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Immune control of oncogenic γ-herpesviruses

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Abstract

Human γ-herpesviruses contain Epstein Barr virus (EBV), the first human tumor virus that was identified in man, and Kaposi Sarcoma associated herpesvirus (KSHV), one of the most recently identified human oncogenic pathogens. Both of these have co-evolved with humans to cause tumors only in a minority of infected individuals, despite their exquisite ability to establish persistent infections. In this review we will summarize the fine-tuned balance between immune responses, immune escape and cellular transformation by these viruses, which results in lifelong persistent, but asymptomatic infection with immune control in most virus carriers. A detailed understanding of this balance is required to immunotherapeutically reinstall it in patients that suffer from EBV and KSHV associated malignancies.

1. Innate immune control of EBV

Epstein Barr virus (EBV) is the prototypic oncogenic γ-herpesvirus. Despite its discovery in the most frequent Subsaharan childhood tumor, Burkitt's lymphoma, 51 years ago [1], it is carried by more than 90% of the human adult population as an asymptomatic persistent infection [2]. EBV infection and tumorigenesis is kept under control by cell-mediated immunity, which targets both the transforming latent and the virus producing lytic program of the virus. This comprehensive immune control of EBV is established by successive waves of innate and adaptive immune responses.

Immune detection of the large double-stranded DNA virus EBV occurs via plasmacytoid dendritic cells (pDCs). These antigen presenting cells (APCs) readily secrete type I interferon (IFN-α/β) upon detection of unmethylated viral DNA via the toll like receptor 9 (TLR9) [3–5]. IFN-α/β restricts EBV infection of human B cells during the first 24h after inoculation [6] and might be even more important for natural killer cell activation during EBV infection [4,7,8]. Even so pDCs are the primary APCs to detect EBV, their ability to

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prime EBV specific T cells remains unclear. In contrast, inflammatory monocyte-derived DCs are able to cross-present EBV antigen from infected B cells [9] and conventional DCs (cDCs), especially the minor $CD141^+$ cDC subset, recognize EBV encoded RNAs (EBERs) via TLR3 after their release from latently EBV infected B cells [10]. Therefore, both pDCs and cDCs get activated during lytic and latent EBV infection, respectively, to restrict infection initially and activate innate and adaptive lymphocytes.

Among the innate lymphocytes NK, NKT and γδ T cells might play a role in innate immune control of EBV [7,11–16]. In particular during symptomatic primary EBV infection, called infectious mononucleosis, NK cells have been found to expand [17,18]. Especially an early differentiated NK cell population accumulates and stays elevated up to six months in peripheral blood of infectious mononucleosis patients [13]. This NK cell subset is maintained at higher frequency in tonsils of EBV positive individuals [19]. These early differentiated NK cells preferentially recognize lytic EBV replicating cells, and NK cells control lytic EBV infection in mice with reconstituted human immune system components (HIS mice) [12,13]. In the absence of this NK cell-mediated immune control lytic EBV replication drives $CD8^+$ T cell lymphocytosis, causing infectious mononucleosis symptoms [12]. Interestingly, infectious mononucleosis affects more frequently adolescents that acquire EBV later in life [20] and the frequency of early differentiated NK cells declines during the first decade after birth [1]. In addition to this recognition of lytic EBV infection by innate lymphocytes, NKT and Vγ9Vδ2 T cells can target latently infected EBV transformed B cells (LCLs) [14,16]. EBV infection activates CD1d restricted invariant NKT cells [7,21]. These are able to kill LCLs and prevent EBV associated lymphomagenesis in HIS mice [14,15]. Furthermore, activated Vγ9Vδ2 T cells also limit LCL growth in vitro and in vivo via recognition by their TCR and the NKG2D receptor and via TRAIL and Fas dependent killing [16]. This limits lymphoproliferative disease after LCL transfer in vivo [22], but it remains unclear if and how Vγ9Vδ2 T cells get activated during EBV infection. Thus, innate lymphocyte compartments control both lytic and latent EBV infection with NK and NKT as well as γδ T cells, respectively.

2. Adaptive immune control of EBV

Comprehensive immune control of latent and lytic EBV infection is long-term maintained by T cell responses, while B cell responses are used for diagnostic purposes, but can be absent in healthy virus carriers [2,23]. Both latent and lytic EBV antigens are recognized by $CD4^+$ helper and $CD8^+$ cytotoxic T cells [2]. However, distinct hierarchies for antigen specificity of these T cells exist with $CD4^+$ T cells most consistently recognizing EBV nuclear antigen 1 (EBNA1) and late lytic antigens, while $CD8^+$ T cells mainly recognize the EBNA3 proteins and immediate early as well as early lytic EBV antigens [24–26]. Both $CD4^+$ and $CD8^+$ T cells contribute to EBV specific immune control and primarily $CD8^+$ T cells prevent EBV induced lymphomas in HIS mice [12,27]. Furthermore, adoptive transfer of EBV specific T cell lines is clinically used to treat some EBV associated lymphomas, primarily post-transplant lymphoproliferative disease (PTLD) [25]. In these cell lines EBV antigen specificities that mediate protection are mostly ill-defined and it is assumed that T cells against transforming latent EBV antigens primarily mediate anti-tumor effects after adoptive transfer. Interestingly, recent studies have suggested that some EBV associated

malignancies might benefit from lytic EBV infection [28,29] and that lytic EBV antigen specific $CD4^+$ and $CD8^+$ T cells might be able to contribute to EBV associated lymphoma suppression [29,30]. In good agreement, plasma EBV viral loads, which might in part result from virus shedding, correlate with the occurrence and progression of some EBV associated malignancies, including PTLD, Hodgkin's lymphoma and nasopharyngeal carcinoma [31–33]. Thus a comprehensive T cell mediated immune control of both latent and lytic EBV infection might not only be required to establish low viral loads in healthy EBV carriers, but also to prevent EBV associated malignancies.

In order to persist, EBV employs a variety of immune escape mechanisms against these comprehensive T cell responses, and the main strategies differ between latent and lytic EBV infection [34] (Figure 1). During latent infection EBV protein down-regulation is the main strategy. For example, EBNA1 translation is limited by its RNA structure and, therefore, barely enough T cell epitopes can be presented on MHC class I molecules for $CD8^+$ T cell recognition [35,36]. Furthermore, EBV persists in memory B cells, in which all EBV protein expression has been down-regulated [37]. In contrast during lytic replication, when the virus needs to express a large number of proteins to build its infectious particles, it employs active immune evasion. The lytic EBV proteins BARF1 and BPLF1 block differentiation and activation of inflammatory DCs for T cell priming [38,39]. BNLF2a and BILF1, which target antigen presentation to $CD8^+$ T cells by limiting peptide supply for MHC class I loading and internalization of the loaded complexes, compromise early and late EBV lytic antigen recognition, respectively [40]. Interestingly, the host-shutoff protein BGLF5 seemed to only minimally compromise this antigen presentation [40]. Finally, BZLF2 (gp42) and BCRF1 (vIL-10) inhibit $CD4^+$ T cell recognition of MHC class II complexes and their priming towards anti-viral Th1 cells as well as their effector functions [41,42]. Thus, EBV limits antigen expression and actively inhibits immune responses for immune evasion during latent and lytic EBV infection, respectively.

3. Innate immune control of KSHV

Kaposi's sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8), is the most recently identified human herpesvirus [43] and its namesake, Kaposi's sarcoma, is the most common cancer in untreated AIDS patients [44]. KSHV is also associated with two rare lymphoproliferative disorders: primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD) [45]. Like other herpesviruses, KSHV establishes lifelong infections in spite of host immune defenses. Both innate and adaptive immunity coordinate the control of KSHV in infected individuals [46–49]. On the other hand, inflammatory cytokines and immune cell infiltrates play a crucial role in the early stages of KS development [50,51]. Moreover, KSHV paradoxical immune reconstitution inflammatory syndrome, a rare but life-threatening complication of KS patients, is precipitated by immune reconstitution following the initiation of HAART [52]. Thus, the interplay between KSHV and host immune system plays an important role of KSHV-associated diseases.

The main target cells of KSHV are B cells and endothelial cells but monocytes and dendritic cells are also susceptible to infection. The engagement of pattern recognition receptors

(PRRs) in turn leads to signaling cascades, leading to the expression of IFNα/β and pro-inflammatory cytokines. Upon *de novo* infection of primary endothelial cells, KSHV genomic DNA is evident within IFNγ-inducible 16 (IFI16) DNA sensor-containing nuclear bodies and this phenotype is accompanied by IFI16-dependent inflammasome formation and caspase-1-mediated secretion of IL-1β [53], which may be particularly relevant to elevated levels of IL-1β and other cytokines in KS lesion [50,54]. RIG-I, a cytosolic RNA sensor, contributes to IFNβ production and suppression viral gene expression upon KSHV infection [8,55], which is, on the other hand, reduced by the ORF64 deubiquitinase activity-containing tegument protein [8]. The KSHV virion delivers the tegument protein, ORF45, which prevents the phosphorylation of IRF7 [56–61], and the RTA induces the proteasomal degradation of IRF3 and IRF7 by recruiting the RTA-associated ubiquitin E3 ligase [62,63]. KSHV encodes an orthologue of miR-155 designated miR-K12-11, which targets IKKε mRNA for degradation, resulting in the reduced IKKε-mediated IRF3 and IRF7 phosphorylation [64–66]. One of the particular features of the KSHV genome is the presence of four homologues of the IRF family of proteins. Interestingly, three of these gene products (vIRF1, 2 and 3 but not 4) are known to block transcription of type I IFN genes or ISGs (reviewed in [67–69]). Finally, several KSHV genes including vIL6 and dUTPase-related proteins (ORF10, ORF11 and ORF54), have been shown to block the second phase of the IFN response by targeting the IFNAR1-JAK-STAT-ISGF3 pathway [70,71]. Thus, the fact that KSHV devotes much of its coding potential to the inhibition of the IFN response (Figure 2) underscores the importance of this pathway in the control of its infections. In contrast, EBV does not seem to dedicate such a substantial effort to actively interfering with the type I IFN response, possibly due to the fact that latent EBV infection with its heavily methylated DNA [72] allows persistence with limited activation of the respective IFN pathways.

Programmed cell death is one of the major innate defense mechanisms against viral infection and can be grouped into apoptosis, autophagic cell death, pyroptosis and necroptosis [73]. KSHV encodes several anti-apoptosis factors, including vBcl-2 [74], vFLIP [75], vIAP [74], K1 [76,77], vIRF4 [78], LANA [79] and miR-K10a [80]. Together, these viral factors target both the extrinsic and intrinsic apoptosis pathways. The sequestration of damaged organelles, protein aggregates or invading pathogens is orchestrated by a homeostatic process called autophagy. KSHV encodes three autophagy inhibitors (vBcl-2, K7 and vFLIP) that are each able to block distinct steps of autophagy. In contrast, EBV seems to benefit from autophagosomal membranes for its enveloping and efficient infectious particle production during lytic replication [81,82]. In summary, the identification and characterization of KSHV innate immune evasion genes has significantly advanced our understanding of viral persistent infection.

4. Cell-mediated immune control of KSHV

A hallmark of KS histology is abundant inflammatory infiltrates, including B cells, T cells, and monocytes. Thus, leukocyte trafficking and effector-target cell interactions are not only crucial for the innate and adaptive immune response to KSHV, but may also play a role in KS development. Several studies have examined Natural Killer (NK) cell-mediated control of KSHV infection and pathogenesis. AIDS-KS patients with ongoing symptoms have

reduced NK cell-mediated immunity compared to patients with indolent classic KS or normal blood donors [46,47]. Active KS is also associated with higher serum levels of cytokines and other secreted factors that dampens NK cell cytotoxicity [47]. While KSHV-infected cells can be predisposed to NK cell recognition, the virus is genetically equipped to circumvent this threat. Two KSHV-encoded, membrane-bound E3 ligases called K3 and K5 selectively remove proteins from the cell surface by triggering ubiquitin-dependent endocytosis [83–86]. K5 expression can reduce the surface expression of activating ligands such as MICA, MICB and AICL; and costimulatory molecules such as ICAM-1 and B7-2 [21,87,88]. As a result, NK cell-mediated cytotoxicity is significantly diminished in K5-expressing target cells [21]. In addition, ORF54 can induce downregulation of NKp44L [89], while miR-K12-7 targets MICB mRNA for degradation [90]. The role of inhibitory ligands is equally important: K5 induces selective downregulation of HLA-A and HLA-B, whereas K3 broadly targets HLA-A, B, C, and E [84]. Delayed expression of K3 may be important for maintaining the expression of inhibitory ligands such as HLA-C and HLA-E during the early stages of lytic replication. Thus, K3, K5, ORF54, miR-K12-7 and other viral factors may function in concert to subvert NK cell surveillance. In contrast, lytic EBV replication renders affected B cells susceptible for NK cell recognition [12,13]. As for the type I IFN response EBV latent infection, which does not seem to render B cells susceptible for NK cell recognition, allows viral persistence without actively compromising NK cell recognition.

Interestingly, the KSHV genome encodes pirated genes with putative roles in modulating leukocyte trafficking: CC chemokines (vMIP-I, vMIP-II, and vMIP-III), a cytokine (vIL-6) and MARCH family members (K3 and K5). Apart from their role in evading cell-mediated immunity, K3 and K5 also downregulate adhesion molecules such as PECAM-1, ICAM-1, ALCAM, VCAM and VE-cadherin [21,91–93], all of which are involved in transendothelial migration [94]. Another modulator of leukocyte trafficking is viral macrophage inflammatory protein II (vMIP-II). vMIP-II antagonizes CCR3 and CCR5 and blocks RANTES-induced chemotaxis of monocytes [95] and also binds to CX3CR1 and CCR5 and occludes the binding of fractalkine and RANTES, respectively, resulting in impaired NK cell chemotaxis [96]. KSHV also has several potential ways of obstructing neutrophil recruitment: for example, vIL-6 is essential for preventing recruitment of neutrophils in KSHV infected endothelial cells [97]. vCD200 is able to block neutrophil recruitment in mice treated with carrageenan, a compound used to induce neutrophil migration [98]. Together, these viral proteins may be part of strategy to divert harmful leukocytes and facilitate viral dissemination through a skewed inflammatory response. EBV seems to also compromise granulocyte maintenance and thereby similar to KSHV prevent inflammatory infiltrates by expression of the inhibitor of Colony Stimulating Factor-1 signaling BARF1 [38].

Although studies have identified KSHV-specific T cell responses largely from HIV-infected KS patients, knowledge of T cell epitopes and their value as targets for the control of KSHV pathogenesis is very limited. The highly active antiretroviral therapy can resolve KS by enabling anti-KSHV immune reconstitution, including NK cell restoration, and by rapidly affecting KSHV replication. However, Guihot et al. [99] has revealed that individuals with KS had less frequent KSHV-specific T cell responses than asymptomatic subjects,

regardless of their HIV status, CD4 count or KSHV load. Furthermore, not all KSHV-infected subjects develop associated diseases, suggesting that disease development is therefore likely dependent upon host factors, occurring through immune surveillance failure. Several studies have suggested certain HLA alleles might be associated with increased KSHV lytic replication and/or pathogenesis, but definitive associations have yet to be determined.

5. Conclusions

Herpesviruses are among the most ubiquitous and successful viruses known, and are thought to have co-evolved with their hosts during speciation. To achieve this, γ-herpesviruses devote multiple strategies and resources to manipulate key signaling pathways, ultimately promoting the survival of virus infected cell, immune evasion and tumorigenesis. However, EBV and KSHV subvert different checkpoints for survival of infected cells and their escape mechanisms from immune control are more similar during lytic than during latent infection.γ-herpesvirus-associated malignancies express varying subsets of virally-encoded antigens that potentially render them susceptible to virus-specific immunological responses. However, their effective immune evasion mechanisms present a considerable problem to immunotherapy. Thus, the ongoing study of immune modulatory activities will provide deeper understanding of the interactions between γ-herpesvirus and the immune system, and offer opportunities to overcome the obstacle for successful immunotherapy.

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• of special interest

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Highlights

- Innate lymphocyte responses determine the outcome of primary EBV infection.
- Different EBV immune evasins compromise early and late lytic antigen recognition by T cells.
- KSHV compromises interferon responses with several immune evasins.
- Different forms of cell death are targeted by KSHV gene products.
- Receptor down-regulation by KSHV blocks both innate and adaptive lymphocytes.

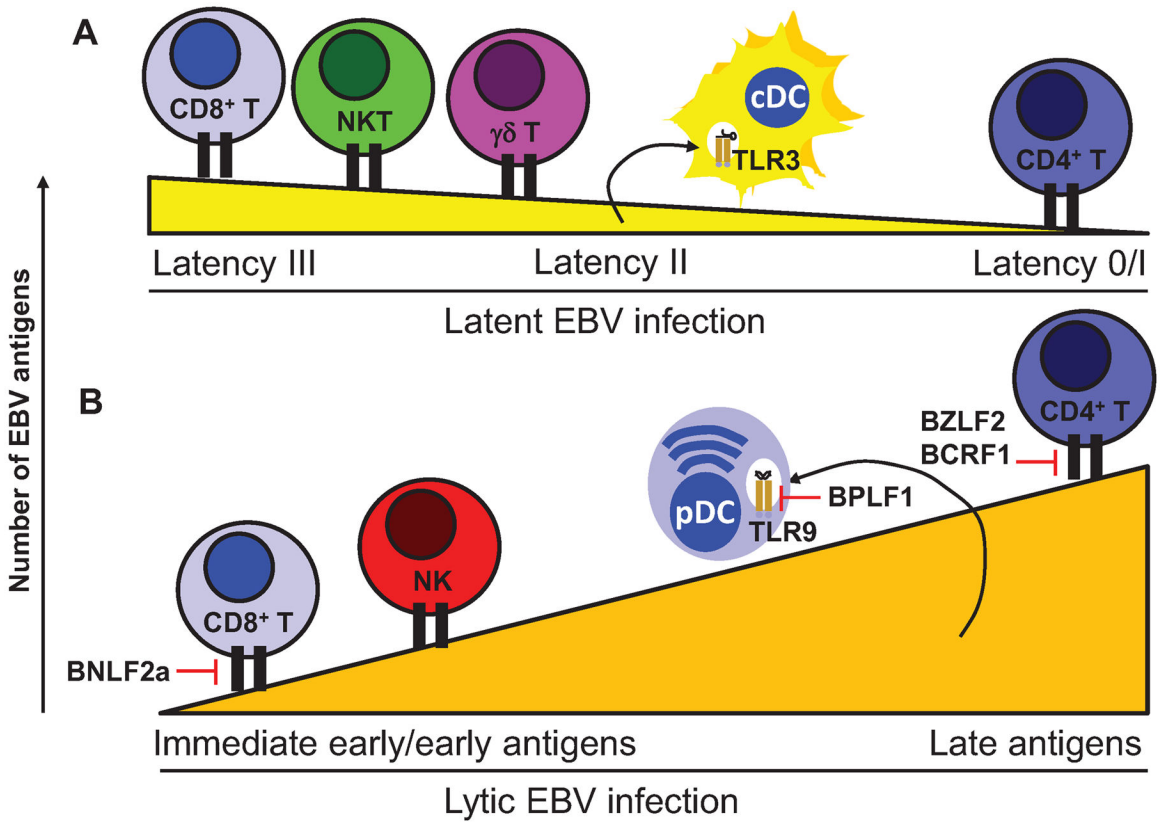

Figure 1. Comprehensive cell-mediate immune control of Epstein Barr virus infection

A) During latent infection viral antigen expression is down-regulated with successive B cell differentiation from 8 (latency III) to 3 (latency II) and 1 (latency I) or none (latency 0). While $CD8^+$ T cells strongly recognize the latency III antigens EBNA3s, $CD4^+$ T cells consistently recognize the latency I antigen EBNA1. NKT and γδ T cells also target latent EBV infection. EBV encoded RNAs (EBERs) are released from latently infected cells and stimulate conventional DCs (cDCs) via TLR3. **B)** During lytic infection successively more EBV gene products are expressed, starting from 2 immediate early antigens to more than 80 proteins. Immediate early and early lytic EBV antigens are preferentially recognized by $CD8^+$ T cells, while late lytic EBV antigens are mainly targeted by $CD4^+$ T cells. NK cells also recognize lytically EBV replicating cells and unmethylated EBV DNA of virus particles is sensed by plasmacytoid DCs (pDCs) via TLR9. BNLF2a blocks MHC class I restricted early lytic EBV antigen presentation to $CD8^+$ T cells and BZLF2 as well as BCRF1 MHC class II restricted late EBV lytic antigen presentation to $CD4^+$ T cells as well as their activity, respectively. BPLF1 is transferred with EBV particles to pDCs and blocks TLR activation.

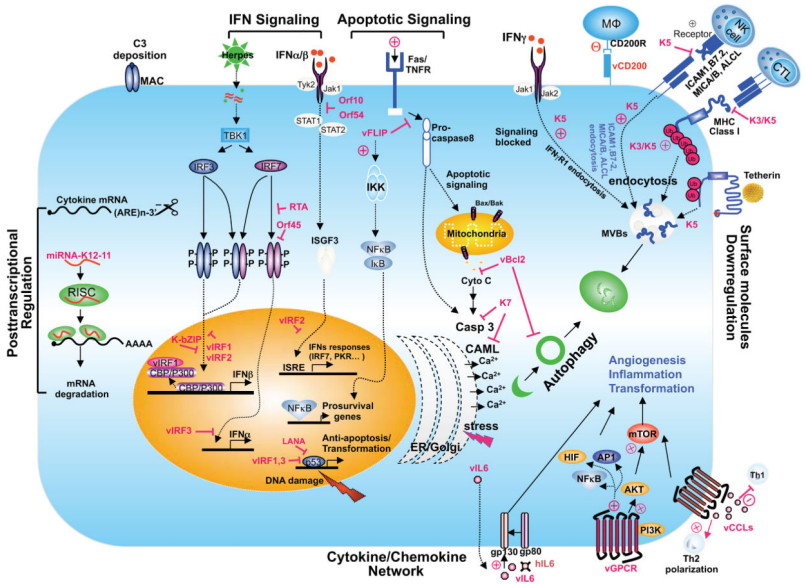

Figure 2. Overview of KSHV-mediated immune evasion

The KSHV proteins are marked with the red color. Detailed mechanisms are described in the text.