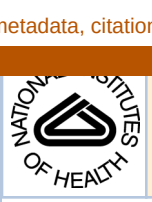

Published in final edited form as:

Future Virol. 2010 March 1; 5(2): 185–196. doi:10.2217/fvl.10.5.

Kaposi's sarcoma-associated herpesvirus and innate immunity

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Abstract

Kaposi's sarcoma-associated herpesvirus (KSHV) is the most recently discovered human herpesvirus, first isolated and identified from a Kaposi's sarcoma lesion in 1994. It is the etiological agent of Kaposi's sarcoma, a vascular lesion that is the predominant cancer among AIDS patients. KSHV is also the primary etiological agent of two B-cell lymphomas, primary effusion lymphoma and multicentric Castleman's disease. KSHV can exist in either a lytic phase, in which the viral DNA is actively replicated and virions are assembled, or in a latent phase, in which the viral genome is tethered to the host chromosome via protein–protein interactions. The lytic cycle generally occurs following primary infection, and within 72–96 h in most cell types, the virus enters the latent state. Reactivation from latency also leads to the intiation of the lytic cycle, which is necessary for virus propagation and survival in the host. Several KSHV proteins have been implicated in modulation of the host immune response to viral infection. This article summarizes recent discoveries involving the innate immune response to KSHV infection.

Keywords

immune modulation; latency; lytic replication; reactivation

Kaposi's sarcoma-associated herpesvirus (KSHV) was identified by Chang and Moore in 1994 [1]. KSHV, also classified as human herpesvirus-8, is a dsDNA virus and a member of the *Herpesviridae* family, and the γ-herpesvirus subfamily. The host cell range of KSHV includes endothelial cells, B cells, monocytes, hematopoietic progenitor cells and dendritic cells [2–6]. In each of these cell types, the virus primarily exists in the latent state, where the viral genome is tethered to the host chromosome via the latency-associated nuclear antigen [7–9]. In a latent infection, KSHV exists in a dormant state and persists for the lifetime of the host. During latency, the viral genome persists in an episomal state, attached to host chromosomes via latency-associated nuclear antigen's interactions with histones [7–9]. There are typically only a subset of viral genes that are actively transcribed during latency.

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Financial & competing interests disclosure: The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

By contrast, upon primary *de novo* infection of the host cell, the virus undergoes lytic replication for approximately 72–96 h, prior to the establishment of latency [10]. The lytic cycle is regulated by the expression of the master viral regulator open reading frame (ORF)50/RTA [11]. During the lytic cycle, the viral genome is actively replicated and progeny virions are assembled and released into the surrounding area where they can infect neighboring cells. In addition to primary infection, KSHV undergoes lytic replication following reactivation from the latent state. Environmental stresses such as superinfection with another virus [12] and chemical treatment with 12-*O*-tetradecanoyl-phorbol-13-acetate [13] can lead to lytic reactivation and the initiation of the lytic cycle.

Kaposi's sarcoma-associated herpesvirus is restricted to humans and its prevalence is geographically defined. For example, KSHV is endemic in some regions of Africa [14–16]. In immune-suppressed individuals such as transplant patients or HIV-infected individuals, KSHV-associated malignancies are increased. In fact, Kaposi's sarcoma is the leading cause of cancer in HIV-infected individuals (reviewed in [17]).

The virus contains 84 ORFs and more than 20 viral proteins have been identified that are capable of modulating proteins and/or pathways of the host immune system [18]. The large number of viral genes dedicated to modulation of the host immune system indicates that immune evasion is a necessity for this virus, and that immune modulation is critical for maintaining the virus in a hidden, latent state.

The KSHV gene encodes a large number of viral genes with homology to cellular genes, particularly ones that are involved in the host response to infection. KSHV also encodes a large number of genes that mimic cellular genes, either in sequence and/or function.

Innate immunity is the body's first line of defense against invading pathogens and is often sufficient in fighting off primary infection. Toll-like receptors (TLRs), RIG-I-like receptors (reviewed in [19]) and nucleotide-binding domain leucine-rich repeat-containing receptors (reviewed in [20]) are pathogen sensors involved in innate immunity [21]. Type I interferon (IFN) is one of the critical defenses against invading pathogens. Activation of the IFN response can lead to the antiviral state, which is characterized by apoptosis, degradation of host cell RNA, a halt in protein processing and increased antigen presentation [22]. The purpose of the antiviral state is to control the ability of the invading pathogen to replicate and reduce its ability to spread, leading to the eventual elimination of the pathogen.

Toll-like receptors

Toll-like receptors are one of the first lines of defense for the innate immune system. They recognize invading pathogens (bacteria, viruses and fungi) and trigger signaling cascades, which lead to the activation of type I IFN, NF-κB and many other proinflammatory cytokines. Human TLRs were first identified as homologs of the Toll proteins from *Drosophila*. TLRs are classified as pattern recognition receptors, as they recognize invading pathogens [23,24]. Currently, there are ten identified human TLRs. TLRs are transmembrane proteins with an immunoglobulin-like extracellular domain and an intracellular domain that contains a Toll/IL-1 receptor domain. TLRs trigger specific cell signaling cascades [25]. TLRs contain 21–25 leucine-rich repeats in their extracellular domains, which are responsible for recognition and binding to pathogen-associated molecular patterns on the surface of the incoming pathogen [26]. However, not all TLRs are expressed at the cell surface. TLR3, -7, -8 and -9 are all expressed in intracellular compartments, primarily the endosome [27,28].

Recent research has identified TLR2, -3, -4, -7, -8, and -9 as being involved in the recognition of viruses through binding of either RNA, DNA or viral glycoproteins [27,28].

Two of the endosomal TLRs, TLR3 and -7, have been shown to be activated by RNA. TLR3 recognizes both ssRNA and dsRNA, while TLR7 recognizes ssRNA [23,29–34]. There are two pathways that TLRs use for signaling, one being dependent on the adaptor protein MyD88 and the other being a MyD88-independent pathway [24,27]. All TLRs signal through the MyD88-dependent pathway with the exception of TLR3 and -4. TLR4 is capable of signaling in a MyD88-independent or -dependent manner, while TLR3 strictly signals via a MyD88-independent pathway [35]. The TLR3 adaptor protein is TRIF which initiates the TLR3 signaling cascade upon binding to TLR3 [36].

The role of TLRs during primary infection

Currently, there are two reports implicating a role for TLRs during KSHV infection. We published the first observation that TLR activation occurs upon infection of monocytes with KSHV [37]. In both a monocytic leukemia cell line (THP-1) and primary human monocytes, KSHV infection resulted in upregulation of TLR3 expression (mRNA and protein) and downstream components of the TLR3 pathway, including IFN-β1 and the chemokine CXCL-10 (IP-10). Knockdown of TLR3 prior to KSHV infection significantly reduced the activation of TLR3 and its downstream effectors (Figure 1).

Lagos *et al.* demonstrated that upon primary infection of endothelial cells, TLR4 expression was suppressed and that this repression allowed KSHV to escape the innate immune response [38]. They also showed that cells lacking TLR4 were more susceptible to KSHV infection and that activation of TLR4-protected cells from infection [38]. They identified the KSHV viral proteins: viral G protein-coupled receptor and viral interferon regulatory factor (IRF)-1, both of which are viral homologs of cellular G protein-coupled receptor and IRF-1, respectively, as inhibiting TLR4 expression following infection (Figure 1).

Much more study is warranted on the effects of KSHV infection on the TLR pathway. Considering that the TLR expression profile varies from cell to cell, and that KSHV is tropic for different cell types, it would be interesting to determine whether a common or different TLR is modulated in different cell types upon primary infection with KSHV. TLR3 is known to be expressed in the following cell types: monocytes, macrophages, dendritic cells, human fibroblasts and endothelial cells, several of which are tropic for KSHV (reviewed in [39]).

The role of TLRs during reactivation

Owing to the fact that KSHV exists primarily in the latent state, reactivation is vital for the survival and spread of the virus. However, not much is known about reactivation and the activation of the innate immune response. Innate immunity is driven by primary infection of a pathogen, and individuals with an established KSHV infection are those who have already experienced primary infection. Our group recently reported that activation of the innate immune response can lead to reactivation of KSHV from latency.

Gregory *et al.* showed that TLR7/8 and IRF-7 play important roles in the reactivation of KSHV from latency [12]. Stimulation of TLR7/8 in KSHV latently infected primary effusion lymphoma, either by synthesized agonist (poly-Uridine) or by infection with a biologically relevant pathogen, vesicular stomatitis virus, a known activator of TLR7 and -8 [40]), led to viral reactivation and progeny virion production (Figure 1). In addition, a dominant negative IRF-7 mutant protein significantly inhibited latent primary effusion lymphoma cells from being able to reactivate and produce virus after TLR7/8 stimulation [12]. If TLR signaling, typically responsible for recognition of new incoming pathogens, can also lead to the reactivation of a latent viral reservoir, then this represents a physiological stimulus that can lead to viral reactivation. It also represents a new role for TLR stimulation

in the context of KSHV and suggests that KSHV takes advantage of a TLR-mediated 'death' signal to reproduce itself and leave a cell that is fated to die [12]. This ensures persistence and spread of KSHV in the human population.

The above studies suggest that KSHV has the ability to both suppress and evade the host response during a primary infection in order to establish latency. In addition, in the context of viral latency, it can also use the activation of the innate immune response to invading pathogens to reactivate and persist in the host. Thus, KSHV responds to environmental conditions by switching between its latent and lytic phases, thereby ensuring lifetime persistence in the infected host.

Complement system

The complement system is also a component of the innate immune response and similar to the TLRs, can respond to both bacterial and viral infection. There are three different pathways through which the complement system activates particular proteins that ultimately lead to the formation of the membrane attack complex [41]. The membrane attack complex is responsible for punching holes in the invading pathogen (bacteria or virus), resulting in killing of the pathogen, and ending the infection. Complement can also act by opsonization, which involves depositing one of two complement proteins (either C3b or C4b) on the surface of the invading pathogen. Opsonization leads to increased phagocytosis and humoral response to infection [42].

Kaposi's sarcoma-associated herpesvirus has developed a mechanism by which the virus can interfere with the activity of the complement system. The KSHV *ORF4* gene encodes a homolog of the human complement control family of proteins, referred to as KSHV complement control protein (KCP) [43,44]. KCP is expressed during the lytic cycle and contains alternative splice sites, which results in the production of three protein isoforms. Each of these isoforms contains the conserved SCR sequence, the sequence common to each of the human complement control proteins, giving these viral homologs the ability to modulate the complement system. KCP manipulates the complement system to ensure the survival of the virus and reduce the chance of viral killing via any host complement proteins. KCP has been shown to inhibit the complement response in three ways: it enhances the decay of C3 convertase; it prevents depositing of C3b on the surface of sensitized cells, preventing opsonization; and KCP acts as a cofactor for factor I-mediated inactivation of C3b and C4b (Figure 2) [43–46]. By enhancing C3 decay, KCP inhibits the complement pathway and the formation of the membrane attack complex, and prevention of opsonization allows infected cells to escape phagocytosis and degradation. Both of these outcomes are positive for the virus and allow the virus to escape a key element of the innate immune system, presumably making the task of establishing latency much easier to accomplish following primary infection.

Viral IRFs

Kaposi's sarcoma-associated herpesvirus encodes four proteins with homology to members of the human IRF protein family (reviewed in [47]). Cellular IRFs are transcription factors that can transactivate type I IFN genes and many other cytokines and chemokines. Considering their role in transcriptional activation of the IFN response and the cytokine/chemokine response, the IRFs are a critical element of the innate immune response (reviewed in [48]). Consequently, it is not surprising that they are a target of several KSHV genes and that their functions are modified in a KSHV-infected cell. The vIRFs are largely responsible for modulation of cellular IRFs; however, several other KSHV proteins have also been identified as modulators of the cellular IRFs.

Viral IRF-1, encoded by the *K9* gene in KSHV, has several functions in the innate immune response. vIRF-1 has been identified as a negative regulator of the type I IFN response, accomplishing this via binding to the p300 protein, a transcriptional coactivator that along with IRF-1 and IRF-3 activates several genes critical in the innate immune response [49–51]. By binding to p300, vIRF-1 prevents p300 association with IRF-1 or -3 and therefore inhibits the transcriptional activity of IRF-1 and -3 (Figure 1). This serves to greatly dampen the innate immune response, possibly creating a more favorable environment for the establishment of latency. vIRF-1 has also been shown to bind cellular IRF-1, -3 and -7; however, only IRF-3-mediated transcription has been shown to be inhibited due to vIRF-1 binding to p300 [51]. vIRF-1 also inhibits IRF-1-mediated transcription, but does so without binding to IRF-1 or competing with IRF-1 for DNA binding [52]. However, the same group has also published that vIRF-1 may not contribute as greatly to innate immune evasion, *in vivo*, owing to its short half-life during KSHV infection [53]. All of the aforementioned studies were performed in the presence of overexpressed vIRF-1. vIRF-1 has also been shown to inhibit TGF-β signaling [54].

Viral IRF-2 is encoded by the *K11* and *K11.1* genes and has also been shown to play a role in the evasion of the innate immune response. Full-length vIRF-2 has been implicated in the inhibition of the IFN response [55], although the exact nature of the inhibition is not yet known. It was determined using an IFN-stimulated response element (ISRE) driven reporter that IFN-α and -λ signaling could both be inhibited by vIRF-2 (Figure 1). vIRF-2 also inhibited transactivation of this reporter via cellular IRF-1, indicating a role for IRF-1 inhibition by vIRF-2. Activation of an IFN-β reporter by IRF-1 or -3 was also blocked by expression of vIRF-2, implicating a role for vIRF-2 in the blockage of IRF-1- and -3-mediated IFN signaling [55]. Recently, a novel role for vIRF-2 was reported, showing that it can hinder the transactivation of cellular IRF-3, a vital component of type I IFN activation, thereby inhibiting the antiviral response [56]. This study showed that in the presence of caspase-3, vIRF-2 expression enhanced caspase-3 degradation of IRF-3.

Viral IRF-3, a viral protein encoded by the *K10.6/10.5* locus, has been reported to inhibit IRF-7-mediated induction of the IFN signaling pathway [57]. It was determined that vIRF-3 was able to accomplish this inhibition by preventing IRF-7 from binding to DNA, consequently blocking production of normal levels of IFN (Figure 1). vIRF-3 can also block NF-κB signaling, a key mediator of the innate response [58]. NF-κB activates the transcription of numerous cytokines and chemokines, as well as type I IFN. In 2000, Lubyova *et al.* reported inhibition of both IRF-3- and -7-mediated activation of IFN-α and in 2004, the same group reported that vIRF-3 can stimulate IRF-3- and -7-mediated activation of IFN-α, via its recruitment to the IFN-α promoter as a complex with IRF-3 and -7 [59,60]. Therefore, depending on the circumstances, vIRF-3 is capable of functioning either as a co-activator or co-repressor of the IFN response.

Viral IRF-4 is the most recently discovered KSHV homolog to a cellular IRF. vIRF-4 was demonstrated to interact with MDM-2, an E3 ubiquitin ligase that targets p53 for proteasomal degradation (Figure 2) [61]. Activation of p53 often leads to apoptosis and tumor suppression. Therefore, the degradation of p53 mediated by vIRF-4 would be extremely beneficial to KSHV, allowing infected cells to escape p53-mediated apoptosis and continue to persist in the host.

Additional viral immune modulatory genes

In addition to the vIRF proteins, several other KSHV proteins have been identified as being important for controlling the host IFN response and helping KSHV avoid eliciting a strong

innate immune response. Several of these proteins also function similarly to the vIRFs in that they target the cellular IRFs and inhibit their transactivation of IFN signaling.

Kaposi's sarcoma-associated herpesvirus ORF45, classified as an immediate early protein, was shown to decrease the type I IFN response by inhibiting IRF-7 function (Figure 1). It was demonstrated *in vitro*, and in the context of a viral infection, that ORF45 blocked phosphorylation of IRF-7 and its accumulation in the nucleus [62,63]. This led to a downregulation of the type I IFN response upon infection of cells with Newcastle Disease virus, a known activator of type I IFN.

Open reading frame 50/RTA, the activator of viral transcription and the lytic cycle, has been reported to modify IRF-7 function. Yu *et al.* showed that RTA can bind to IRF-7 and target it for degradation (Figure 1) [62,64]. The E3 ligase activity of RTA targets IRF-7 for ubiquitination, and eventual degradation by the proteasome. This mechanism is yet another way for KSHV to manipulate the innate immune response, and evade detection by the host cell, making the establishment of latency much easier.

Viral Bcl-2, a protein encoded by the *ORF16* locus, is the viral homolog of members of the cellular Bcl-2 family of proteins. Cellular Bcl-2 family members can have either antiapoptotic activity (Bcl-2 or Bcl-xL) or proapoptotic activity (BAK, BAD and BAX) [65]. KSHV vBcl-2 can bind peptide sequences from three proapoptotic death proteins, BAK, BAX and BAD [66]. However, another paper reported contradictory results, concluding that vBcl-2 inhibited apoptosis without binding to BAX or BAK [67]. Clarification of how vBcl-2 aids in evading the apoptotic response after infection is needed, but it is clear that vBcl-2 plays a role in inhibiting this facet of the innate immune response. More recently, vBcl-2 has been implicated in the modulation of autophagy, a cell survival mechanism in which the cell sequesters cytoplasmic components in response to viral infection, and delivers them to the lysosome for degradation [68,69]. In 2005, Pattingre demonstrated that KSHV vBcl-2 can inhibit the process of autophagy by binding to Beclin-1, a protein which promotes autophagy and inhibits tumorigenesis (Figure 2) [70]. Inhibition of both apoptosis and autophagy, two of the primary means by which an infected host cell is able to prevent viral spread and tumorigenesis, is key for the survival of KSHV and its persistence in the host.

Kaposi's sarcoma-associated herpesvirus also encodes a viral FLICE inhibitory protein (*K13*), known as vFLIP. Reports have shown that vFLIP also plays a role in immune modulation including the activation of NF-κB and also the upregulation of IL-8, both key players in the immune response [71,72]. Recently, vFLIP has also been shown to modulate autophagy [73]. Kaposin, encoded by the *K12* gene, also modulates cytokine expression by stabilizing cytokine mRNA, which may be important for disease progression and virus survival [74]. KSHV also encodes several viral miRNAs, which perform a myriad of different functions. In particular, KSHV miRNA 12–11 (mirK11) is an ortholog of cellular miR-155 and has been shown to downregulate BACH-1 and Fos [75,76] O'Connell *et al.* have previously reported that cellular miR-155 is a TLR-responsive and IFN-β-inducible miRNA. They showed that cellular miR-155 served as a common target of inflammatory cytokines [77]. Thus, it is plausible that KSHV mirK11 may also play a similar role.

Direct IFN effects

Since the IFN response is probably the most critical aspect of the innate immune response, it is not surprising that KSHV can directly modulate type I IFN responses. Multiple reports have shown that KSHV infection can lead to suppression of the IFN-response and also to suppression of several IFN responsive elements. Targeting the IFN response is a common theme among human herpesviruses, specifically downregulation of the type I IFN response.

Several recent studies have shown that KSHV is not the only human herpesvirus that targets the IFN system in order to aid its goal of achieving latency. Paladino *et al.* discuss multiple mechanisms by which HSV-1 downregulates the IFN response [78]. Recently, for HSV-2 a similar result was observed, IFN-α and -β were both present at decreased levels in biopsy samples from HSV-2-infected lesions [79]. In addition, an Epstein–Barr virus-encoded protein, LMP1, can decrease type I IFN [80]. Overall, KSHV shows strong similarities to other human herpesviruses in its ability to evade the host innate immune response and a common target amongst the herpesviruses is the type I IFN response.

In a comprehensive study, investigating KSHV infection of endothelial cells, B cells and human fibroblasts [81], there were a myriad of IFN-responsive genes whose transcription was upregulated following KSHV infection. However, direct activation of type I IFN was not shown. This could be caused by viral products that suppress the IFN response. Interestingly, a recent paper has identified a 100 base pair repeat region in MHV-68 that is required for activation of IFN-α [82]. They also identified a colinear region in the KSHV genome and after transfection into 293 cells determined that this region in KSHV also stimulates IFN-α production. It is possible that the overwhelming number of viral genes dedicated to shutting down the IFN response masks this effect in a live virus infection; however, more research of this repeat region could yield very informative results regarding the activation of the IFN response after KSHV infection.

Viral IL-6, the viral homolog of human IL-6, has been reported to inhibit the IFN response by a unique mechanism [83]. The vIL-6 promoter contains an ISRE that is specifically activated by IFN-α treatment. However, it was also shown that vIL-6 could prevent the binding of the IFN transcriptional activator, IFN-stimulated gene factor-3 to ISRE-containing probes, indicating a mechanism by which vIL-6 could negatively regulate the IFN response in a virus infected cell (Figure 2). This is a unique mechanism by which the cells' natural IFN response is used against itself, resulting in the activation of a viral protein (vIL-6) that, in turn, shuts down the host IFN response [83]. It is possible that a very small IFN response is needed to activate vIL-6; however, only a small increase in vIL-6 may be enough to lead to a significant reduction in the IFN response. This is just one more avenue by which KSHV modulates the cellular innate immune response to minimize detection.

Yet another mechanism has been reported by which KSHV downregulates the type I IFN response, in this case specifically the IFN-β response. The viral protein K-bZIP, encoded by *K8*, is able to suppress IFN-β production by binding to the promoter within the IRF3 binding site in the IFN-β gene [84]. It binds specifically to the positive regulatory domain I/III region, the region which is normally occupied by IRF3 to promote IFN-β gene transcription.

So far, we have only discussed the inhibition of the IFN response by KSHV, whether it be direct inhibition, or one mediated by inhibition of a transcription factor. Recently, however, our lab has reported that in response to KSHV primary infection, human monocytic leukemia (THP-1) cells show a significant increase in IFN-β transcription and a concomitant increase in secreted IFN-β [37]. This increase in IFN was observed at 16 h postinfection but declined shortly thereafter [West JA, Damania B, Unpublished Observations]. This indicates that a small, short-lived innate immune response may be necessary for the virus to enter latency. In a situation in which no innate immune response was present, there would likely be rampant lytic replication that would be detrimental to the host. Without an innate immune response, there would not be a strong trigger for an adaptive immune response, through which the host could eradicate the virus. Thus, the activation of innate immunity may actually aid KSHV to establish latency and evade the subsequent wave of adaptive immunity.

Another aspect of the innate immune response is cell killing, usually mediated by natural killer (NK) cells. NK cells are able to kill infected cells in the absence of antigen presentation. NK cells accomplish this via specific surface receptors, which are activated upon binding their ligands. The viral gene *K5*, also known as MIR2, has been shown to play a key role in the ability of KSHV to avoid the cell killing potential of NK cells. Two reports have shown that *K5* downregulates four separate molecules that are specific to the cell surface receptors expressed by NK cells. Coscoy and Ganem, along with Ishido *et al.*, demonstrated that K5 reduced the expression of ICAM-1 and B7-2, both of which normally activate NK cell-mediated killing when expressed on the cell surface (Figure 2) [85,86]. K3/K5 have also been shown to reduce surface expression of MHC class I chains, which allows KSHV to evade recognition by the host immune system, in this case specifically recognition by cytotoxic T lymphocytes, which typically recognize viral peptides presented on the surface of infected cells (Figure 2) [87]. K3 and K5, also known as modulators of immune recognition (MIR1 and -2), regulate expression of these cell surface markers via ubiquitination, which leads to their endocytosis [88]. In addition, K5 was also shown to be responsible for the downregulation of two more NK cell receptor ligands, MICA and MICB (MHC class I-related chains A and B), both of which normally trigger the cell killing response of NK cells, via binding to two NK cell specific surface receptors, NK2GD and NKp80, respectively [89]. K5 induces the internalization of MICA/B, via ubiquitination of lysine residues on the cytoplasmic tails of MICA/B [18,89]. The reduction in expression of these ligands is vital for KSHV to avoid NK cell-mediated lysis, and provides yet another route by which KSHV can escape the innate immune response. K3 and K5 have also been shown to inhibit the production of IFN-γ by downregulating the expression of γ-interferon receptor 1 (IFN-γR1) [90]. This represents another aspect of the IFN response that can be negatively regulated by KSHV upon infection.

Conclusion & future perspective

It is clear that one of the key components of the KSHV lifecycle is its ability to manipulate the host innate immune response. It is also evident that the virus employs several different strategies to accomplish this, such as the repression of host cellular transcription factors IRF-1, -3 and -7, and IFN-stimulated gene factor-3, which leads to the disruption of the innate immune response. KSHV infection can lead to stimulation of the innate immune response and the virus can also respond to innate immune signals by reactivating and replicating its genome, or making viral proteins that work to shut down the host innate immune response.

The study of KSHV primary infection is critical for understanding the host innate immune response to KSHV infection and the modulation of host responses by the virus. In order to enter latency, the virus must avoid the detrimental consequences of innate immune activation, and hence understanding how the latent state is established after primary infection is key.

Another question relates to the activation of TLR signaling by KSHV. It has been reported that KSHV encodes and packages 11 RNA molecules in the tegument of an infectious particle [91]. Since TLR3 can respond to RNA, it is possible that upon infection and virus entry, the packaged RNA in the tegument is responsible for TLR3 stimulation. Another possibility is that a viral gene activates TLR3 once the genome reaches the nucleus early after infection and that this leads to the upregulation of the TLR3 signaling pathway. Further investigation of how exactly KSHV activates the TLR3 pathway would provide clues into the role of TLR activation during primary KSHV infection.

Elucidation of the roles of vIRF-3 and -4 are also important for determining the ability of KSHV to modulate the innate immune response. At this point only one report on the role of vIRF-4 has been published, and based on the evidence provided thus far for other KSHV vIRFs, and the homology of vIRF-4 to -1 and -2, it is likely that vIRF-4 has additional functions in the subversion/control of the innate immune response. Furthermore, vIRF-3 has been reported to have both stimulatory and repressive activities on IRF-3- and -7-mediated transcription of the IFN response [57–60]. Hence, there is much to be learned about the role of this protein and its contribution to KSHV's ability to manipulate the host immune response.

Viral Bcl-2 is another interesting viral protein that may be involved in innate immunity as it relates to apoptosis and autophagy. Inhibition of both apoptosis and autophagy by vBcl-2 points to a critical role for vBcl-2 during both primary infection and reactivation. Further study on the mechanism(s) by which vBcl-2 can inhibit these responses will provide information about KSHV persistence in the host.

Almost all viruses induce some sort of type I or II IFN response upon primary infection, and we reported that IFN-β is induced in monocytes as well as a monocytic leukemia cell line (THP-1) after KSHV infection [37]. It is unclear if type I or II IFN responses are induced in other cell types in response to KSHV infection. However, Naranatt *et al.* showed that a number of IFN-inducible genes are activated upon KSHV infection [81]. Hence, the ability of KSHV to induce IFN responses may depend on cell type and/or the multiplicity of infection.

In summary, KSHV, with its myriad of immune evasion genes, is an excellent model system for studying immune modulation of the host response to viral infection. This virus is able to evade innate immune responses and enter a latent state for the lifetime of the host. Without clearance of this virus, an infected individual is always at risk for viral reactivation and KSHV-associated pathogenesis. Discovering the mechanisms that KSHV employs to evade host innate and adaptive immune responses, and establish life-long latency, is paramount for the development of future vaccines and therapeutics against this herpesvirus.

Executive summary

- Kaposi's sarcoma-associated herpesvirus (KSHV) is the leading cause of cancer in HIV-infected individuals.
- KSHV has pirated multiple cellular genes to regulate/control the innate immune response to primary infection.

Toll-like receptors

- Toll-like receptors (TLRs) recognize incoming pathogens and aid in the initiation of the innate immune response.
- Multiple TLRs have been shown to be involved in virus recognition.
- TLR3 can be upregulated in response to KSHV infection, while TLR4 is suppressed upon KSHV infection.
- Stimulation of TLR7/8 can lead to reactivation and production of infectious KSHV virions from latently infected B cells.

Complement system

- The complement system is involved in recognition of invading pathogens. Complement activation leads to:

- Lysis of the pathogen via membrane attack complex
- Degradation via opsonization

- KSHV encodes a complement control protein, KCP, which can prevent both opsonization and the formation of the membrane attack complex.

Viral interferon regulatory factors

- Viral interferon regulatory factors (IRFs) are homologs of the cellular IRF family of proteins.
- Viral IRFs have been shown to interfere with the transcriptional activity of the cellular IRFs, thereby inhibiting the host innate immune response, primarily the type I IFN response.
- Viral IRF-4 can also inhibit apoptosis via degradation of p53.

Additional viral immune modulators

- Open reading frame 45 inhibits cellular IRF-7.
- Open reading frame 50 can induce IRF-7 degradation via ubiquitination.
- Viral Bcl-2 can inhibit proapoptotic death signals and is also an inhibitor of autophagy.
- Viral IL-6 can inhibit the IFN response to KSHV infection.
- K-bZIP can suppress the IFN-β1 response to virus infection.
- K5 downregulates ligands that induce cell death via natural killer cells and also downregulates MHC I molecules.

Acknowledgments

The authors thank Sean Gregory for critical reading of the manuscript and Michelle West for help with the manuscript figures. Due to space restrictions and the restriction on the number of citations over 5 years, we regret that we had to omit many important references.

JA West is supported by a NRSA fellowship, F32-AI078735. B Damania is a Leukemia & Lymphoma Society Scholar and a Burroughs Wellcome Fund Investigator in Infectious Disease. Her work is supported by grants CA096500, DE18281 and HL083469 from the NIH.

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Papers of special note have been highlighted as:

■ of interest

■■ of considerable interest

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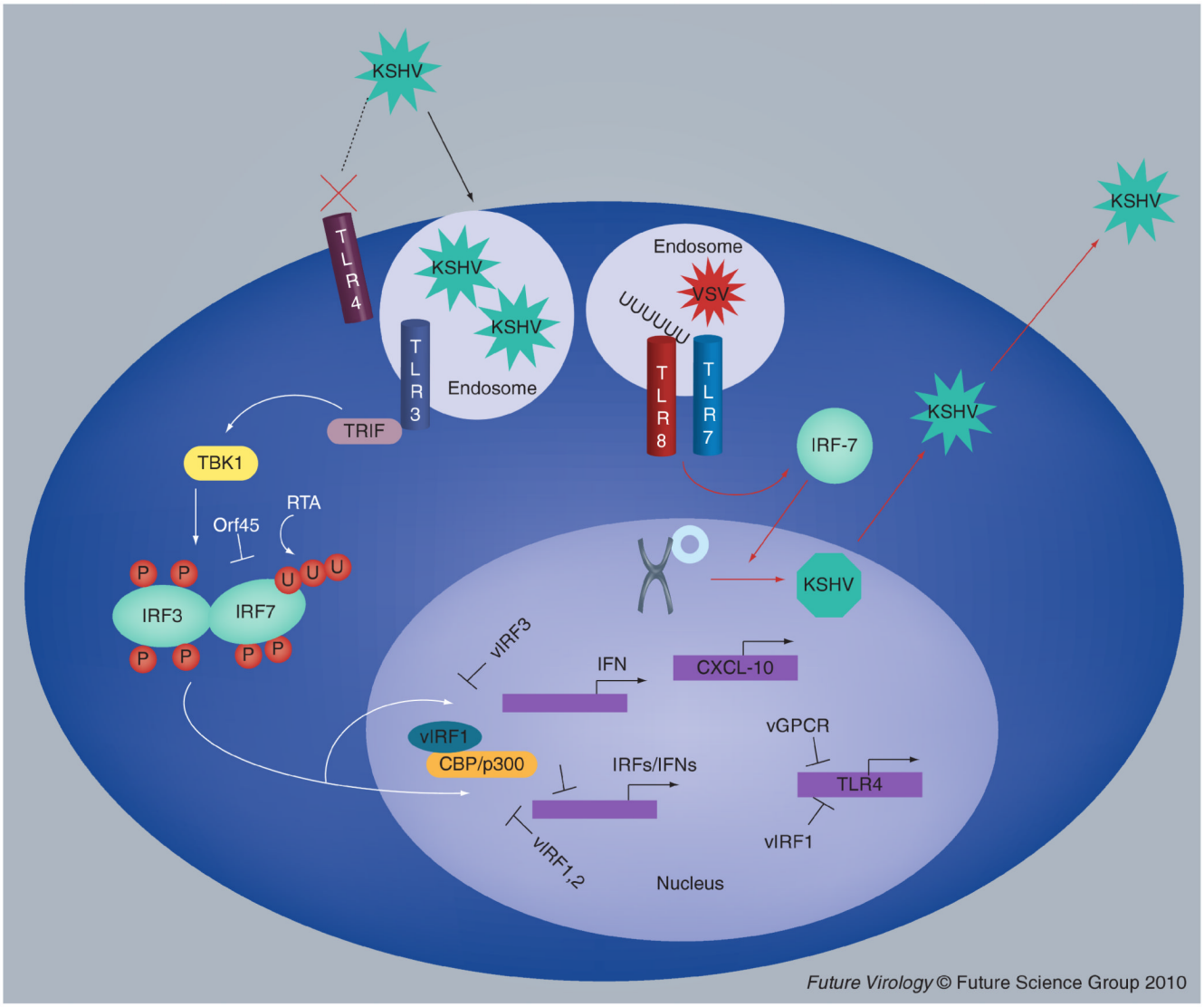

Figure 1. Modulation of the Toll-like receptor pathway by Kaposi's sarcoma-associated herpesvirus

After entry via endocytosis, KSHV stimulates TLR3, which leads to upregulation of downstream cytokines such as CXCL-10 and IFN-β1 in monocytes, while KSHV can downregulate the expression of TLR4 after endothelial cell infection. KSHV vGPCR along with vIRF1 are responsible for this TLR4 inhibition. The KSHV *ORF45* IE gene inhibits IRF-7, while KSHV RTA targets IRF for degradation via ubiquitination. vIRF-1 binds CBP/p300, inhibiting the transcription of cellular IRFs and the IFN response. vIRF-3 blocks the activation of the IFN response by blocking IRF-7 binding to IFN promoters. vIRF-2 also blocks the IFN response via inhibiting the transcription function of cellular IRFs. Finally, in the context of latency, TLR7/8 stimulation with poly-(U)ridine or vesicular stomatitis virus, leads to reactivation of latent KSHV and infectious virion production. IFN: Interferon; IRF: Interferon regulatory factor; KSHV: Kaposi's sarcoma-associated herpesvirus; TLR: Toll-like receptor; vGPCR: Viral G protein-coupled receptor; vIRF: Viral interferon regulatory factor; VSV: Vesicular stomatitis virus.

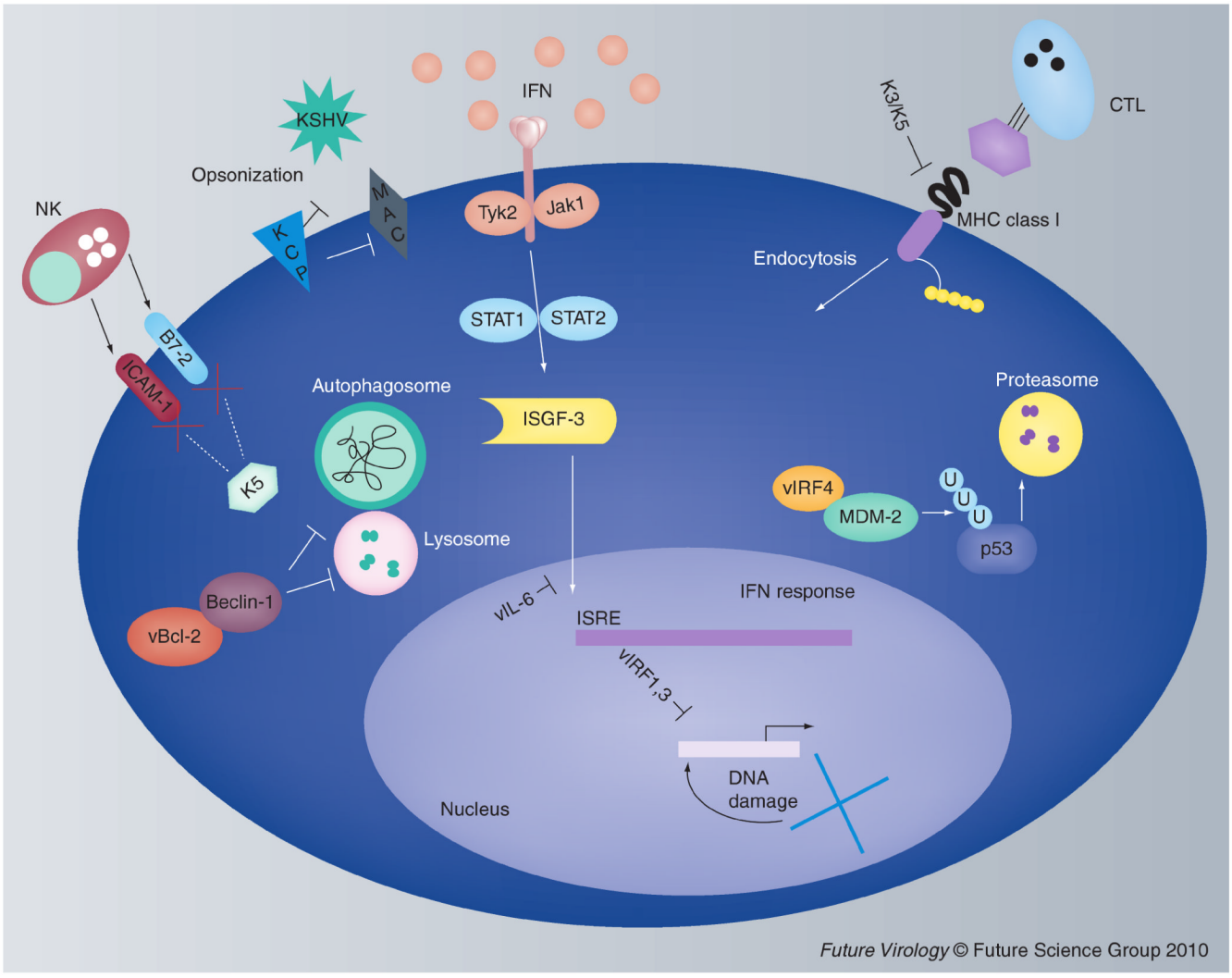

Figure 2. Kaposi's sarcoma-associated herpesvirus complement protein blocks two aspects of the host complement response, opsonization and the membrane attack complex

K3/K5 block the expression of cell surface ligands ICAM-1 and B7-2, which activate NK-mediated cell death. K5 also enhances the endocytosis of MHC class I molecules, which inhibits recognition by CTLs. vIL-6 blocks ISGF-3 from binding the IFN promoter, inhibiting the production of IFN. vBcl-2 binds the autophagy enhancement protein Beclin-1, inhibiting the process of autophagy, a process involving autophagosomes, and lysosomes in which cellular components are degraded by lysosomes. vIRF-4 can bind and stabilize MDM-2, which in turn leads to the ubiquitination and subsequent degradation of p53 by the proteasome.

CTL: Cytotoxic T lymphocyte; IFN: Interferon; ISGF: Interferon-stimulated gene factor; ISRE: Interferon-stimulated response element; KSHV: Kaposi's sarcoma-associated herpesvirus; NK: Natural killer; STAT: Signal transducer and activator of transcription; vBcL: Viral Bcl; vIL: Viral IL; vIRF: Viral interferon regulatory factor.