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Interplay between Kaposi's sarcoma-associated herpesvirus and the innate immune system

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Abstract

Understanding of the innate immune response to viral infections is rapidly progressing, especially with regards to the detection of DNA viruses. Kaposi's sarcoma-associated herpesvirus (KSHV) is a large dsDNA virus that is responsible for three human diseases: Kaposi's sarcoma, primary effusion lymphoma and multicentric Castleman's disease. The major target cells of KSHV (B cells and endothelial cells) express a wide range of pattern recognition receptors (PRRs) and play a central role in mobilizing inflammatory responses. On the other hand, KSHV encodes an array of immune evasion genes, including several pirated host genes, which interfere with multiple aspects of the immune response. This review summarizes current understanding of innate immune recognition of KSHV and the role of immune evasion genes that shape the antiviral and inflammatory responses.

Keywords

KSHV; Innate Immunity

Introduction

Kaposi's sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8), is the most recently identified human herpesvirus [1] and one of seven viruses known to cause cancer in humans [2]. Its namesake, Kaposi's sarcoma, is the most common cancer in untreated AIDS patients [3]. KSHV is also associated with two rare lymphoproliferative disorders: primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD) [4]. KSHV is a γ -herpesvirus, a subfamily that also includes Epstein-Barr virus (EBV) and murine herpesvirus 68 (MHV-68). Like other herpesviruses, KSHV establishes lifelong infections in spite of host immune defenses. Both innate and

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adaptive immunity coordinate the control of KSHV in infected individuals [5-8]. On the other hand, inflammatory cytokines and immune cell infiltrates play a crucial role in the early stages of KS development [3, 9]. Moreover, KSHV paradoxical immune reconstitution inflammatory syndrome (KS-IRIS), a rare but life-threatening complication of KS patients, is precipitated by immune reconstitution following the initiation of HAART [10]. Thus, a better understanding of the interplay between KSHV and the immune system is needed. This review focuses on the recognition of KSHV by pattern recognition receptors (PRRs), NK cells and phagocytes, and the strategies used by KSHV to interfere with innate immune responses.

Innate immunity is the first line of protection against invading pathogens and consists of both cellular components (e.g. NK cells, neutrophils, macrophages and pDCs) as well as secreted factors (e.g. type I IFNs and pro-inflammatory cytokines). Innate immune responses are initiated by germline-encoded PRRs, which include Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), Nod-like receptors (NLRs), AIM2-like receptors (ALRs) and C-type lectin receptors (CLRs). Engagement of TLRs and RLRs leads to activation of latent transcription factors such as NF κ B and interferon regulatory factor (IRF) family members, which in turn control the activation of hundreds of target genes. In addition, activation of certain NLRs controlling the release of cytokines, PRR activation also leads to higher expression of MHC-II, CD40, CD80 and CD86, key players in mobilizing the adaptive immune response.

The KSHV lifecycle

KSHV uses a variety of receptors to enter target cells [11-13]. Upon entry, the capsid and the contents of the tegument are released into the cytosol [11]. Then the capsid is transported to the nucleus where the KSHV genome is released [11]. The default outcome of KSHV infection is the establishment of latency, during which active transcription is mostly restricted to a ~10kb region of the genome called the latency locus. The core latency genes include LANA (latency-associated nuclear antigen), vCyclin, vFLIP (viral FADD-like IL-1 β -converting enzyme (FLICE)-inhibitory protein), Kaposin-A -B and -C, and 12 pre-miRNA [14-16]. The expression of these latency genes occurs from a complex set of spliced, polycistronic transcripts [17], one of which harbors the intronic precursor of miRNAs [18]. In addition to these core latency genes, PEL and MCD tissues show expression of an additional latent gene, vIRF-3, also known as LANA-2 [19]. Most recently, limiting-dilution analysis of mRNAs from KSHV-infected cells showed that K1 is expressed at low levels in a variety of latently infected cell-types and latent vIL-6 transcripts could also be detected in some context [20].

Upon certain stimuli, latently infected cells can enter the lytic phase, which is defined by replication of linear viral genomes and an ordered cascade of viral gene expression that culminates in the lysis and release of mature virion particles from the host cell. Replication and transcription activator (RTA), the major transcription factor involved in reactivation, activates many lytic promoters on the KSHV genome [21]. In addition to the latent and lytic gene expression programs, non-canonical induction of lytic genes can occur in some contexts. For example, Notch signal transduction activates a subset of lytic genes, including

v-IL6, K3 and K5, but does not result in full-blown lytic replication in BCBL-1 cells [22, 23]. Lymphatic endothelial cells undergo a unique transcription program that includes expression of several lytic genes such as ORF45 [24, 25]. Similarly, expression of RTA, as well as several immune modulatory proteins such as vIL-6, vMIP-II, K5 and ORF54, is evident following *de novo* infection of KSHV [26].

Innate immune recognition of KSHV

Innate immune recognition of herpesviruses involves a variety of PAMPs and PRRs (reviewed in [27]). The main target cells of KSHV are B cells and endothelial cells [28, 29] but monocytes [30, 31] and dendritic cells [32, 33] are also susceptible to infection. Thus, KSHV encounters a broad repertoire PRRs, many of which have been shown to play important roles in the innate immune response to KSHV (Table 1). While information on KSHV PAMPs is sparse, studies implicate envelope glycoproteins and viral nucleic acids [34-37], consistent with what is known for other herpesviruses [27]. Following target cell entry, KSHV-infected cells are subject to inspection by a variety of immune cells, including NK cells, macrophages, and neutrophils. During this process, plasma membrane proteins, such as MHC-I, MHC-class-I-polypeptide-related sequence (MIC) A and B, and CD200, play pivotal roles in innate immune recognition. However, these responses may not be universally detrimental to persistent infection: KSHV-encoded factors such as vFLIP and Kaposin B, selectively promote activation of innate immune responses [38-40], which may ultimately contribute to the survival and proliferation of infected cells and the dissemination of the progeny virus.

Nucleic Acid Sensors

Foreign or aberrantly localized DNA and RNA are a potent trigger of type I IFN and pro-inflammatory cytokine production. Several DNA sensors have been proposed, such as IFN γ -inducible (IFI16) and cGAMP synthetase (cGAS), and viral DNA recognition can occur in the cytosol, endosomal compartments and nucleus (reviewed in [41, 42]). KSHV virions harbor viral DNA within the capsid shell and viral mRNAs are present in the tegument layer [43]. Thus, there are several opportunities for viral nucleic acids to be detected by host sensors.

IFI16 is a member of the PYHIN protein family, characterized by an N-terminal Pyrin domain and at least one C-terminal HIN domain [44]. It is distinguished from other known DNA sensors by its ability to shuttle between the cytosol and the nucleus [41], a process regulated by the acetylation status of lysine residues within the NLS of IFI16 [45]. Although originally shown to sense HSV-1 DNA in the cytosol [46], accumulating evidence suggests IFI16 primarily functions in the nucleus [45, 47-49]. As early as 2 hours following *de novo* infection of primary endothelial cells, KSHV genomic DNA is evident within IFI16-containing nuclear bodies and this phenotype is accompanied by IFI16-dependent inflammasome formation and caspase-1-mediated secretion of IL-1 β [47]. IFI16 also plays a crucial role in the persistent release of IL-1 β from latently infected B cells and endothelial cells [50]. This may be particularly relevant to KS pathogenesis, which is characterized by elevated levels of IL-1 β and other cytokines [9, 51]. IFI16 was originally shown to interact with BRCA1 at sites of DNA damage. While KSHV is known to induce the DNA damage

response (DDR), the potential link between KSHV-induced DDR and IFI16 remains unexplored.

TLR9 is an endosomal TLR that can detect virion-associated nucleic acid or replication intermediates [52]. Like other endosomal TLRs (TLR3, 7 and 8), TLR9 relies on endocytosis or autophagy for the delivery of PAMPs [53]. TLR9 is mainly expressed in B cells and pDCs, where it triggers IRF7-dependent activation of type I IFNs, in particular, IFN- α [52]. *De novo* infection of pDCs by KSHV results in the induction of IFN- α and this phenotype is at least partly dependent on TLR9 [33]. On the other hand, UV-treated KSHV is unable to do so, supporting the notion that KSHV DNA is the potential trigger of TLR9 activation in this cell type [33]. Although other TLR9 ligands have been proposed, unmethylated CpG motifs of double-stranded DNA (dsDNA) is the best characterized TLR9 agonist [52]. Interestingly, the KSHV genome has a normal CpG abundance [54], suggesting that the viral genome itself is not under selective pressure to avoid TLR9 stimulation. In contrast, reduced CpG content and suppression of CpG motifs is a prominent feature of other γ -herpesvirus genomes [54, 55]. In mice, TLR9 is critical for controlling viral loads during both acute and latent infection of MHV-68 in mice [56].

TLR3 senses viral replication intermediates such as dsRNA and this leads to TRIF-dependent induction of inflammatory cytokines and type I IFN [52]. *De novo*, KSHV infection of the monocytic THP-1 cells causes a subset of cellular genes to become transiently upregulated, including TLR3 itself and TLR3-dependent genes such as CXCL10 and IFN β [31, 57]. While the TLR3 pathway is clearly affected by KSHV, it is not known whether this involves direct stimulation of TLR3 by a KSHV PAMP. TLR3 is important for controlling mouse cytomegalovirus (MCMV) replication in mice [58]. Furthermore, TLR3-deficiency is associated with childhood HSV-1 encephalitis and an intact TLR3 pathway is necessary for controlling HSV-1 replication in the CNS of mice [59-61]. On the other hand, MHV-68 latency establishment is not affected by TLR3-deficiency in mice [62] and KSHV infection does not appear to upregulate TLR3 expression in lymphatic endothelial cells (LEC) [63]. Thus, the role of TLR3 in sensing KSHV is still not well understood.

RIG-I, a cytosolic RNA sensor, can recognize 5' triphosphate RNA of both RNA and DNA viruses [52] and requires TRIM25-mediated ubiquitination for its signaling activity [64]. Upon KSHV infection, RIG-I contributes to IFN β production and suppression viral gene expression [35, 65]. Moreover, lytic replication of KSHV and MHV-68 was increased in RIG-I^{-/-} cells relative to wildtype cells [35]. RNA purified from KSHV-infected cells undergoing lytic replication were sufficient to activate RIG-I signaling upon delivery by transfection [35]. Although the identity of the RNA PAMP(s) involved in RIG-I activation remains unknown; PAN RNA, which accounts for ~80% of polyadenylated KSHV RNA [66], does not appear to play a role in RIG-I activation [35]. The same study demonstrated that expression of ORF64, a conserved herpesviral tegument protein, results in reduced TRIM25-dependent ubiquitination of RIG-I and IFN β promoter activity [35]. ORF64-homologs carry DUB enzymatic activity [67] and an MHV-68 mutant with impaired ORF64 DUB activity is attenuated in WT mice [68]. Taken together, the RIG-I pathway can be activated by KSHV infection and ORF64 expression is important to counter this effect.

Other Sensors

TLR4 recognizes LPS from bacteria but it also has a protective role against viruses. Following KSHV infection of LECs, lack of TLR4 resulted increased levels of LANA mRNA and a reduction in inflammatory cytokines (TNF α , IL-1 β , IL6) and type I IFN (IFN β) [63]. Although it is not known how KSHV triggers a TLR4-dependent response, UV-inactivated KSHV retains the ability to induce TLR4 signaling, suggesting that glycoproteins such as gB and K8.1 may act as ligands [63]. The human respiratory syncytial virus (RSV) F protein is a known trigger of TLR4 and TLR4 has a protective role against RSV infection in mice [69] as well as humans [70]. It is known that treatment of fibroblasts with a purified soluble version of K8.1 is sufficient to induce IFN β and ISGs [34, 37]. Thus, TLR4 appears to contribute to innate immunity against KSHV by recognizing glycoproteins on the KSHV envelope. Of note, HIV-1-infected patients harboring a TLR4 SNP were more likely to suffer from MCD compared to other subjects [63]. The significance of TLR4 in the regulation of KSHV is further highlighted by evidence that vIRF-1 and vGPCR are able to suppress the transcription of TLR4 [63].

NLRP1 is currently the only nucleotide binding and oligomerization leucine-rich repeat family member implicated in the detection of KSHV infection [71]. It is one of many cytosolic proteins known to form inflammasomes, oligomeric protein complexes that mediate proteolytic activation of inflammatory caspases [72]. The major outcome of inflammasome activation is the maturation and release of IL-1 β and IL18 and the induction of pyroptosis [72]. Inflammasome activation is initiated by the NLRs, in response to a variety of stimuli, including uric acids, muramyl dipeptide (MDP), potassium efflux and anthrax toxin [72]. Expression of a large tegument protein encoded by KSHV ORF63 prevents MDP-dependent inflammasome formation by blocking the oligomerization of NLRP1 as well as the interaction between NLRP1 and pro-caspase-1 [71]. A small domain of ORF63 was predicted to be distantly related to NLRP1 [71], although subsequent computational analysis predicts that ORF63 is a U30 domain containing protein that lacks significant homology to NLRP1 [73]. Nevertheless, knockdown of NLRP1 resulted in more efficient TPA-induced lytic replication of KSHV in BCBL-1 cells, a finding which correlated with reduced IL-1 β secretion [74]. Thus, inflammasomes appear to be important for curbing lytic replication. As with other studies involving KSHV and PRRs, future studies are needed to determine how KSHV infection triggers an NLRP1-dependent response.

Tetherin is best characterized as a restriction factor [75, 76]. However, there is now evidence that it also functions as an innate sensor of viral infection [77-79]. Tetherin can induce TAK1-dependent activation of the NF κ B pathway in response to HIV infection [77, 78]. HIV virion tethering or antibody-mediated crosslinking of surface tetherin significantly enhance this signaling activity [77]. There is also evidence that tetherin mediates type I IFN production, a finding that potentially stems from enhanced exposure of the virion to endosomal TLRs [77]. Knockdown experiments show that lower tetherin expression correlates with higher levels of infectious KSHV recovered from HeLa cell supernatants [80, 81], suggesting the “tethering” mechanism that blocks HIV virion release can also restrict KSHV. Taken together, these observations hint at a role for tetherin as a PRR for KSHV,

although so far, the sensing function of tetherin has only been characterized in the context of HIV.

The complement system can be triggered by either the innate (lectin and alternative pathways) or adaptive immune system (classical pathway) [82]. While the classical pathway is dependent on antibody-antigen interaction, the lectin pathway is activated through soluble pattern recognition receptors such as mannose-binding lectin (MBL), which recognize carbohydrate moieties, including envelope glycoproteins of viruses [83]. The alternative pathway is triggered by the binding of C3 to the surface of pathogens and functions to amplify complement activation [82]. The major outcomes of complement activation are opsonization of pathogens and the assembly of the terminal complement components that lead to the formation of the membrane attack complex (MAC) [82]. The relevance of complement activation to viral infections is well established and many viruses, including KSHV, encode at least one complement antagonist [84, 85]. Although there is no direct evidence for complement activation by KSHV, the complement regulatory protein of MHV-68 is essential for viral fitness in WT mice but not in C3-deficient mice [86]. Furthermore, the KSHV complement regulatory protein (KCP) antagonizes this process by eliminating C3b and C4b [85, 87, 88], major opsonizing components generated by the C3 convertase of the complement system [82]. Since KCP is a component of the virion envelope [89], it can potentially block complement-opsonization of virion particles as well as infected cell surfaces. This suggests KSHV may also be recognized through the complement system and thus has evolved to evade the complement system, although a potential mechanism of detection involving MBL has not been elucidated.

Cell-mediated Recognition

Whether through PRR activation, expression of chemokines and cytokines homologues (vIL6, vMIP-I, II, III, vGPCR) or modulation of host gene expression, KSHV infection triggers a significant inflammatory response. Furthermore, 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.

NK cells—NK cells are prototypic innate lymphoid cells that can be divided into two subsets: CD56DimCD16+ (~90%), which destroy infected or damaged cells through direct lysis (via perforin and granzymes), and CD56BrightCD16- (~10%), which aid in the recruitment of other immune cells through the production IFN- γ and other cytokines. NK cells identify virus-infected cells through cell surface receptors that transduce both positive and negative signals. MHC-I molecules are the major ligands for inhibitory receptors such as killer Ig-like receptors (KIR) and CD94/NKG2A [90]. On the other hand, activating ligands such as MICA, MICB, UL16 binding proteins (ULBP1-4 and 6), activation-induced C-type lectin (AICL) and NKp44L trigger cytotoxic effector functions through activating NK cell receptors, including NKG2D, 2B4, DNAM-1, NKp80 and the natural cytotoxicity receptors (NCR): NKp30 (NCR3), NKp44 (NCR2) and NKp48 (NCR1) [90]. The surface expression of NK cell ligands can be modulated by viral infection and other cellular stresses such as DNA damage [91].

Several studies have examined NK cell-mediated control of KSHV infection and pathogenesis. Latently infected PEL or fibroblast cells are sensitive to NK cell lysis [5, 92]. Furthermore, AIDS-KS patients with ongoing symptoms have reduced NK cell-mediated immunity compared to patients with indolent classic KS or normal blood donors [5]. In addition, analysis of 115 patient blood samples showed that NK cells from patients with active KS have reduced cytolytic capacity and NKG2D surface expression, defects that were not seen in normal blood donors or patients with resolved KS [6]. Active KS is also associated with higher serum levels of cytokines and other secreted factors, in particular prostaglandin E2 (PGE2), a pleiotropic hormone that dampens NK cell cytotoxicity, in part by the downregulation of NKG2D expression [6]. KSHV infection induces expression of the Cyclooxygenase-2 (COX-2) and production of its metabolite PGE2 [93, 94]. Thus, it is possible that overproduction of PGE2 by KSHV-infected cells may directly contribute to the systemic hyporesponsiveness of NK cells observed in active KS patients, suggesting a potential link between NK cell phenotype and KS pathogenesis.

The expression of activating ligands is modulated by KSHV infection. KSHV infection of tonsillar B cells causes higher expression of MICA, MICB and ULBP2 [95]. Similar observations were made in human microvascular endothelial cells (HMEC) and immortalized HIV-KSHV-KS cell lines [6]. Upregulation of NK cell activating ligands was shown to be at least partly dependent on the induction of the DDR and correlated with upregulation of activation-induced cytidine deaminase (AID) [95], a member of the AID/APOBEC family with roles in both antibody diversification and intrinsic defense against pathogens [96]. Analogously, a DDR-dependent effect involving APOBEC3G increases NKG2D ligand expression on HIV-infected primary T cells, resulting in enhanced NK cell-mediated lysis [97]. KSHV-mediated upregulation of the DDR has been reported in several other contexts [98-100], suggesting this pathway may be particularly important for NK cell recognition of KSHV-infected cells. On the other hand, NK cell ligand surface expression on fibroblasts latently infected with KSHV is not obviously altered compared to uninfected cells, suggesting MICA, MICB, ULBP2 upregulation may be a cell-type specific phenotype [92].

While KSHV-infected cells can be predisposed to NK cell recognition through induction of the DDR pathway, the virus is genetically equipped to circumvent this threat. Two KSHV-encoded, membrane-bound E3 ligases called K3 and K5 (also known as MIR1 and MIR2, respectively) selectively remove proteins from the cell surface by triggering ubiquitin-dependent endocytosis [101-104]. 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 [105-107]. As a result, NK cell-mediated cytotoxicity is significantly diminished in K5-expressing target cells [106]. In addition, ORF54 can induce downregulation of NKp44L [108], while miR-K12-7 targets MICB mRNA for degradation [109]. 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 [102]. K5 is expressed immediately upon entry into the lytic phase, the expression of K3 is restricted to later stages (Brulois et al., in press). 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. vFLIP may contribute to NK cell inhibition

through the upregulation of NF κ B-dependent MHC-I transcription [110]. Thus, K3, K5, ORF54, miR-K12-7 and other viral factors may function in concert to subvert NK cell surveillance, especially when the risk of recognition is heightened, e.g. by low expression of MHC-I molecules or induction of the DDR.

Phagocytes—Analogously to NK cells, phagocytes interrogate cell and pathogen surfaces using an array of receptors, including activating receptors (e.g. Fc receptors and complement receptors) and inhibitory receptors (e.g. CD200R). CD200R is highly expressed on myeloid and T cell lineages [111], while its cognate ligand, CD200, is a broadly expressed type I transmembrane protein of the IgG superfamily [111]. CD200 has immunosuppressive effects in mice [112, 113]. KSHV encodes a homologue of CD200 called vCD200, which has been shown to inhibit the activation of macrophages [114], neutrophils [115] and basophils [115]. It also acts as a negative costimulatory molecule for antigen-specific T cell responses [116]. On the other hand, vCD200 has also been shown to act as positive regulator by triggering release of inflammatory cytokines (IL-1 β , IL-6, MCP-1, TNF- α) [111, 117]. CD200 homologues can be found in the genomes of several herpesviridae and poxviridae family members, suggesting this is an evolutionarily conserved viral immune evasion strategy [118, 119].

Leukocyte Trafficking—While KS lesions are characterized by significant inflammatory infiltrates, including B, T, monocyte and mast cells [120, 121], certain cell types such as NK cells are notably absent [6]. 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 [106, 122-124], all of which are involved in transendothelial migration (TEM) [125]. It should also be noted that PECAM-1 was shown to be targeted by K5 but not K3 in immortalized endothelial cells (E-DMVECs) [122], while K3 but not K5 is able to downregulate PECAM-1 in primary endothelial cells [124], suggesting these viral proteins may have cell-type specific roles. Nevertheless, a recent screening approach identified more than 70 new plasma membrane substrates of K5, including CD99 [126], one of the key mediators of TEM [127, 128]. Functional studies show that while K3 can block TCR-dependent TEM of EM CD4+ T cells by removal of PECAM-1 [124]. K5 is able to block the capture of flowing EM CD4+ T cells, a TCR-independent step that involves ICAM-1 [124]. This suggests that the role of K5 in TEM likely extends to leukocytes of the innate immune system. KSHV may also interfere with interendothelial cell junctions as downregulation of VE-cadherin by K5 was shown to cause increased cell permeability [123].

Another modulator of leukocyte trafficking is viral macrophage inflammatory protein II (vMIP-II). Although originally characterized as a chemoattractant for Th2 cells ([129, 130], it also broadly inhibits recruitment of other lymphocytes such as monocytes [131] and NK cells [132]. vMIP-II antagonizes CCR3 and CCR5 and blocks RANTES-induced chemotaxis of monocytes [131]. vMIP-II also binds to CX3CR1 and CCR5 and occludes the binding of Fractalkine and RANTES, respectively, resulting in impaired NK cell chemotaxis [132]. The

anti-inflammatory effects of vMIP-II are also evident in Wistar-Kyoto (WKY) rats, an in vivo model of Glomerulonephritis (a kidney inflammatory disease) [133]. On the other hand, vMIP-II has been shown to bind CCR3 and promote chemotaxis of eosinophils [134] and a monocytic cell line [135]. KSHV also has several potential ways of obstructing neutrophil recruitment: for example, vIL-6 is sufficient to block neutrophil recruitment in an in vivo mice model of peritoneal inflammation [136]. Furthermore, vIL-6 is essential for preventing recruitment of neutrophils in KSHV infected endothelial cells [137]. vCD200 is able to block neutrophil recruitment in mice treated with carrageenan, a compound used to induce neutrophil migration [115]. Chemotaxis is also modulated during latent infection: LANA-1 expression in TIVE cells reduces IL-8 expression, resulting in impaired neutrophil migration [138]. Together, these viral proteins may be part of strategy to divert harmful leukocytes and facilitate viral dissemination through a skewed inflammatory response.

KSHV as a Sensor of innate immune activation

The innate immune system can recognize KSHV infection through various PRRs and cell surface receptors. Conversely, KSHV has evolved ways of sensing the status of innate immune activation, perhaps to optimally respond to secondary pathogen infections [139, 140] or local inflammation [141-143]. This aspect of KSHV biology may be particularly relevant to KS, where preexisting inflammation and the maintenance of latency are thought to be key factors for pathogenesis [3, 144-147].

Reactivation of latently infected cell cultures can be triggered by a variety of stimuli including those involving innate immune signaling pathways. Stimulation of TLR7/8 with single-stranded polyuridine results in the upregulation of NF κ B activity and the induction of KSHV lytic reactivation [148], although it is not clear how the TLR7/8 pathway, which activates NF κ B and type I IFNs, leads to lytic replication. Nevertheless, activation TLR3, 4, 5, and 9 leads to reactivation of MHV-68 [149]. It has also been shown that dsRNA-mediated activation of TLR3 increases RTA expression by enhancing translation [150]. On the other hand, the overexpression of IKK ϵ , the downstream kinase for the TLR3-TRIF pathway, does not affect RTA expression in the absence of TPA but it can enhance TPA-induced lytic replication of KSHV [151]. Interestingly, RTA causes ubiquitin-dependent degradation of the major TLR3 adaptor, TIR domain-containing adaptor-inducing IFN (TRIF) [152]. Thus, latent KSHV genomes are poised to reactivate in response to a variety of innate immune signaling pathways.

Selected KSHV genes can be induced in the absence of full-blown lytic replication. Two interferon-sensitive response elements (ISRE) within the vIL6 promoter enable vIL6 production in latently infected PEL cells to upon IFN α treatment [153]. vIL6 can in turn disrupt the resulting signal transduction through IFN α receptor (IFNAR) [153], forming a negative feedback loop analogous to RTA and the TLR3 pathway [152]. An ISRE can also be found in the K1 promoter [154]. Although this ISRE is still uncharacterized, K1 has been shown to express at a low level in latently infected cells [155] and its promoter is enriched in the active mark, H3K4me3 but depleted for the repressive mark, H3K27me3 [156], features consistent with an inducible gene. HIF-1 production is an integral part of inflammatory responses [157] and can be regulated by NF κ B [158]. Functionally characterized hypoxia

response elements (HRE) are distributed throughout the KSHV genome, e.g. the promoters of LANA [159], RTA [160] and ORF34 and ORF35-37 [161, 162], suggesting another avenue through which KSHV rapidly responds to innate immune activation. On the other hand, phosphorylated IRF7 binds to an RRE within the ORF57 promoter, acting as a competitive inhibitor that prevents RTA-mediated induction of this essential lytic gene [163, 164]. An ISRE with the M2 promoter of MHV-68 is occupied by the type I IFN-inducible transcription factor, IRF2, resulting in reduced lytic replication *in vivo* [154].

Innate immunity can also contribute to the maintenance and establishment of latency by suppressing lytic gene expression. Central to this is the activation of NF κ B, a major transcription regulator for genes involved in cell proliferation, survival, angiogenesis and inflammation. NF κ B not only regulates host cell gene express, but also promotes latency of γ -herpesviruses by suppressing lytic gene expression [165]. Consistent with this, lytic reactivation can be triggered by inhibition of NF κ B [165]. Among 34 RTA-responsive promoters within the KSHV genome, 32 are repressed by NF κ B, a process that involves displacement of the major co-activator, RBP-J κ , from its core binding sites on the KSHV genome [166]. NF κ B activation is also crucial for the establishment of latency since knockdown of IKK β or IKK ϵ leads to increased lytic gene expression and impaired latent infection [167]. In addition to NF κ B, IRF4 was shown to occupy the RTA promoter and suppress lytic reactivation [168]. RIG-I and MAVS significantly contribute to the suppression of lytic gene expression, likely through the activation of the NF κ B pathway [35, 65]. On the other hand, MAVS and IKK β enhance lytic replication of MHV-68 by activating MHV-68 RTA through IKK β -mediated phosphorylation [169]. Thus, the role of NF κ B in the regulation of γ -herpesviruses is complex. Nevertheless, the gene expression of KSHV is regulated through a variety of innate immune signaling pathways.

Innate Immune system as a mediator for viral lifecycle regulation

Several KSHV encoded factors modulate NF κ B and other constituents of innate immune responses. This is an effective means of controlling viral latency because many KSHV promoters, particularly those of LANA and RTA, are responsive to NF κ B and other cellular transcription factors as described earlier. Although originally characterized as an inhibitor of death receptors [170, 171], vFLIP is now understood to be the major latently expressed activator of NF κ B in KSHV infected cells [172, 173]. In fact, the role of vFLIP in resistance to cell death can be attributed to NEMO-dependent activation of NF κ B as this in turn upregulates antiapoptotic genes such as Bcl-XL [38, 174]. Activation of NF κ B by vFLIP not only maintains latency, it leads to the production of proinflammatory cytokines and chemokines [175, 176] and is both necessary and sufficient for the induction of spindle cell morphology [177], a prominent characteristic of KSHV-infected cells in KS tumors [9]. Besides its NF κ B-mediated effects, vFLIP also prevents the activation of AP-1, an essential transcription factor for the induction of the RTA promoter [178]. Several other KSHV proteins have been shown to regulate NF κ B, including K1, vIRF3, vGPCR, K15 and ORF75 (reviewed in [179]). The lytically-expressed tegument protein, ORF75, upregulates NF κ B, albeit to a lesser extent than vFLIP [173].

In addition to ORFs, KSHV encodes 12 pre-miRNAs that are expressed during latency and processed to form approximately 25 mature miRNAs [180]. Some of these miRNA play a role in modulating the viral lifecycle by targeting components of the NF κ B pathway [151, 181, 182]. miR-K1 upregulates NF κ B by targeting *I κ B α* transcripts for degradation [183]. Moreover, suppression of miR-K1 in chemically-induced PEL cells leads to enhanced lytic gene expression [184]. Similarly, miR-K12-11 contributes to the NF κ B-mediated suppression of lytic gene expression by downregulating IKK ϵ [151]. Interestingly, miR-K9 and miR-K5 can respectively target IRAK1 and MYD88, crucial downstream adaptors for the TLR7/8 pathway. Since TLR7/8 activation triggers lytic reactivation of KSHV in PEL cells, it will be interesting to see whether these miRNAs affect the reactivation of latently infected cells upon treatment of TLR7/8 agonists. It should also be noted that KSHV miRNAs can exert control over the viral lifecycle by directly suppressing the expression of RTA [185-187]. These examples further highlight the importance of the NF κ B pathway in the maintenance of KSHV latency.

Evasion of innate immune responses

PRRs trigger a number of antiviral innate immune responses, including the induction of type I interferons and the activation of autophagy and cell death pathways. Like other persistent viruses, KSHV is well equipped to cope with these responses. In addition to targeting upstream molecules such as sensors and adaptors, KSHV encodes factors that interfere with downstream signaling molecules.

Interferon inhibition

The first phase of the type I interferon response is initiated by the engagement of PRRs, which in turn leads to signaling cascades that culminate in the activation of latent transcription factors, in particular NF κ B, IRF3, IRF7 and AP-1. Nuclear accumulation of these transcription factors leads to the expression of IFN α/β and proinflammatory cytokines. During the second phase, secreted IFN α and IFN β bind to IFNAR and activate the JAK-STAT pathway, which triggers translocation of the ISGF3 complex to the nucleus where it controls the expression of IFN-stimulated genes (ISGs). The ISGF3 complex controls the expression of IFN α/β genes and this positive feedback regulation is important for signal amplification and the establishment of an “antiviral state.” Since KSHV-mediated antagonism of the IFN response has been thoroughly covered in a recent review [188], this section provides an overview of this topic with an emphasis on recent developments.

IFN induction Pathway

Upon *de novo* infection, the KSHV virion delivers the tegument protein, ORF45, which prevents the phosphorylation of IRF7 by binding to IRF7 and acting as a decoy substrate of IKK ϵ and TBK1 [37, 189-193]. In addition, RTA induces the proteasomal degradation of IRF3 and IRF7 by recruiting the HECT E3 ligase, RAUL (RTA-associated ubiquitin ligase; also known as KIAA10 or UBE3C) [194, 195]. KSHV encodes an orthologue of miR-155 designated miR-K12-11, which targets IKK ϵ mRNA for degradation, resulting in the reduced IKK ϵ -mediated IRF3 and IRF7 phosphorylation [196-198].

Type I IFN induction is also antagonized within the nucleus, where LANA, K-bZIP (K8), ORF36, vIRF1, vIRF2 and vIRF3 each prevent transcription at the IFN α and IFN β promoters, although the inhibitory mechanism is slightly different for each protein. For example, K-bZIP displaces IRF3 from its DNA binding site (PRD-I/III) within the IFN β promoter, resulting in reduced expression of IFN β and other IRF3-dependent genes such as RANTES [199]. LANA also occupies the PRD-I/III site and thereby blocks IFN β induction during latency [200]. The conserved herpesvirus kinase encoded by ORF36 has also been shown to have anti-IFN activity; its MHV-68 homologue binds and inhibits the activated form of IRF3, resulting in (1) abrogated interaction between IRF3 and the CBP/p300 coactivator and (2) suppression of IRF3-dependent recruitment of RNA polymerase II to the IFN β promoter [201]. The anti-IFN effect of KSHV ORF36 likely involves an analogous mechanism, although this has not been rigorously demonstrated yet.

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 [202-204]). For example, vIRF1 interacts with p300 and blocks the association between p300 and IRF3 [205-207]. vIRF1 has also been shown to block transcription of TLR4 [208]. Unlike vIRF1, which targets IRF3, vIRF3 inhibits IRF7 and prevents IFN α production [209]. The closely related rhadinovirus, RRV, contains a vIRF locus harboring 8 vIRF genes, designated R6-R13. Interestingly, two clusters of RRV vIRF genes (R6-R9 and R10-R13) appear to originate from a duplication event. Nevertheless, the presence of this locus is crucial for stemming the type I IFN response during primary infection of rhesus fibroblasts and PBMCs [210]. Furthermore, lack of the vIRF locus leads to an earlier and more sustained release of cytokines and a more rapid T cell response following experimental infection of rhesus macaques [211], emphasizing the role of the innate immune response in prompt coordination of adaptive immunity. Even though most of the type I IFN viral antagonists described here are only expressed during lytic replication, LANA and miR-K12-11 are expressed during latency. Interference with IFN β expression may be particularly crucial during latency: although vFLIP does not activate type I IFN by itself, vFLIP-mediated NF κ B activation predispose latently infected cells to a more robust IFN response [39].

IFN Signaling Pathway

Several KSHV genes have been shown to block the second phase of the IFN response by targeting the IFNAR1-JAK-STAT-ISGF3 pathway. For example, vIL6 prevents the formation of the ISGF3 complex possibly by blocking Tyk2 phosphorylation [153] while vIRF2 inhibits ISGF3-mediated transcription [212]. In addition, functional screens in protein-coding genes of KSHV, EBV and MHV-68 have identified a handful of distantly related IFN antagonists [213-216] referred to as dUTPase-related proteins (DURPs), which comprise ORF10, ORF11 and ORF54 [217]. ORF10 was shown to form an inhibitory complex that includes IFNAR subunits, Jak1 and Tyk2, and STAT2 [214]. As a result, ISGF3 failed to accumulate in the nucleus in the presence of ORF10 [214]. While the anti-IFN effect of KSHV ORF54 has not been mechanistically characterized, its MHV-68 homologue induces degradation of IFNAR1 [215]. Currently, there is no report regarding KSHV ORF11 and its potential involvement in IFN signaling but it has been shown that the

MHV-68 and EBV homologues can antagonize the type I IFN response, albeit via distinct mechanisms [213, 216]. Thus, DURPs appear to be an emerging family of anti-IFN genes analogous to the vIRFs. Of note, dUTPase activity is absent from ORF10 and ORF11 and is dispensable for the ORF54-mediated degradation of IFNAR1 [215, 217]. It is interesting to consider the evolutionary path from metabolic enzyme to IFN antagonist. The fact that KSHV devotes much of its coding potential to the inhibition of the IFN response underscores the importance of this pathway in the control of viral infections.

Cell Death and Autophagy

Programmed cell death (PCD) is one of the major innate defense mechanisms against viral infection and can be grouped into apoptosis, autophagic cell death, pyroptosis and necroptosis [218]. The innate immune response can promote cell death through a variety of mechanisms [218]. For example, the type I IFN response leads to upregulation of the death receptor ligands, such as TRAIL [219]. Alternatively, effector cells such as NK cells, rely on the perforin-granzyme system to trigger intrinsic cell death [218]. KSHV encodes several antiapoptosis factors, including vBcl-2 [220], vFLIP [174], vIAP [220], K1 [221, 222], vIRF4 [223], LANA [224] and miR-K10a [225]. 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. It is divided into four sequential phases: initiation, nucleation, elongation and lysosomal fusion. Autophagy is a major component of antiviral immunity [226] and can be upregulated by a variety of innate immune signaling pathways, including TLRs [227]. Furthermore, there is crosstalk between autophagy and innate immunity [228]. For example, upon activation, the DNA sensor cGAS becomes a positive regulator of autophagy, thereby facilitating clearance of pathogen DNA from the cytosol; in the meantime Beclin-1 tempers cGAS-induced cytokine production, ensuring a well-balanced immune response [229].

Many viruses, including KSHV, have evolved ways of modulating the autophagy pathway [230]. KSHV encodes three autophagy inhibitors (vBcl-2, K7 and vFLIP) that are each able to block distinct steps of autophagy. vBcl-2 blocks the vesicle nucleation step through its inhibitory interaction with Beclin1 [231]. K7 blocks lysosomal fusion by interacting with Rubicon and enhancing the interaction between Rubicon and the Beclin1/UVRAG/Vps34 complex [232]. vFLIP inhibits vesicle elongation by binding and inhibiting the activity of Atg3, a protein for LC3 processing and vesicle elongation [233]. vFLIP is important for maintaining the proliferation of latently infected cells as it serves to counter balance the side effect of another latent protein, v-Cyclin, whose expression leads to autophagy and oncogene induced senescence [234].

Conclusions

There are a variety of ways by which KSHV triggers as well as evades the innate immune system and our understanding of these processes continues to deepen. However, many questions still remain. For example, although many PRRs have been shown to be involved in the innate immune response to KSHV, it is not clear which virion component(s) or

KSHV-associated products elicit PRR activation. Despite the identification of numerous cytosolic DNA sensors involved in HSV-1 detection, TLR9 (endosomal) and IFI16 (nuclear) are currently the only reported DNA sensors for KSHV. Are cytosolic DNA sensors such as the recently identified cGAS [235] involved in KSHV detection? Future studies may shed light on these topics.

The identification and characterization of immune evasion genes has significantly advanced our understanding of persistent infection. On the other hand, because KSHV encodes so many factors with seemingly redundant roles, it is becoming increasingly difficult to predict the physiological circumstances in which a given gene will be important. Moreover, many immune evasion genes are not expressed during latency, which is the predominant gene expression program driving the proliferation of malignant cells in KS, PEL and to a lesser extent MCD. Thus, the current challenge is to go beyond the limitations of cell culture models and knockdown experiments. The ongoing refinement of genetic engineering techniques and in vivo infection models offers unprecedented opportunities to further examine the interactions between KSHV and the immune system.

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Figure 1. Recognition of KSHV infection by the innate immune system

KSHV infection triggers activation of a variety of PRRs, including IFI16, RIG-I, TLR9 and TLR3. At the same time, KSHV-encoded proteins (red) can directly antagonize PRRs. The green circle indicates KSHV DNA.

Figure 2. KSHV-mediated regulation of NK cell activation

NK cell activation is controlled by a series of membrane bound (HLA-A/B/C/E, NKG2D ligands, MICA/B, AICL, ICAM-1, B7-2, NKp44L) and secreted factors (e.g. PGE2). These factors can be grouped into two categories: activators (right side of dashed line) or suppressors (left side of dashed line). KSHV infection alters the transcription of Cox-2, which leads to the upregulation of PGE2. At the same time, KSHV induces DNA damage via the upregulation of AID, ultimately enhancing expression of NKG2D ligands. KSHV-encoded factors can inhibit (red) or activate (green) various cellular components involved in NK cell activation.

Figure 3. The KSHV genome is responsive to innate immune activation

Several viral promoters are response to innate immune signaling pathways such as NFκB, IRF7 and IFNα/β.

Figure 4. Strategies for evading the type I IFN response

More than a dozen KSHV-encoded factors (red) have been shown to block various components of first (left side) and second (right side) phases of the type I IFN response pathways.

Table 1

PRR	PAMP	Localization	Response	Reference
IFI16	Genomic DNA	Nucleus/Cytoplasm	IL-1 β and IL-18	[47, 50]
RIG-I	Lytic RNA	Cytoplasm	NF κ B, type I IFN	[35]
TLR9	Viral DNA?	Endosomal compartment	NF κ B, type I IFN	[33]
TLR3	Viral RNA?	Endosomal compartment	NF κ B, type I IFN	[31]
TLR-4	Envelope glycoproteins?	Plasma Membrane	NF κ B, type I IFN	[208]
NLRP1	?	Cytoplasm	IL-1 β and IL-18	[74]
Tetherin?	Virion?	Plasma membrane	NF κ B, type I IFN	[77, 80]