The comparison of molecular pathways and pathologies during immunodeficiencies that predispose for uncontrolled EBV and KSHV infection reveals similarities and differences in cell mediated immune control, and suggests that latent transforming EBV infection of epithelial cells does not play a significant role in healthy virus carriers.

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ABSTRACT

Human γ-herpesviruses include the closely related tumor viruses Epstein Barr virus (EBV) and Kaposi sarcoma-associated herpesvirus (KSHV). EBV is the most growth-transforming pathogen known and is linked to at least seven human malignancies. KSHV is also associated with three human cancers. Most EBV- and KSHV-infected individuals fortunately remain disease-free despite persistent infection and this is likely due to the robustness of the immune control that they mount against these tumor viruses. However, upon immune suppression EBV- and KSHV-associated malignancies emerge at increased frequencies. Moreover, primary immunodeficiencies with individual mutations that predispose to EBV or KSHV disease allow us to gain insights into a catalog of molecules that are required for the immune control of these tumor viruses. Curiously, there is little overlap between the mutation targets that predispose individuals to EBV versus KSHV disease, even so both viruses can infect the same host cell, human B cells. These differences will be discussed in this review. A better understanding of the crucial components in the near-perfect life-long immune control of EBV and KSHV should allow us to target malignancies that are associated with these viruses, but also induce similar immune responses against other tumors.

Keywords: Epstein Barr virus; Kaposi sarcoma-associated herpesvirus; primary effusion lymphoma; Kaposi sarcoma; Hodgkin's lymphoma; Burkitt's lymphoma; hemophagocytic lymphohistiocytosis

INTRODUCTION

There are several human tumor viruses. These include Epstein Barr virus (EBV), Kaposi sarcoma-associated herpesvirus (KSHV), human papillomavirus, Merkel cell polyomavirus, hepatitis B virus, hepatitis C virus and human T-cell lymphotropic virus type 1 (Hopcraft and Damania 2017). Two of the seven human tumor viruses belong to the γ-herpesviruses, namely EBV or human herpesvirus 4, and KSHV or human herpesvirus 8 (Parkin 2006; Bouvard *et al.* 2009). Each of them contributes 1–2% to the 20% of infectious disease-associated cancer burden among all malignancies in humans. EBV is mainly associated with lymphomas and carcinomas of B and epithelial cell origin, respectively (Cesarman 2014), including Burkitt's lymphoma, in which the virus was originally identified (Epstein *et al.* 1965; Epstein, Achong and Barr 1964). However, epithelial cancers constitute the majority of the newly diagnosed 200 000 EBV-associated malignancies each year (Cohen *et al.* 2011). In contrast, KSHV is

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mainly associated with endothelial and B cell-derived malignancies (Chang *et al.* 1994; Cesarman 2014). The endothelial cell cancer Kaposi sarcoma (KS) is one of the acquired immune deficiency syndrome (AIDS)-defining illnesses in human immunodeficiency virus (HIV)-infected patients and KSHV was originally identified in this tumor (Chang *et al.* 1994). Both EBV and KSHV have co-evolved with humans and are part of the primate associated γ1- and γ2-herpesviruses, respectively (McGeoch 2001; Ehlers *et al.* 2010). Through this co-evolution they have both achieved a remarkable penetration of the human population, with EBV establishing persistence in more than 95% of the adult human population across the globe, while KSHV prevalence is more variable with over 50% seropositivity in equatorial Africa (Cesarman 2014). In light of this high prevalence, associated malignancies are still pretty rare and are likely to emerge from combinations of the viruses' growth-transforming capacities and the failure of the immune system to control the virus. In this regard, studies on the gene expression programs in healthy EBV and KSHV carriers and associated diseases that emerge in patients with immunodeficiencies can inform us as to which viral gene expression programs continuously threaten healthy EBV and KSHV carriers with tumorigenesis and which associated malignancies can be prevented by an intact immune system during persistent infections with these γ-herpesviruses for life.

EBV is the more transforming of the two viruses and readily immortalizes human B cells upon infection *in vitro* (Miller and Lipman 1973a,b). Eight latent EBV proteins, two clusters of EBV-encoded microRNAs (miRNAs) and two small non-translated RNAs (EBERs) out of a total of around 90 open reading frames are expressed in the resulting lymphoblastoid cell lines and this latency III gene expression pattern can also be found in naïve B cells of healthy EBV carriers (Babcock, Hochberg and Thorley-Lawson 2000; Palser *et al.* 2015). This latency gene expression program can also be found in EBV-associated large B cell lymphomas that primarily occur in immune-suppressed individuals, as in the case of post-transplant lymphoproliferative disease due to iatrogenic inhibition of the immune system to preserve a transplant or due to compromised immune reactivity upon HIV co-infection leading to immunoblastic lymphomas (Cesarman 2014). A much more restricted gene expression pattern with only one of the six nuclear proteins of EBV (EBNAs), the two latent membrane proteins and the non-translated RNAs expressed, can be found in germinal center B cells of healthy EBV carriers and in Hodgkin's lymphoma (Babcock and Thorley-Lawson 2000; Babcock, Hochberg and Thorley-Lawson 2000). A similar latency II gene expression pattern is also found in many of the EBV-associated epithelial cell cancers, like nasopharyngeal carcinoma (Kutok and Wang 2006). Finally, Burkitt's lymphoma, the tumor that EBV was discovered in, expresses only EBNA1 and the non-translated RNAs, but compensates for the loss of the pro-proliferative expression of the other latent EBV gene products with translocations of the cellular oncogene c-*myc* into the immunoglobulin loci (Cesarman 2014). This latency I gene expression pattern is also found in homeostatically proliferating memory B cells of healthy EBV carriers and in the 10% of EBV-positive gastric carcinomas (Hochberg *et al.* 2004; Kutok and Wang 2006). EBV persists in quiescent memory B cell compartments with only non-translated RNA expression (Babcock *et al.* 1998). This latency 0 in memory B cells might be reached upon B cell differentiation of latency III via latency II in a germinal center-dependent fashion or after early EBNA2-driven proliferation without the expression of *EBNA3A* or *EBNA3C* viral oncogenes (Murer *et al.* 2018). It can reactivate from this persistence reservoir upon B cell receptor cross-linking by cognate antigen (Binne, Amon and Farrell 2002) and lytic EBV replication is found in the resulting plasma cells of healthy EBV carriers (Laichalk and Thorley-Lawson 2005). Early lytic EBV gene products of the around 80 open reading frames of EBV replication are thought to support tumor microenvironment changes that are beneficial for the establishment of EBV-associated lymphomas (Hong *et al.* 2005; Ma *et al.* 2011; Antsiferova *et al.* 2014). Indeed, primary central nervous system lymphoma treatment benefitted from lytic EBV replication inhibition (Dugan *et al.* 2018). Therefore, premalignant EBV gene expression programs are carried by B cells of healthy EBV carriers, but it remains unclear if epithelial cell infection and especially latent EBV gene expression in epithelial cells as in nasopharyngeal and gastric carcinoma contributes to persistent infection by this γ-herpesvirus in humans.

Similar to EBV, KSHV is thought to be transmitted by saliva exchange (Pauk *et al.* 2000) and can be found in B cells of KSHV carriers (Ambroziak *et al.* 1995). However, latent and lytic KSHV gene expression are much less segregated in the KSHV-associated malignancies KS, primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD) (Schulz and Cesarman 2015). Most of the tumor cells express the classical KSHV latency gene products [latency-associated nuclear antigen (LANA), viral D-type cyclin (vCyclin) and viral FLICE inhibitory protein (vFLIP), K15 and viral miRNAs] (Dittmer and Damania 2016; Abere *et al.* 2017). However, a small percentage of the tumor cells do express lytic proteins including K1, K15, viral interleukin (IL)-6 and viral G protein-coupled receptor (Dittmer and Damania 2016). These lytic proteins are thought to contribute to tumor growth in a paracrine fashion by increasing angiogenesis and cell proliferation (Schulz and Cesarman 2015). Furthermore, inhibiting lytic KSHV replication might prevent the development of KS (Martin *et al.* 1999), possibly eliminating the inflammatory tumor-nurturing microenvironment, similar to the contribution of early lytic EBV replication for virus-associated lymphomagenesis (Dugan *et al.* 2018). Lytic EBV replication also seems to be important for PEL formation, a tumor entity that in up to 90% of cases contains both KSHV and EBV (McHugh *et al.* 2017). This is also consistent with plasma cell differentiation being associated with lytic EBV replication (Laichalk and Thorley-Lawson 2005) and KSHV infection or the KSHV latent genes *vFLIP* and *LANA* driving immunoglobulin M λ light chain-expressing plasma cell accumulations (Ballon *et al.* 2011; Hassman, Ellison and Kedes 2011; Sin and Dittmer 2013; Sin *et al.* 2015), reminiscent of MCD (Du *et al.* 2001). Thus, for both EBV and KSHV, B cells are proposed as the latency reservoir, and both lytic as well as latent gene products seem to contribute to tumorigenesis by these two human γ-herpesviruses. However, the role that epithelial and endothelial cell infection play for EBV and KSHV infection, respectively, remains unclear. We propose that immunodeficiencies caused by monogenic mutations or co-infections can at least document to what extent these non-hematopoietic infections by the two human γ-herpesviruses occur and by which means immune control of the different pre-malignant EBV and KSHV reservoirs is maintained.

IMMUNODEFICIENCIES THAT PREDISPOSE FOR EBV-ASSOCIATED DISEASES

Lymphomas and especially those associated with EBV are considered AIDS-defining diseases and constitute currently more than 50% of cancers that are associated with HIV co-infection (Simard and Engels 2010; Simard, Pfeiffer and Engels 2011). While non-Hodgkin's lymphomas, primarily latency III tumors,

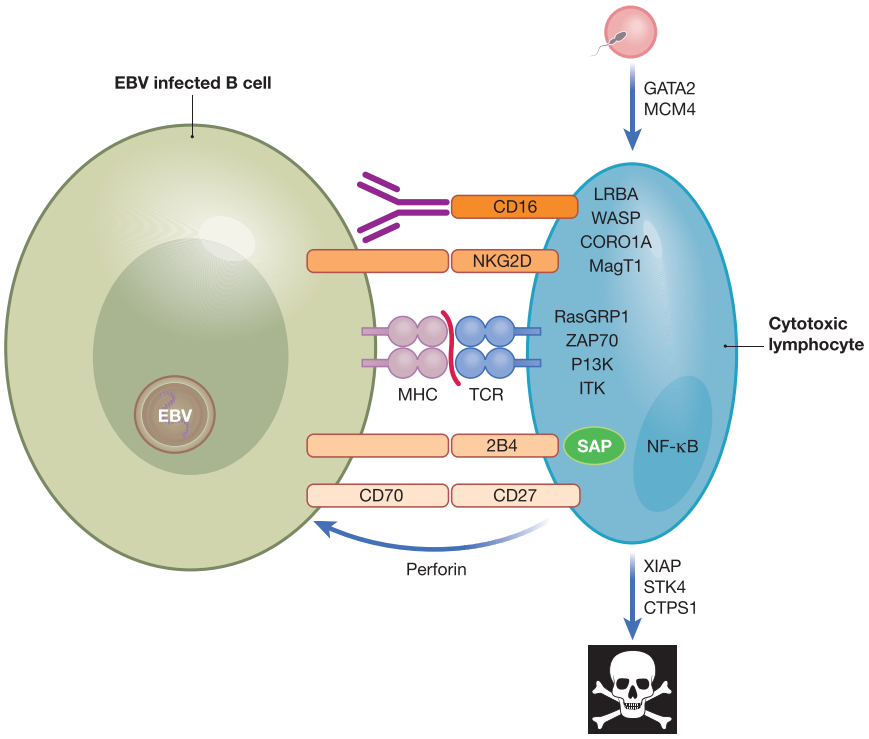

Figure 1. Primary immunodeficiencies that compromise the function of cytotoxic lymphocytes and predispose for EBV-associated diseases. Immune control of EBV-infected B cells is compromised upon deficiencies in TCR signaling, co-stimulation, leucocyte development, lymphocyte cell death and cytotoxic effector functions. For TCR signaling, RasGRP1, ZAP70, PI3K and ITK are required during EBV-specific immune control. CORO1A and WASP deficiencies compromise actin cytoskeleton arrangements during EBV-specific immune control. GATA2 and MCM4 compromise the development of protective lymphocytes against EBV, and loss of XIAP, STK4 and CTPS1 accelerate their cell death. LRBA and MAGT1 influence the expression levels of co-receptors on cytotoxic lymphocytes, of which CD16, NKG2D, SLAM receptors like 2B4, which is compromised by SAP mutations, and CD27 are required for EBV-specific immune control. NF-κB is involved in the signaling of CD27 and NKG2D. Perforin-mediated cytotoxicity is crucial for EBV-specific immune control. TCR, T cell receptor.

have significantly decreased in incidence due to combined anti-retroviral therapy (cART), EBV-positive Hodgkin's lymphomas have rather increased in frequency (Carbone *et al.* 2014; Brugnaro *et al.* 2015). In addition, EBV-associated smooth muscle tumors are increased during HIV co-infection (McClain *et al.* 1995; Ehresman *et al.* 2018). In contrast, EBV-positive epithelial cell-derived malignancies, such as nasopharyngeal carcinoma, are not significantly increased in HIV-infected individuals (Melbye *et al.* 1996); even so, in most of these studies the prevalence of nasopharyngeal carcinoma was in general too low to draw firm conclusions (Shebl, Bhatia and Engels 2010; Zhang *et al.* 2011; Grulich and Vajdic 2015). However, lytic EBV replication can progress uncontrolled in tongue epithelium after AIDS development and then causes oral hairy leukoplakia (Becker *et al.* 1991). These observations during immune suppression caused by HIV-mediated $CD4^+$ T cell elimination seem to suggest that defective immune control allows for the emergence of EBV-associated non-Hodgkin's lymphomas and more rarely EBV-positive smooth muscle tumors and oral hairy leukoplakia, but not EBV-associated epithelial cell cancers like nasopharyngeal carcinoma. Thus, HIV-mediated $CD4^+$ T cell depletion does not seem to compromise immune control of a premalignant state of epithelial cell infection by EBV.

This picture is also mirrored by monogenic primary immunodeficiencies that predispose for EBV-associated pathologies, and affect primarily the development and function of cytotoxic lymphocytes (Cohen 2015; Tangye, Palendira and Edwards 2017; Münz 2017a) (Fig. 1). The affected patients present with a variety of EBV-associated diseases ranging from uncontrolled viremia, as in chronic active EBV infection (CAEBV), which often spreads from B cells to T and natural killer (NK) cells, EBV infection driven immunopathologies, like infectious mononucleosis and hemophagocytic lymphohistiocytosis (HLH), to EBV-associated malignancies, including lymphoproliferative diseases, non-Hodgkin's lymphomas, Hodgkin's lymphomas, smooth muscle tumors and EBV-associated Castleman's disease. Interestingly, again no increased incidence of EBV-associated epithelial cell-derived cancers, such as nasopharyngeal carcinoma, has so far been reported. Furthermore, different monogenic deficiencies predispose for different EBV-associated pathologies, which might pinpoint the protective role of individual immune pathways in the control of distinct virus-induced diseases. Along these lines, deficiencies in the effector machinery of cytotoxic lymphocytes, affecting NK and non-classical innate as well as classical T cell populations, result in EBV-driven HLH immunopathologies (Katano *et al.* 2004; Rohr *et al.* 2010; Cohen *et al.* 2015). The respective loss of cytotoxicity compromises either perforin itself or the degranulation machinery for cytotoxic granules, like Munc13-4 and 18-2 (Table 1).

Of similar severity are GATA2 loss-of-function mutations that affect the development of multiple leucocyte populations, including NK and $CD4^+$ T cells (Cohen 2017). These patients present with CAEBV, HLH and EBV-positive smooth muscle tumors. In contrast EBV-associated lymphoproliferations develop when just one cytotoxic lymphocyte population is compromised. This is for example the case for loss-of-function mutations in the minichromosome maintenance complex component 4 (MCM4), which compromises NK cell development

Table 1. Primary immunodeficiencies that predispose for EBV-associated diseases.

Affected protein 'name of syndrome'	EBV-associated diseases	Innate immune system changes	Adaptive immune system changes	References
Cytotoxic machinery				
Perforin 'FHL2'	HLH, EBV VIR	Low neutrophils, compromised NK cell killing	Compromised T cell killing	Katano *et al.* 2004
Munc13-4 'FHL3'	EBV VIR	Low neutrophils, compromised NK cell killing	Compromised T cell killing	Rohr *et al.* 2010
Munc18-2 'FHL5'	EBV VIR, EBV NHL	Low neutrophils, compromised NK cell killing	Compromised T cell killing	Rohr *et al.* 2010; Cohen *et al.* 2015
Leucocyte development				
GATA2 'MonoMac'	IM, EBV SMT, EBV VIR, HLH	Low NK, DC and monocytes	$CD4^+$ T cell lymphopenia	Biron, Byron and Sullivan 1989; Mace et al. 2013
MCM4	EBV NHL	Low NK	–	Eidenschenk *et al.* 2006; Gineau *et al.* 2012
TCR signaling				
ITK	EBV HL, HLH	Loss of NKT	$CD4^+$ T cell lymphopenia	Huck *et al.* 2009; Linka *et al.* 2012
PI3K 110δ 'PASLI, APDS'	EBV NHL, EBV VIR	Compromised NK cell killing	$CD4^+$ T cell lymphopenia	Angulo *et al.* 2013, Kuehn *et al.* 2013; Lucas *et al.* 2014
RasGRP1	EBV NHL	Loss of NKT	$CD4^+$ T cell lymphopenia	Salzer *et al.* 2016; Winter *et al.* 2018
ZAP70	EBV NHL	Loss of NKT	$CD4^+$ T cell lymphopenia, compromised $CD8^+$ T cell function	Hoshino *et al.* 2018
CORO1A	EBV NHL	Loss of NKT	$CD4^+$ and $CD8^+$ T cell lymphopenia	Moshous *et al.* 2013
Co-stimulation				
CD27	HLH, EBV NHL	Loss of NKT, compromised NK cell function	Compromised T cell function	Salzer *et al.* 2012; van Montfrans *et al.* 2012
CD70	EBV HL	Loss of NKT	Compromised B cell recognition by T cells	Alkhairy *et al.* 2015; Abolhassani *et al.* 2017; Izawa *et al.* 2017
CD16	EBV CD	Compromised NK cell function	–	de Vries *et al.* 1996; Grier *et al.* 2012
CTLA-4	EBV NHL	Low NK	Low T and B cells	Schwab *et al.* 2018
MagT1 'XMEN'	EBV NHL	Compromised NKG2D expression on NK cells	$CD4^+$ T cell lymphopenia, impaired B cell recognition by T cells	Li *et al.* 2011; Chaigne-Delalande *et al.* 2013; Dhalla *et al.* 2015
SAP 'XLP1'	EBV NHL, IM, HLH	Loss of NKT, compromised NK cell function	Compromised T cell function	Coffey *et al.* 1998; Nichols et al. 1998; Sayos et al. 1998; Sumegi et al. 2000; Booth et al. 2011; Pachlopnik Schmid et al. 2011
NF-κB1	EBV VIR, EBV NHL	–	Compromised T cell function	Boztug *et al.* 2016; Schipp *et al.* 2016
LRBA	EBV NHL, EBV VIR	–	–	Alangari *et al.* 2012
Cell death				
XIAP 'XLP2'	HLH, IM	Low NKT	Compromised T cell survival after activation	Rigaud *et al.* 2006; Pachlopnik Schmid et al. 2011; Speckmann *et al.* 2013
STK4	EBV NHL	Low neutrophils	$CD4^+$ T cell lymphopenia	Abdollahpour *et al.* 2012; Nehme *et al.* 2012
Cell proliferation				
CTPS1	IM, EBV NHL	Loss of NKT	$CD4^+$ T cell lymphopenia	Martin *et al.* 2014

IM, infectious mononucleosis; EBV VIR, EBV viremia; EBV NHL, EBV-associated non-Hodgkin's lymphoma; EBV HL, EBV-positive Hodgkin's lymphoma; EBV CD, EBV-positive Castleman's disease; EBV SMT, EBV-associated smooth muscle tumor.

and leads to absence of CD56^{bright} NK cells (Eidenschenk *et al.* 2006; Gineau *et al.* 2012).

Similarly, compromised as well as hyperactive T cell receptor signaling leads primarily to EBV-associated lymphomas. The signaling components, which are affected by mutations that predispose for EBV-associated diseases, are IL-2 inducible T cell kinase (ITK), phosphoinositide 3-kinase (PI3K) 110δ (both loss- and gain-of-function mutations), the guanine nucleotide exchange factor RasGRP1, caspase recruitment domain-containing protein 11 (CARD11), phospholipase Cγ1, which is affected by deficient Mg^{2+} influx due to mutations in the magnesium transporter MAGT1, and ZAP70 (Huck *et al.* 2009; Li *et al.* 2011; Stepensky *et al.* 2011; Linka *et al.* 2012; Mansouri *et al.* 2012; Snow *et al.* 2012; Angulo *et al.* 2013; Chaigne-Delalande *et al.* 2013; Kuehn *et al.* 2013; Ghosh *et al.* 2014; Lucas *et al.* 2014; Bienemann *et al.* 2015; Cipe *et al.* 2015; Dhalla *et al.* 2015; Patiroglu *et al.* 2015; Salzer *et al.* 2016; Brigida *et al.* 2017; Hoshino *et al.* 2018; Latour and Winter 2018; Winter *et al.* 2018). In addition, loss of the ability for cytoskeletal rearrangement by actin at immune synapses for efficient T cell receptor signaling due to Coronin actin binding protein 1A (CORO1A) deficiency also predisposes for EBV-associated lymphoproliferations (Moshous *et al.* 2013).

NK and cytotoxic T cell function can also be compromised by deficient NK cell receptor or T cell co-receptor expression or signaling. Along these lines mutations in CD16, CTLA-4, CD27 and its ligand CD70, as well as in the adaptor molecules for the co-stimulatory SLAM family (SAP), including 2B4, and compromised NKG2D expression due to MAGT1 mutations have been found to predispose for EBV-associated lymphomas (de Vries *et al.* 1996; Grier *et al.* 2012; Salzer *et al.* 2012; van Montfrans *et al.* 2012; Chaigne-Delalande *et al.* 2013; Alkhairy *et al.* 2015; Abolhassani *et al.* 2017; Izawa *et al.* 2017; Schwab *et al.* 2018). Interestingly, nuclear factor (NF)-κB1 deficiency, which is required for SAP and CD27 signaling, was also reported to be associated with EBV-driven lymphoproliferations (Boztug *et al.* 2016; Schipp *et al.* 2016). Moreover, lipopolysaccharide-responsive beige-like anchor (LRBA) protein regulates co-receptor internalization and its mutations have been found associated with EBV-induced lymphoproliferations (Alangari *et al.* 2012). However, the pathological manifestations of EBV infection differ between these different primary immunodeficiencies that affect co-stimulation. In particular, CD16 deficiency leads to EBV-positive Castleman's disease and all patients with CD70 deficiency have so far presented with EBV-positive Hodgkin's lymphoma, while CD27 loss leads to more overt lymphoproliferations and sometimes even HLH.

A final category of primary immunodeficiencies that predispose for symptomatic EBV infection are mutations that affect survival and expansion of cytotoxic lymphocytes. These include deficiencies in serine/threonine kinase 4 (STK4), cytidine triphosphate synthase 1 (CTPS1) and X-linked inhibitor of apoptosis (XIAP) (Rigaud *et al.* 2006; Abdollahpour *et al.* 2012; Nehme *et al.* 2012; Speckmann *et al.* 2013; Martin *et al.* 2014). CD27 and CD70 also play important roles in this cytotoxic lymphocyte expansion (Latour and Winter 2018). Depending on the role of these proteins in EBV-transformed B cell expansion, their deficiencies either preferentially cause immunopathologies such as HLH (for XIAP mutations) or, when preferentially T cell expansion is affected, EBV-associated lymphoproliferative disease (for STK4 mutations).

Of these primary immunodeficiencies some have a particularly high penetrance of EBV diseases, including deficiencies in SAP, CD27 and CD70 (Coffey *et al.* 1998; Nichols *et al.* 1998; Sayos *et al.* 1998; Sumegi *et al.* 2000; Booth *et al.* 2011; Pachlopnik Schmid *et al.* 2011; Salzer *et al.* 2012; van Montfrans *et al.* 2012; Alkhairy *et al.* 2015; Abolhassani *et al.* 2017; Izawa *et al.* 2017).

For immune suppression by HIV co-infection and the primary immunodeficiencies in cytotoxic effector function, cytotoxic lymphocyte differentiation, T cell receptor signaling, lymphocyte co-stimulation, expansion and survival, however, affected patients have so far not been described to suffer from epithelial cell cancers. This suggests that latent EBV infection either does not occur in epithelial cells of healthy EBV carriers, or is not cell growth transforming, even in inflammatory settings like HIV co-infection and XIAP deficiency. Thus, the growth-transforming latency programs observed in nasopharyngeal carcinoma and the 10% of EBV-associated gastric carcinoma are most likely not a component of the EBV life cycle in healthy virus carriers.

IMMUNODEFICIENCIES THAT PREDISPOSE FOR KS

KS is the most common AIDS-associated cancer and in contrast to EBV, all of the KSHV-associated malignancies are considerably increased in the HIV-infected population, although these cancers can be seen in HIV-negative individuals as well (Bouvard *et al.* 2009; Powles *et al.* 2009a,b; Yarchoan and Uldrick 2018). Interestingly, as for EBV latency III tumors, KS incidence has declined and stabilized under cART (Krown *et al.* 2008), while PEL and MCD development seem to be rather unaffected, similar to EBV-associated Hodgkin's lymphoma. KS also occurs during iatrogenic immune suppression after transplantation, especially under cyclosporine or tacrolimus (FK506) inhibition of calcineurin to prevent NF-AT activation downstream of T cell receptor signaling (Stallone *et al.* 2005; Riva *et al.* 2012; Jackson *et al.* 2016), further suggesting that KSHV infection needs to be continuously immune-controlled during persistent infection.

Despite the increased frequency of PEL and MCD during immune suppression, KSHV-positive B cell malignancies have so far not been found associated with monogenic immunodeficiencies, although KSHV-positive MCD has been reported in a child born to consanguineous parents (Leroy *et al.* 2012). Only KSHV-negative EBV-positive PELs have been reported as individual cases in combined and common variable immunodeficiencies (CVIDs) (Hisamoto *et al.* 2003; Lam *et al.* 2016), suggesting that EBV-associated plasmacytomas are very efficiently controlled by the immune system (Chatterjee *et al.* 2017). In contrast, monogenic primary immunodeficiencies have been characterized that predispose either for isolated KS development or more generally for susceptibility to infectious diseases, including KS (Table 2). KS has been described in the context of CVID. CVID is a heterogeneous class of primary immune deficiencies associated with reduced level of serum antibodies, absent or impaired antibody production, and frequent infections. KS has been demonstrated to occur in the context of CVID (Wheat *et al.* 2005; Gangemi, Allegra and Musolino 2015; Stenton *et al.* 2016). Furthermore, mutations in both stromal interaction molecule 1 (STIM1) and tumor necrosis factor receptor superfamily member 4 (TNFRSF4, OX40 or CD134) predispose selectively for KS in children (Byun *et al.* 2010; Byun *et al.* 2013) (Fig. 2). STIM1 assists in the Ca^{2+} mobilization after T cell receptor signaling, while OX40 is a co-stimulatory receptor on non-classical innate and classical T cells as well as NK cells, and is expressed upon their activation (Saheki and De Camilli 2017; Buchan, Rogel and Al-Shamkhani 2018). OX40 ligand (OX40L) is expressed on many hematopoietic cells upon their activation, but can also be

Table 2. Primary immunodeficiencies that predispose for KSHV-associated diseases.

Affected protein 'name of syndrome'	KSHV-associated disease	Innate immune system changes	Adaptive immune system changes	References
Th1 effector function				
IFNγR1	KS	–	$CD4^+$ T cell lymphopenia	Camcioglu *et al.* 2004
STAT4	KS	–	Decreased Th1 differentiation	Aavikko *et al.* 2015
TCR signaling				
STIM1	KS	–	Deficient T cell activation due to compromised Ca^{2+} influx	Byun *et al.* 2010
WASP 'Wiskott Aldrich syndrome'	KS	–	$CD4^+$ T cell lymphopenia, deficiency in immunological synapse formation	Picard *et al.* 2006
Co-stimulation				
OX40	KS	–	Impaired effector memory T cell populations	Byun *et al.* 2013
MagT1 'XMEN'	KS	Decreased NK cell maturation and NKG2D expression	Compromised T cell receptor signaling	Brigida *et al.* 2017

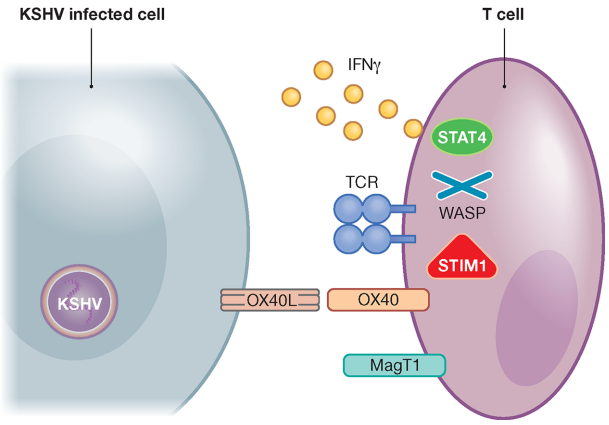

Figure 2. Primary immunodeficiencies that compromise the function of Th1-polarized lymphocytes and predispose for KSHV-associated diseases. Immune control of KSHV-infected endothelial cells is compromised upon deficiencies in TCR signaling, co-stimulation and Th1 cytokine functions. STIM1 is required for TCR signaling during KSHV-specific immune control. WASP deficiencies compromise actin cytoskeleton arrangements thereby hindering immune control of KSHV. OX40 is required to keep KSHV in check and MAGT1 allows co-receptor maintenance on lymphocytes. IFNγ plays an essential role in the immune surveillance of KSHV and STAT4 is required for its Th1-polarizing signaling. TCR, T cell receptor.

induced on endothelia and smooth muscle cells. This suggests that the OX40 interaction with OX40L is required for immune surveillance of KSHV-infected endothelial cells, which otherwise can give rise to KS. It is much less clear why STIM1 deficiency selectively predisposes for KS. In addition, KS has been found in children with mutations in interferon (IFN) γR1, STAT4, MAGT1 and Wiscott Aldrich syndrome protein (WASP) (Camcioglu *et al.* 2004; Picard *et al.* 2006; Aavikko *et al.* 2015; Brigida *et al.* 2017). While deficiencies in IFNγR1 and signaling for IFNγ production involving IL-12 are primarily known to confer susceptibility to mycobacterial infection (Jouanguy *et al.* 1996; Newport *et al.* 1996; Zhang *et al.* 2008; Boisson-Dupuis *et al.* 2015), IFNγR1 deficiency and diminished Th1 differentiation ability due to STAT4 mutations that compromise IL-12 signaling for IFNγ production seem to also predispose individuals towards developing KS (Camcioglu *et al.* 2004; Aavikko *et al.* 2015). This suggests an important role for IFNγ in KSHV-specific immune control. WASP deficiencies compromise actin stabilization of immunological synapse formation for T cell activation and have also been described to compromise EBV-specific immune control. Patients with WASP mutations have been reported to develop EBV-associated lymphomas (Du *et al.* 2011). Furthermore, MAGT1 deficiencies have been proposed to compromise both NK- and T cell-mediated immune control of EBV (Chaigne-Delalande *et al.* 2013), in addition to predisposing individuals to developing KS (Brigida *et al.* 2017). Finally, KS has also been reported in a patient with Good's syndrome, which is a combined B- and T-cell immunodeficiency that occurs in association with a thymoma (Agarwal *et al.* 2011). Thus, T cell-mediated immune control seems essential for maintaining asymptomatic KSHV infection. In contrast to EBV, however, both endothelial as well as B cell infection by this virus need to be immune controlled with cell-mediated immunity. In addition, IFNγ production by T cells might be more important for KSHV- than for EBV-specific immune control.

DIFFERENCES IN THE REQUIREMENT FOR IMMUNE SURVEILLANCE OF INFECTED NON-HEMATOPOIETIC COMPARTMENTS DURING PERSISTENT EBV AND KSHV INFECTION

The studies discussed above suggest an essential role for cytotoxic classical and innate non-classical T as well as NK cells in

the immune control of EBV and KSHV. For EBV this was indeed functionally tested in preclinical *in vivo* models of mice with reconstituted or adoptively transferred human immune system compartments, and by therapeutic transfer of EBV-specific T cell populations into patients with EBV-associated malignancies (Münz 2017a,b).

During primary EBV infection in patients with infectious mononucleosis and mice with reconstituted human immune system components there is an expansion of NK cells (Williams *et al.* 2005; Balfour *et al.* 2013; Chijioke *et al.* 2013; Azzi *et al.* 2014; Dunmire *et al.* 2015). In these mice, NK cell depletion during EBV infection leads to increased viral loads and tumorigenesis (Chijioke *et al.* 2013; Landtwing *et al.* 2016). The expanding NK cells primarily control lytic EBV infection *in vivo* and *in vitro* (Pappworth, Wang and Rowe 2007; Chijioke *et al.* 2013; Azzi *et al.* 2014). In addition to NK cells, Vγ9Vδ2 innate T cells expand in up to 50% of infectious mononucleosis patients (Djaoud *et al.* 2017). Expansion or adoptive transfer for these Vγ9Vδ2 T cells in mice with reconstituted human immune system compartments reduces tumorigenesis after EBV-transformed B cell transfer or infection (Xiang *et al.* 2014; Zumwalde *et al.* 2017). Primarily, latency I Burkitt's lymphoma cells stimulate these Vγ9Vδ2 T cells by producing their mevalonate metabolite ligands and expressing the BTN 3A1 (CD277) restriction element (Djaoud *et al.* 2017). As a third innate lymphocyte subset, NKT cells with the invariant Vα24-Jα18/Vβ11 T cell receptor can restrict EBV-associated lymphomas in mice with reconstituted human immune system components (Yuling *et al.* 2009). They seem to primarily recognize latency II Hodgkin's lymphoma cells (Chung *et al.* 2013).

Apart from these innate lymphocyte populations, CD4$^+$ and CD8$^+$ $\alpha\beta$ T cells are thought to mediate EBV-specific immune control. Depletion of T cells or their CD4$^+$ and CD8$^+$ subpopulations individually increases EBV viral loads and associated lymphomagenesis in mice with reconstituted human immune system components (Strowig *et al.* 2009; Yajima *et al.* 2009; Chijioke *et al.* 2015). Adoptive transfer of EBV-specific T cell lines was successfully used for the treatment of several EBV-associated lymphomas in patients (McLaughlin *et al.* 2017). In addition, adoptive transfer of T cells against distinct EBV antigens provided clinical benefits in EBV infected mice with reconstituted human immune system components and patients (Icheva *et al.* 2013; Antsiferova *et al.* 2014). These studies corroborate the findings in immunodeficient patients that cytotoxic innate and adaptive lymphocytes mediate immune control of EBV, but so far no similar information on the function of cell-mediated immune control against KSHV infection *in vivo* is available, although immune restriction of KSHV infection by innate immune pathways has been demonstrated in cell culture studies (West and Damania 2008; West *et al.* 2011; Ma *et al.* 2015). This knowledge gap is mostly due to the absence of a preclinical *in vivo* model of persistent KSHV infection and associated pathologies, and to the lack of clinical trials of adoptive T cell transfer into patients with KSHV-associated malignancies.

Such an *in vivo* model to test these immunotherapeutic modalities might now be at hand. While previously transient infection was reported (Wang *et al.* 2014), only co-infection with EBV allows for persistence of KSHV infection in mice with reconstituted human immune system components (McHugh *et al.* 2017). Double-infection leads to PEL-like lymphoma formation with characteristic plasma cell differentiation. This in turn results in elevated lytic EBV replication and co-infection with a mutant EBV virus that cannot switch into lytic infection abolishes increased lymphomagenesis upon KSHV co-infection. This model should now allow us to dissect EBV- and KSHV-specific cell-mediated immune control in the same mice with reconstituted human immune system components to better understand the differences and similarities of cell-mediated immune control of these two oncogenic γ-herpesviruses, and how the genes affected by primary immunodeficiencies compromise it.

These models allow only lymphotropic infections by KSHV and EBV. Therefore, it is important to know if and how infection of non-hematopoietic cells contribute to the life cycle of these γ-herpesviruses. One criterion for the importance of a certain host cell is the adaptation of the virus to use specific entry receptors of the respective cell type. EBV and KSHV entry into B cells uses quite different receptors. Complement receptors 1 and 2 (CD35 and CD21) are used for EBV attachment and human major histocompatibility complex class II molecules are required as co-receptors for EBV entry into B cells (Fingeroth *et al.* 1984; Li *et al.* 1997; Ogembo *et al.* 2013). In contrast, KSHV seems to use dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin for entry into B cells (Rappocciolo *et al.* 2008). Curiously, both KSHV and EBV have been reported to use ephrin A2 receptor and the integrin $\alpha_v\beta_5$ for endothelial or epithelial cell infection, respectively (Akula *et al.* 2002; Garrigues *et al.* 2008; Chesnokova and Hutt-Fletcher 2011; Hahn *et al.* 2012; Chen *et al.* 2018; Zhang *et al.* 2018). Therefore, the entry mechanisms of EBV and KSHV do not seem to be specific for epithelial or endothelial cells. Most likely, establishment of latent KSHV infection in endothelial cells, and possibly lytic EBV replication in epithelial cells after entry, rather than differences in entry mechanisms seem to determine the non-hematopoietic tropism of these two γ-herpesviruses. Moreover, EBV entry into epithelial cells seems to prefer infection from the basolateral side (Tugizov, Berline and Palefsky 2003), and EBV lytic reactivation was suggested to occur only efficiently from epigenetically silenced viral DNA, requiring about 2 weeks of DNA methylation (Woellmer, Arteaga-Salas and Hammerschmidt 2012). Therefore, lytic EBV replication might only play a role for viral shedding into saliva and further transmission. Similarly, endothelial cell infection by KSHV might occur secondary to submucosal B cell infection after salivary transmission of KSHV. Therefore, the above suggested cell-mediated immune control of EBV and KSHV infection in B cells should also be relevant for secondary epithelial and endothelial cell infections, which most likely only amplify the lymphotropic infections by the two viruses.

While increased incidence of KS in the context of immune deficiencies argues for transforming KSHV infection of endothelial cells being present also during asymptomatic KSHV infection, the lack of increased epithelial cell tumors argues against latent epithelial cell infection being part of the EBV life cycle in healthy virus carriers.

CONCLUSIONS AND OUTLOOK

The comparison of the influence of immunodeficiencies on persistent EBV and KSHV infections reveals interesting insights into the life cycle and immune control of these tumor viruses in healthy virus carriers. Firstly, both are controlled by cell-mediated immunity and cause AIDS-defining malignancies in HIV-infected individuals (AIDS-associated EBV lymphomas, PEL, MCD and KS). However, cytotoxicity might be primarily responsible for restricting EBV, while lymphocyte-derived IFNγ production seems to contribute to KSHV-specific immune control. Secondly, this cell-mediated immune control seems to depend on different T cell receptor signaling and co-stimulatory components for T cells to control persistent EBV and KSHV infection. These include ITK, PI3K 110δ, ZAP70 and RasGRP1 for

T cell receptor signaling, or CD27, the SLAM receptor 2B4 and NKG2D for co-stimulation during EBV-specific immune control. For KSHV immune control, STIM1-assisted T cell receptor signaling and OX40-mediated co-stimulation seem to be more important. Thirdly, loss of these immune control components reveals in which cells the two oncogenic γ-herpesviruses need to be restricted to avoid EBV- and KSHV-associated pathologies. Surprisingly, transforming KSHV infection may be present in both B and endothelial cells from apparently healthy individuals, while EBV latent oncogene expression might be restricted to B cells.

These considerations suggest that transforming latent EBV infection that contributes to epithelial cell cancers like nasopharyngeal carcinoma and a subset of gastric carcinoma, constituting the majority of EBV-associated malignancies, does not readily occur in healthy virus carriers. Additional environmental factors and possible premalignant modifications of epithelial cells could render these susceptible to latent EBV infection. The characterization of these requirements and premalignant transformation should be important to understand and target EBV-associated epithelial cell cancers.

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