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Evasion of adaptive and innate immune response mechanisms by γ-herpesviruses

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Abstract

γ-Herpesviral immune evasion mechanisms are optimized to support the acute, lytic and the longterm, latent phase of infection. During acute infection, specific immune modulatory proteins limit, but also exploit, the antiviral activities of cell intrinsic innate immune responses as well as those of innate and adaptive immune cells. During latent infection, a restricted gene expression program limits immune targeting and cis-acting mechanisms to reduce the antigen presentation as well as antigenicity of latency-associated proteins. Here, we will review recent progress in our understanding of γ-herpesviral immune evasion strategies.

γ-Herpesviruses evolved elaborate strategies to evade and exploit host immune defense mechanisms to persist within their hosts. Innate immunity serves as the first line of defense against viral infection. The cellular intrinsic innate immune response is achieved through signal transduction that initiates pathways to alert neighboring cells (inflammatory response), to digest virus (autophagy), or to induce suicide of the infected cells (apoptosis or necrosis). The adaptive immune response, conveyed by T cells and B cells, directly targets virion particles or virus-infected cells for elimination by phagocytosis and cytotoxic cell-mediated lysis. As reviewed here, every aspect of the immune response is modulated by γ-herpesviruses.

Evasion of adaptive cellular immune responses

The fact that T cell depletion by HIV or by iatrogenic treatment leads to reactivation and proliferation of γ-herpesviruses, eventually leading to cancers such as KS, strongly suggests a key role of T cell control of γ-herpesvirus latency. The switch from acute to latent infection is reflected in the T cell response, which initially responds broadly to antigens highly expressed during lytic infection, but this short-lived response is then replaced with a long-term response to latency-associated antigens [1˙,2]. Limiting antigen expression is thus the first and foremost long-term T cell evasion mechanism (Figure 1). Moreover, latency

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levels are controlled by T cells since introduction of immunodominant epitopes into latent antigens reduces latent viral load [3,4].

Limiting T cell recognition of latently-infected cells seems paramount to maintaining γ-herpesvirus latency. In the complete absence of gene expression, T cells would not notice infected cells since they depend on MHC-I display of viral peptides. However, at least one genome maintenance protein is present in all latently infected cells and γ-herpesviruses have evolved ingenious methods to protect this Achilles heel from immune exposure [5]. The main strategy is to limit the availability of antigenic peptides from latency-associated proteins. On a population level, this is achieved by selecting against MHC-I binding motifs [6]. Within an infected organism, each virus evolved unique strategies to avoid alerting T-cells. EBNA-1 of EBV controls its own transcription, translation and degradation to achieve minimal protein turnover [5]. Central Gly-Ala repeats encoded by purine-rich codons are central for biosynthetic control [5]. In mature EBNA-1 these repeats reduce the rate of proteasomal degradation [7] in a position-dependent manner [8]. Gly-Ala repeats additionally inhibit EBNA-1 translation initiation thus inhibiting production of defective ribosomal products (DRiPs) considered the main source of MHC-I bound peptides [9,10˙, 11]. EBNA-1 mRNA translation might be further restricted by purine-biased codon usage [12].

Similar to EBNA-1, the major latency protein LANA-1 of KSHV contains central repeat regions that enhance LANA-1 stability and retard protein translation [13]. When fused to a heterologous antigen, the central repeat region of LANA-1 prevents antigen presentation [14]. Interestingly, inhibition of antigen presentation maps to the CR1 region whereas protein levels are regulated by CR2 and CR3 regions [15]. How LANA-1 regulates antigen processing in cis is thus still unclear. Even less is known about how non-human γ-herpesviruses escape T cell clearance during latency, although there is evidence that presentation of their respective ORF73 orthologs is limited [4,16].

During lytic infection, global stealth mechanisms limit T cell recognition of virus infected cells (Figure 1) Most γ-herpesviruses studied to date (with the notable exception of RRV) globally prevent MHC-I antigen presentation as part of the lytic gene expression program (for a recent review see [17]). EBV interferes with MHC-I antigen presentation at several levels: the protein BNLF2A inhibits peptide transport across the ER membrane by TAP [18,19,20¨] and thus inhibits antigen presentation of EBV-infected B cells to CD8+ T cells [21]. BNLF2A is a small 60AA protein that is post-translationally tail-anchored to the ER-membrane [22,23]. In addition, MHC-I at the cell surface is endocytosed by BILF1, a constitutively signaling G protein coupled receptor [24,25].

KSHV, MHV68 and rhesus fibromatosis herpesvirus (RFHV) hijack members of the MARCH transmembrane ubiquitin-ligase family found from yeast to man (for recent reviews see: [26,27]). MARCH proteins are transmembrane-spanning and locate to subcellular vesicular compartments, including the ER, Golgi, TGN and the plasma-membrane. They contain a RING-CH-domain structurally and functionally related to the RING-domain of E3 ubiquitin-ligases that catalyze the formation of poly-ubiquitin chains in the presence of the ubiquitin-activating and ubiquitin-conjugating enzymes. KSHV encodes

two MARCH-homologs, K3 and K5, whereas MHV68 and RFHV encode a single homolog [28]. All of these proteins share the ability to downregulate MHC-I molecules suggesting that inhibition of antigen presentation to CD8+ T cells is the central function of this protein family. In addition, co-stimulatory molecules such as ICAM-1 and B7-2 as well as NK-cell ligands and cell adhesion molecules are targeted, particularly by K5 (reviewed in Ref. [29]). More recently, it was also shown that KSHV-K5 downregulates receptor tyrosine kinases and the antiviral protein BST2/Tetherin [30,31]. *In vivo*, MHC-I-downregulation by the MARCH-homolog MK3 of MHV68 did not alter the course of primary infection whereas, in the absence of MK3, latent virus levels were reduced in the spleen, which could be rescued by CD8+ T cell depletion [32]. Thus, MHC-I inhibition promotes optimal seeding of latency sites but does not prevent the induction of a robust and broad T cell response during lytic infection [1˙,2]. Moreover, under extreme T cell pressure, the virus is able to mutate immunodominant epitopes [33˙].

In addition to CD8+ T cells, MHC-II restricted CD4+ T cells are a major factor in controlling the establishment and maintenance of γ-herpesvirus latency [34,35˙,36]. In mixed cultures of tonsillar B and T cells, lytic replication of KSHV was suppressed by CD4+ T cells, which were essentially driving the virus into latency [35˙]. The finding that CD4+ T cells lyse latently MHV68-infected B cells [36], suggests that CD4+ T cells directly control latency rather than through helper T cell function. CD4+ T cells seem to be continuously stimulated by infected B cells and dendritic cells [34]. However, γ-herpesviruses also counteract CD4+ T cell activation. The KSHV vIRF3 protein was shown to inhibit the class II transactivator (CIITA) which is essential for transcriptional induction of MHC-II and auxiliary proteins [37]. Consequently, PEL cells expressing vIRF3 are not recognized by LANA-1 specific MHC-II-restricted CD4+ cells [38]. Adding CIITA restored some recognition. In EBV-infected B-cells, MHC-II-dependent antigen presentation is limited by BZLF1-mediated downregulation of invariant chain (CD74) [39¨]. Similarly, KSHV-infected endothelial cells were not optimally recognized by MHC-II restricted human CD4+ T cells due to inhibition of IFNγ-induced MHC-II transcription [40]. In latently infected monocytes, KSHV additionally down-regulates co-stimulatory molecules, which could affect T cell priming [41]. In addition, KSHV-infected endothelial cells were shown to secrete a factor that inhibits MHC-II expression on neighboring cells [40]. This might aid KSHV to prevent T cell stimulation by non-infected APC cross-presenting viral antigens.

Evasion of cell-intrinsic innate immune responses

Evasion of apoptosis

Extracellular apoptosis stimuli induce the oligomerization of death receptors whereas intracellular ‘danger’ signals perturb mitochondrial homeostasis. The death-inducing signal complex (DISC) and the permeabilization of mitochondrion membrane are key checkpoints of extrinsic and intrinsic pathway, respectively. To circumvent apoptosis, γ-herpesviruses express viral FLIP (vFLIP) and Bcl-2 (vBcl-2) homologs during the latent and lytic phase [42] (Figure 2). Death receptor-mediated apoptosis (triggered by CD95 and TNFa) delivered by cytotoxic T cells is counteracted by vFLIP via interfering with the assembly of DISC. Counterintuitively, vFLIP potently activates NFkB, which effectively enables the survival of

KSHV-infected lymphoma cells [43 47]. Studies using cultured cells and transgenic mouse models demonstrated that vFLIP activated the IKK complex and was implicated in KSHV-associated lymphoproliferative diseases [47 51]. Surprisingly, vFLIP of herpesvirus saimiri was shown to be dispensable for viral replication, transformation, and pathogenesis in a primate model [52]. It would be interesting to examine the roles of vFLIP in the infection and pathogenesis of RRV using nonhuman primate models.

During productive lytic infection, processes of viral replication frequently induce stress responses that perturb cellular homeostasis. Cell death or survival is dictated by opposing activities between pro-apoptotic and anti-apoptotic factors, known as Bcl-2 homology proteins, which reside within the outer membrane of mitochondria (Figure 2). All γ-herpesviruses express anti-apoptotic Bcl-2 homologs during various stages of their infection cycle [53]. Viral Bcl-2 has lost the inhibitory loop that, when cleaved by an activated caspase, converts cellular antiapoptotic Bcl-2 into a proapoptotic product via removing the N-terminal BH4 domain [54,55]. Thus, viral Bcl-2 proteins either are not cleaved or, even if cleaved by caspase, do not behave as apoptosis-inducers. Our understanding of the *in vivo* functions of the antiapoptotic activity of vBcl-2 is largely derived from studies using MHV68. Recombinant MHV68 expressing a vBcl-2 mutant that fails to suppress apoptosis establishes normal latent infection in splenocytes, but is crippled to reactivate *ex vivo* [56]. Thus, viral antagonism of apoptosis is crucial to promote cell survival during early stages of lytic infection. Similarly, vBcl-2 expression immediately after infection by EBV promotes cell survival by enabling latent infection and transformation of lymphoma cells *ex vivo* [57]. The viral mitochondrial antiapoptotic protein (vMAP) of MHV68 displays a two-pronged mechanism to counteract intrinsic apoptosis [58]. vMAP binds to Bcl-2 to enhance its recruitment to mitochondria and subsequent inhibition of the BH3-only molecules, and impedes cytochrome c release through physical association with VDAC, effectively negating the mitochondrion apoptotic pathway. Viral infection with recombinant MHV68 demonstrated that this antiapoptotic activity was important for the lytic phase of infection.

It is also necessary to inactivate p53 during active viral replication and the growing list of such proteins includes the KSHV latent nuclear antigen (LANA), the EBV nuclear antigen 3C (EBNA3C), and the KSHV K7 and vIRF3. KSHV LANA and EBV EBNA3C are major latent gene products and both inactivate p53-mediated apoptosis. While KSHV LANA induces p53 degradation [59], EBNA3C stabilizes a cellular factor that prevents p53 to access DNA and sequestrates a co-activator key for p53-mediated transcription [60,61]. The KSHV K7 protein is a lytic gene product that antagonizes apoptosis by multiple mechanisms (Figure 2). Anchored in the membrane, K7 interfaces with the mitochondrion-dependent apoptotic pathway, the ER stress responses, and the proteasome/ ubiqutin system [62 64]. K7 expression protects cells from apoptosis induced by intrinsic stresses, including DNA damage and ER stress. Similar to LANA, vIRF4 targets p53 for degradation via two distinct mechanisms governing ubiquitination [65]. These findings highlight the importance of inhibiting intrinsic apoptosis triggered by viral replication events, danger signals within the infected cells.

Evasion of autophagy

Autophagy is a homeostatic process that engulfs and, upon fusion with lysosomes, digests bulk cytoplasm under nutrient-deprived conditions. Recent studies indicate that host cells deploy autophagy to defeat pathogen infection. vBcl-2 and vFLIP can inhibit autophagy, implying an inherent crosstalk between autophagy and apoptosis. vBcl-2 targets Beclin 1, a key regulator of autophagy, to negate autophagy [66]. Subsequently, vBcl-2 was found to target UVRAG, an integral component of the Beclin-1-PI3K complex, which arrests the PI3K complex and suppresses autophagy [67]. The anti-autophagic activity of viral Bcl-2 is conserved within γ-2-herpes-viruses (Figure 2). Using recombinant MHV68 carrying mutations that differentially ablate the anti-autophagic or anti-apoptotic activity of vBcl-2, Xiaofei *et al*. showed that inhibition of autophagy by MHV68 Bcl-2 was essential for the establishment of latent infection in splenocytes [56]. Viral and cellular Bcl-2 proteins show a difference in affinity for Beclin 1. Structural studies illustrated that this difference likely stems from the specific sequence of the hydrophobic groove of Bcl-2 that directly contacts the BH3 of Beclin 1 [68,69]. Recently, the KSHV vFLIP protein was discovered to bind to the LC3-processing enzyme, ATG3 [70]. As such, vFLIP and cellular FLIP molecules potently inhibit LC3 processing and autophagosome membrane elongation. Interestingly, vCyclin, another latent protein, induces autophagy and senescence, both of which are diminished by vFLIP [71]. These data suggest a complex stimulation and inhibition of autophagy during the lytic phase of γ-herpesviruses.

Evasion of interferon production

Type 1 interferon (IFN) and IFN-stimulated genes (ISGs) represent the first line of defense against virus infection. γ-Herpesviruses interfere with the IFN pathway at several levels as reviewed recently [72,73] (Table 1). Virus-infected cells secrete IFN upon recognition of specific viral signatures by pattern-recognition receptors (PRR). These PRRs include the Toll-like receptors (TLRs), nucleotide-binding and oligomerization, leucine-rich repeat (NLR) proteins, retinoic acid inducible gene (RIG)-I-like receptors (RLRs) and C-type lectin receptors (CLRs). Via adaptor proteins, these innate sensors in turn activate a family of transcription factors, the IFN regulatory factors (IRFs), which translocate to the nucleus to initiate transcription of IFN α/β genes. Secreted IFN binds to the type 1 IFN receptor (IFNAR) to trigger a signaling cascade that culminates in the expression of ISGs. γ-Herpesviruses antagonize both the expression and function of different components of the IRF pathway.

Interferon regulatory factors—KSHV encodes four homologs of cellular IRFs, vIRF1 through 4, which interfere with the transactivating activity of specific IRFs. vIRF-1 binds to host IRF-1 or the coactivator protein p300, the latter action inhibiting formation of the transcriptionally active IRF3-CBP/300 complex [74]. vIRF-2 interferes with the transactivational activity of IRF-1 and IRF-3 [75,76] by direct binding to IRF1 and degradation of IRF3 via a caspase 3-dependent mechanism [75,77]. vIRF-2 also interacts with protein kinase R (PKR), inhibiting its autoactivation and antiviral function [78]. IRF7, together with IRF3, constitute the master regulators of type 1 IFN production, and KSHV vIRF3 antagonizes IRF 5 [79] and IRF7 [80] via direct inhibitory interactions. vIRF-4 does not appear to antagonize IFN-mediated signaling; instead, vIRF4 enhances the degradation

of p53 (which is also targeted by vIRF1 and 3) via a stabilizing interaction with the E3 ubiquitin ligase MDM2 [70,81]. vIRF4 also interacts with CSL/CBF1, potentially antagonizing Notch/CBF1 signal transduction, and cooperates with RTA to facilitate KSHV reactivation [82,83]. Despite similar functional activities, the vIRFs display differential expression patterns, indicating that they may act at different times, and/ or in different cells [81]. Interestingly, a recent study identified mechanistic differences between the ability of the KSHV vIRFs to inhibit TLR3-dependent IFN signaling [84].

KSHV encodes additional gene products to antagonize host IRFs while EBV and MHV68 target host IRFs with non-homologous viral proteins. This common strategy underscores the importance of the IRF family in antiviral defense. Two KSHV proteins, LANA1 (ORF73) and K-bZIP (K8), bind competitively to the IFN-β promoter, preventing IFN-β induction during latency and virus reactivation [85,86]. The conserved viral kinase ORF36 inhibits IFN production. MHV68 ORF36 binds to nuclear IRF-3 to prevent activation of the IFN-β promoter [87]. Importantly, the growth and spread of an ORF36-null MHV68 in immunocompetent mice was attenuated, exemplifying the need to antagonize the IFN pathway for successful infection. The EBV ORF36 homolog, BGLF4, also binds to IRF3 to suppress IRF3-mediated signaling [88]. KSHV ORF45, a conserved tegument and IE protein, binds to the inhibitory domain of IRF7 to prevent its phosphorylation and nuclear translocation by acting as an alternate substrate for the virus-activated kinases IKKε and TBK1 [89 91]. As a virion component, ORF45 could inhibit IFN production at the earliest stages of *de novo* infection, as suggested by studies with an ORF45-null recombinant KSHV [92]. MHV68 ORF45 is also essential for an early stage of viral replication, suggesting a similar role in evasion of the early IFN response [93]. KSHV RTA (ORF50) also targets IRF7, promoting its ubiquitination and degradation [94].

Like KSHV, RRV expresses a set of viral IRFs [95]. As such, the RRV model provides insight into the role of the vIRFs in regulating the host response to infection. Accordingly, a vIRF deletion clone of RRV that inhibits IFN release from PMC *in vitro* exhibits attenuated replication *in vivo* and induces a more robust anti-inflammatory and anti-RRV T cell response [96,97]. Macaques infected with the vIRF knockout also display diminished B cell hyperplasia, a pathology characteristic of acute RRV infection.

While EBV does not express IRF homologs, it encodes several proteins that target host IRFs. The EBV IE transactivator protein BZLF1 (Zta) binds to IRF7 and inhibits its transactivational activity [98], while BRLF1 (Rta) inhibits transcription of IRF3 and IRF7, thus inhibiting IFN-β production during lytic infection [99]. In addition, binding of the tegument protein LF2 to IRF7 prevents IRF7 dimerization and IFN-α production [100]. Interestingly, a positive regulatory circuit exists between IRF7 and the EBV oncoprotein LMP1 [101]. LMP1 possesses potent immune escape functions, including induction of immunomodulatory cytokines, receptors and exosomes [102] and induction of miR-146a, a cellular miRNA that inhibits IFN response pathways [103,104], and inhibition of TLR9 expression [105,106] (discussed below). LMP2A and 2B enhance IFN receptor turnover in epithelial cells, inciting a broad effect on ISG expression [107]. These LMP functions likely contribute to the immune escape of EBV-positive tumors.

Recent work with MHV68 illustrates a novel mechanism of immunomodulation whereby a host IRF is co-opted to establish viral latency [108]. Specifically, transcription of the M2 protein, which plays a critical role in virus reactivation, is repressed by IRF2, which is in turn upregulated by the IFN produced in response to initial virus infection. The authors speculate that this IRF-sensing mechanism allows MHV68 to time virus reactivation to periods of localized immune quiescence. It is likely that other examples of 'cooperative subversion' between γ-herpes-viruses and host immune effectors will be identified.

Pattern recognition receptors and adaptor proteins—KSHV modulates TLR signaling by influencing the expression of TLRs or their adaptor molecules. Infection of monocytes leads to an upregulation of TLR3 and downstream innate immune effectors (CXCL10, IRF-1, CCL2, and IFN-β), an event that may facilitate establishment of latency [109]. In contrast, infection of endothelial cells results in downregulation of TLR4 mediated by the lytic proteins vIRF1 and ORF74 [110]. Interestingly, stimulation of PEL cells with agonists to TLR7 and 8 reactivates virus, suggesting a viral strategy to escape from cells targeted for immune attack [111]. Recent studies indicate that KSHV targets other PRRs in addition to TLRs. Inn *et al.* show that the tegument protein, ORF64, specifically targets and suppresses RIG-I-mediated signaling via its deubiquitinase activity [112]. Gregory *et al.* report that another tegument protein, ORF63, is a functional homolog of NLRP1 that disrupts the formation and activity of the NLRP1 inflammasome [113¨]. While NLRP1 is a cytoplasmic inflammasome, a study by Keruer *et al.* shows that, during KSHV infection of endothelial cells, IFN-γ-inducible protein 16 (IFI16) interacts with a caspase-1 activating complex to form a functional nuclear inflammasome, suggesting that KSHV may manipulate this pathway to promote latency after nuclear delivery of the viral genome [114,115]. These recent studies indicate a broader role for PRRs in sensing γ-herpesvirus infection and suggest that additional viral antagonists and strategies remain to be identified.

Similar to KSHV, MHV68 can be reactivated from latently-infected B cells with ligands for TLR3, 4, 5 and 9, and reactivation in vivo is accomplished by administration of LPS (TLR4) or CpG DNA (TLR9) [116]. Interestingly, LPS/CpG-induced reactivation led to an increase in the number of latently-infected splenocytes, suggesting that TLR sensitivity contributes to homeostatic maintenance of chronic infection. This phenomenon could also underlie the sensitivity of KSHV to TLR7/8 agonists. Alternatively, innate immune signaling pathways are hijacked by MHV68 to enable lytic replication that replenishes the latent pool. Indeed, it was shown that MHV68 exploits the MAVS-IKKbeta pathway to promote viral transcriptional activation and disable antiviral cytokine production [117 119]. It remains unclear how the MAVS-IKKbeta pathway is activated during MHV68 infection.

TLR signaling is mediated through one of two adapter proteins, myeloid differentiation primary-response protein 88 (MyD88) or Toll-interleukin-1 receptor (TIR) domain-containing adaptor-inducing b-interferon protein (TRIF) [120]. KSHV targets both adaptors. TRIF, an adaptor for TLR 3 and 4, is degraded in the presence of RTA, via either its E3 ligase activity or an unidentified mediator [121]. MyD88, which transmits signals from TLRs 7, 8 and 9, is downregulated by the viral microRNA miR-K9, which also targets a critical kinase, interleukin-1 receptor-associated kinase 1 (IRAK1), in the same pathway

[122˙]. These data indicate that KSHV may block TLR7/9-induced IFN-α production via miRNA targeting.

In B cells, EBV infection exerts opposite effects on expression of TLR7 and TLR9. In naïve B cells, exposure to EBV downregulates TLR9 while inducing expression of TLR7 and key downstream adaptor (MyD88) and effector (IRF5) molecules, a scenario that promotes the initial phase of B cell proliferation; IRF5 activity is subsequently negatively regulated to allow for establishment of latency [123]. EBV proteins responsible for TLR9 downregulation have been identified: LMP1 downregulates TLR9 through NF-kB-dependent inhibition of TLR9 transcription [105], while BGLF5 degrades TLR9 mRNA [106]. EBV-infected B cells are also unresponsive to TLR7/8 and 9 agonists [124]. In plasmacytoid dendritic cells (pDC), EBV infection increases IFNa production by activating the TLR9 signaling pathway, but the simultaneous production of IL-10 from the pDC serves to blunt the net antiviral effect [125].

Evasion of inflammatory signaling

Inflammatory chemokines and cytokines produced in response to viral infection play an important role in the outcome of the immune response. Accordingly, the γ-herpesviruses have developed different strategies to imitate or neutralize these inflammatory mediators, including production of homologs, receptors and binding proteins.

Virus-encoded chemokines

KSHV encodes three viral chemokines with agonist or antagonist function against host chemokine receptors; vCCL1 (ORF K6), vCCL2 (ORF K4), vCCL3 (ORF K4.1). This family possess agonist function against CCR8 (vCCL1 and 2), CCR3 (vCCL2) and CCR4 (vCCL3), indicating a role in chemoattraction of Th2 T cells, which typically downmodulate immune responses [126]. Interestingly, vCCL2 also has broad-spectrum antagonist activity, binding promiscuously to several CC and CXC chemokine receptors and inhibiting the chemotactic responses of monocytes and Th1 T cells [126]. In combination with Th2 T cell recruitment, this would provide an effective means of blunting an inflammatory cytotoxic antiviral response.

As an alternate strategy for chemokine modulation, the EBV microRNA BHRF1, which is expressed in several EBV+ lymphomas, suppresses expression of CXCL11/I-TAC, an IFN-inducible T cell chemoattractant [127].

Other inflammatory modulators (vCD200 and vIL-6)

KSHV encodes a homolog of CD200, a molecule that negatively regulates myeloid-lineage cells [128], and a homolog of IL-6, a multifunctional inflammatory cytokine [129]. KSHV vCD200 is encoded by ORF K14 and binds with high affinity to the host receptor CD200R with immunosuppressive consequences [130]. KSHV vIL-6 is encoded by ORF K6 and, unlike human IL-6, can bind and signal exclusively through gp130 without the need for CD126 (gp80) [131,132]. In the presence of gp80 however, vIL-6 signaling is qualitatively different from that induced by human IL-6 [133]. These properties have relevance for

immune evasion as well as oncogenesis, since IFN-modulation of the IL-6R complex would differentially impact virus and host IL-6 activity.

Like KSHV, RRV encodes a CD200 homolog, R15, which inhibits macrophage production of TNF [134] and a vIL-6, which signals through gp130 and is expressed in RRV-infected rhesus macaques [135,136].

The IL-10 homolog encoded by the EBV BCRF1 gene encodes a functional homolog of IL-10 that exhibits diverse immunosuppressive properties, including inhibition of T cell function, macrophage activation and synthesis of IRN-γ [137 140]. BCRF1 is functionally expressed during the earliest phase of *de novo* infection of primary B cells, a consequence of translation of virion-delivered mRNA, or transduced viral RNA (tvRNA) [21]. Additional immunomodulatory EBV tvRNAs were recently identified, including those encoding BGLF5, BNLF2a and LMP1; immediate translation of tvRNAs likely contributes to immune evasion in a crucial period before *de novo* gene expression [21]. EBV BARF1 could also contribute to immunomodulation via binding and neutralization of the pleiotropic cytokine colony-stimulating factor-1 (CSF-1) [141].

The MHV68 M3 protein is a secreted viral protein that binds selected CC and CXC chemokines with antiviral activity [142]. While an M3-deficient virus is not impaired in its capacity to establish latency in experimental hosts (C57BL/6 or BALB/c mice), when tested in a natural host (wood mice) it did attenuate infection and modulate the host inflammatory response in a manner consistent with its chemokine-binding properties [143,144·], indicating that specific immunoevasins may only function effectively in the appropriate host.

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· of special interest

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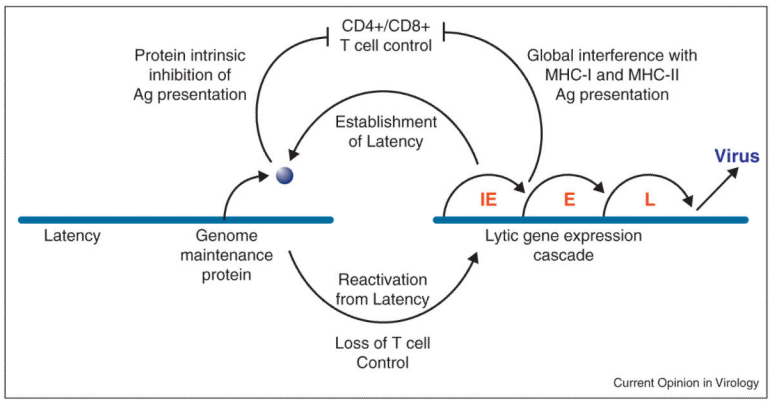

Figure 1.
Evasion of T cell responses by g herpesviruses.

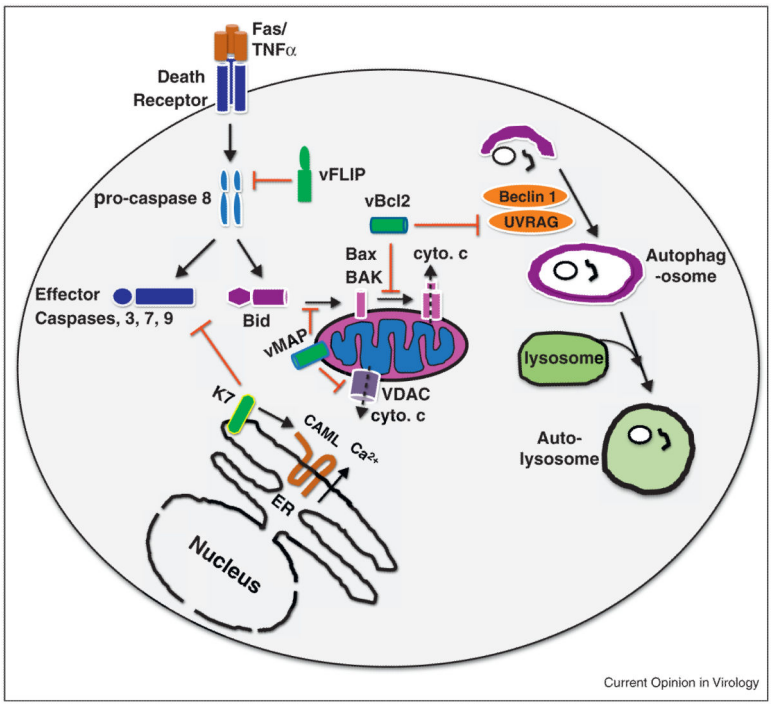

Figure 2.

Inhibition of the classical apoptosis and autophagy pathway by γ-herpesvirus proteins. KSHV vFLIP and K7 target pro-caspase 8 and activated caspase 3 for inhibition, whereas vBcl2 and MHV-68 vMAP antagonize the oligomerization of Bax/Bak and VDAC that release cytochrome c (cyto. c). Additionally, KSHV K7 activates CAML in releasing calcium from the ER to attenuate stress induced apoptosis. Of the classic autophagy pathway, vBcl2 suppresses UVRAG in autophagosome formation. Viral proteins are colored in green.

Table 1

Antagonism of IFN signaling by human γ-herpesvirsues

Virus	ORF	Gene product	Functional mechanism(s)
	K9	vIRF-1	Suppresses IRF-1 and IRF-3 transactivational activity; inhibits IRF3 nuclear translocation; inhibits TLR3-driven IFN-β promoter activation and IFNβ production; downregulates TLR4
	K11.1/K11	vIRF-2	Suppresses IRF-1 and IRF-3 transactivational activity; inhibits TLR3-driven IFN-β promoter activation and IFNβ production; inhibits PKR function
	K10.5/K10.6	vIRF-3	Inhibits IRF7 DNA binding and function; Inhibits IRF5-mediated promoter activation
	ORF45	ORF45	Prevents phosphorylation and nuclear translocation of IRF7
KSHV	ORF50	RTA	Promotes IRF7 ubiquitination and degradation; degrades the TLR3/4 adaptor TRIF
	ORF63		Disrupts formation and activity of the NLRP1 inflammasome
	ORF64		Suppresses RIG-I-mediated signaling
	ORF73	LANA1	Prevents IRF3-mediated induction of IFN-β during latency
	ORF74	vGPCR	Downregulates TLR4
	ORFK8	K-bZIP	Prevents IRF3-mediated induction of IFN-β during virus reactivation
	miR-K9		Downregulates MyD88 and IRAK1
	BGLF4	PK	Binds and suppresses IRF3 transactivational activity; inhibits of IFN-β production
	BGLF5	DNase	Degrades TLR9 transcript
	BZLF1	Zta	Binds and suppresses IRF7 transactivational activity
EBV	BRLF1	Rta	Inhibits IRF3 and IRF7 transcription; inhibits IFN-β production during lytic infection.
	LF2	LF2	Prevents IRF7 dimerization and IFN-α production
	LMP1	LMP1	Negatively regulates IFN response *via* induction of miR-146a; downregulates TLR9
	LMP2A/2B	LMP2A/2B	Enhances turnover of type I/II IFN receptors