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REVIEW

KSHV strategies for host dsDNA sensing machinery

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The innate immune system utilizes pattern recognition receptors cyclic GMP-AMP synthase (cGAS) to sense cytosolic double-stranded (ds) DNA and initiate type 1 interferon signaling and autophagy pathway, which collaborate to limit pathogen infections as well as alarm the adaptive immune response. The genomes of herpesviruses are large dsDNA, which represent a major class of pathogen signatures recognized by cellular DNA sensor cGAS. However, to successfully establish the persistent infection, herpesviruses have evolved their viral genes to modulate different aspects of host immune signaling. This review summarizes the evasion strategies of host cGAS DNA sensing pathway by Kaposi's Sarcoma-associated Herpesvirus (KSHV) and their contributions to KSHV life cycles.

KEYWORDS Kaposi's sarcoma-associated herpesvirus (KSHV); innate immune response; cyclic GMP-AMP synthase (cGAS); interferon; autophagy; evasion strategies

INTRODUCTION

Kaposi's sarcoma-associated herpesvirus [KSHV/human herpesvirus 8 (HHV-8)] belongs to the *gammaherpesvirus* family, which includes Epstein-Barr virus (EBV), herpesvirus saimiri (HVS), and murine gammaherpesvirus 68 (MHV-68) (Mesri et al., 2010). KSHV is a DNA tumor virus and etiologically linked to Kaposi's sarcoma (KS) as well as two rare B-cell proliferative diseases, primary effusion lymphoma and multicentric Castleman's disease (Mesri et al., 2010; Avey et al., 2015). In order to efficiently establish the life-long persistency as well as their life cycle, KSHV displays two alternative life cycles, latency and lytic replication (Ye et al., 2011). Latency is a dormant state during which KSHV maintains its genome as a multi-copy circular episomal DNA and only expresses a few viral genes, whereas the lytic cycle leads to the expression of a full panel of viral genes, assembly and release of progeny viral particles, and *de novo* infection of other cells (Sun et al., 1999). The establishment of latency from *de novo* infection and modulation of host immune responses are essential steps for the KSHV life-long persistent infection and pathogenesis. Therefore, KSHV has developed numerous genes for immunomodulatory proteins that subvert the host immune system (Liang et al., 2008). This review will focus on the evasion strategies for dsDNA-mediated host type 1 interferon (IFN) signaling and autophagy pathway by KSHV.

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PART ONE: EVASION OF TYPE 1 IFN SIGNALING

The innate immune system is the first line against pathogen infection and the induction of type 1 IFN is critical for host innate defense mechanisms (Pichlmair and Reis e Sousa, 2007). Infection by herpesviruses, such as herpes simplex virus 1 and KSHV, triggers host pattern recognition receptors (PRRs), which finally induce the production of IFN and inflammatory cytokines through PRRs-adaptors-transcriptional factors cascades. Among these

PRRs, the novel identified DNA sensor cyclic GMP-AMP synthase (cGAS) plays a major role for herpesviruses-induced cytokine production and cellular autophagy pathway (Sun et al., 2013; Wu et al., 2015; Gray et al., 2016; Vance, 2016). The recognition of herpesviral DNA causes the conformational change and exposure of the enzymatic domain of cGAS, which catalyzes the synthesis of cyclic GMP-AMP (cGAMP) from GTP and ATP (Sun et al., 2013). cGAMP serves as a second messenger and binds to the downstream endoplasmic reticulum (ER)-resident adaptor protein STING, leading to the dimerization of STING and subsequently translocation from ER to perinuclear compartment, where STING serves as a scaffold protein to recruit downstream kinase TBK1 and transcriptional factor IRF3 (Ishikawa et al., 2009; Sun et al., 2013; Liu et al., 2015). The phosphorylation of IRF3 by TBK1 leads to the dimerization of IRF3 and translocation from cytoplasm to nucleus, which finally binds to the promoter regions of *IFNβ* gene and promotes its transcription (Stetson and Medzhitov, 2006). The secreted IFNβ binds to the IFNR1 receptor of the neighbor cells and turns on hundreds of interferon stimulated genes (ISGs) through JAK-STAT pathway, which have direct or indirect effect for the cellular anti-viral responses (Schoggins et al., 2011). At the meantime, the recognition of herpesviral DNA also causes the association between cGAS and the major autophagy protein Beclin-1, which not only induces the cellular autophagy pathway to eliminate the viral DNA but also directly reduces cGAS enzymatic activity to turn off IFN signaling as a feedback regulation (Liang et al., 2014a, 2014b). The cooperation between cellular IFN induction and autophagy pathway limits the virus infection and alerts the action of host adaptive immunity.

To evade host IFN response, KSHV targets the key steps of host IFN-mediated anti-viral innate immune responses (Figure 1). In this part, we present our current knowledge of innate immune evasion strategies employed by KSHV to control host type 1 IFN signaling.

LANA

The latency-associated nuclear antigen (LANA) of KSHV is the major latent gene and plays the essential role in maintenance of latent viral episomal DNA (Uppal et al., 2014). Although LANA is mainly localized in the nucleus, some isoforms of LANA interacts with the DNA sensor

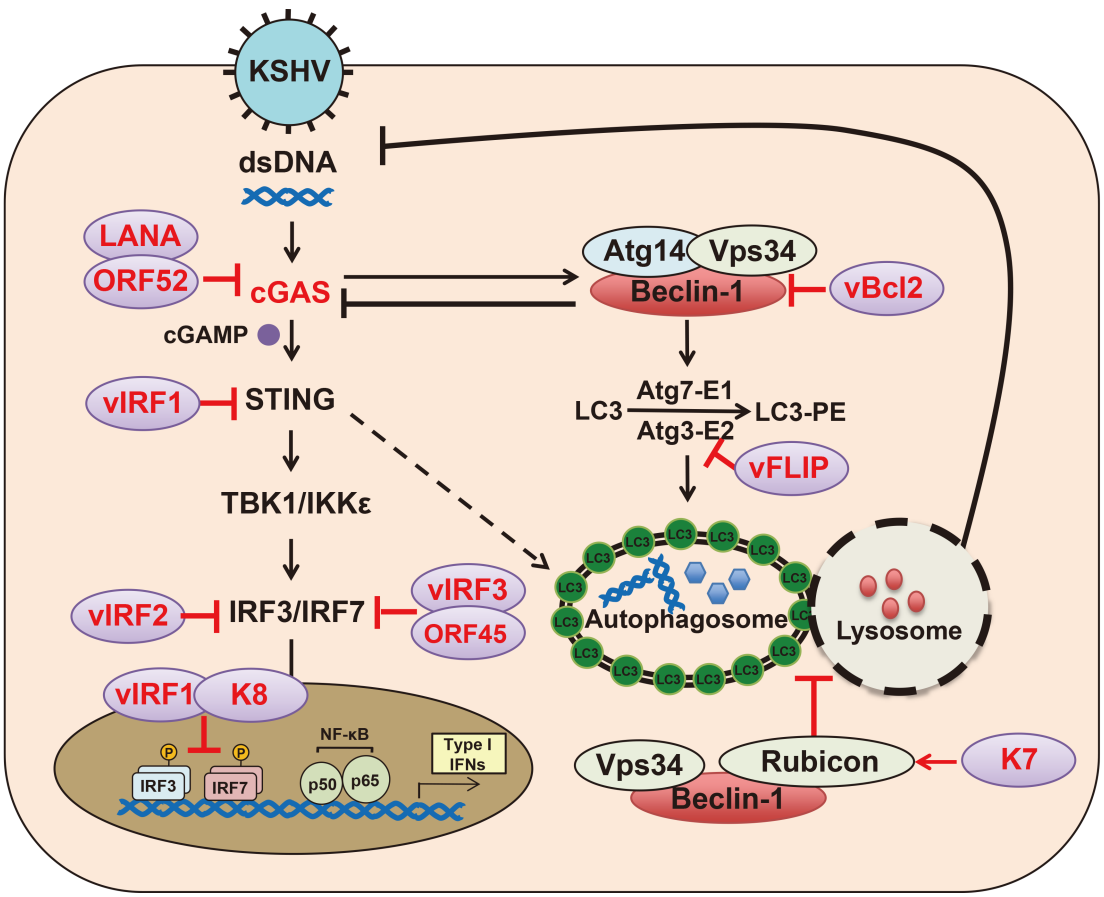

Figure 1. Schematic diagram of evasion strategies of KSHV for dsDNA-mediated IFN and autophagy pathways.

cGAS in the cytoplasm during lytic replication and inhibits cGAS's function to promote the reactivation of the KSHV from latency (Zhang et al., 2016).

vIRFs

KSHV has incorporated four viral homologs of the cellular interferon regulator factor (vIRFs) into its genome to antagonize cellular IFN-mediated immune response and growth control mechanisms (Lee et al., 2015). Among four vIRFs, three of them (vIRF1-vIRF3) have been shown to negatively regulate the IFN pathway. The nonstructural lytic gene *vIRF1* (*K9*) directly targets p300 to inhibit its activity. The association of vIRF1 with p300 interferes with the CBP/p300-IRF3 complex formation, as well as p300 histone acetyltransferase activity, leading to the inhibition of IRF3-mediated transcriptional activation of type 1 IFN. In contrast, vIRF1 does not block another close transcription factor IRF7, although it binds to IRF7 weakly (Li et al., 2000; Lin et al., 2001; Jacobs et al., 2013). vIRF1 has also been shown to target the important DNA sensing adaptor STING by preventing it from the association with downstream kinase TBK1, thereby blocking STING's phosphorylation, and resulting in an inhibition of the DNA sensing pathway (Ma et al., 2015). vIRF2 (K11) inhibits the expression of the IFN-stimulated genes (ISGs) driven by IRF1, IRF3, and ISGF3, but not IRF7 (Fuld et al., 2006;Aresté et al., 2009; Mutocheluh et al., 2011). vIRF2 also controls the cellular protein synthesis during viral infection by preventing the activation of PKR (Burysek et al., 1999; Burysek and Pitha, 2001). Unlike vIRF1 and vIRF2, which mostly target IRF3-mediated IFN signaling, vIRF3 (K10.5 or LANA2) specifically binds to IRF7 and inhibits the DNA-binding activity of IRF7, and thereby suppressing IRF7-mediated IFN production (Joo et al., 2007). The down-regulation of IFN pathway is a common characteristic of the vIRF1-vIRF3, which targets the key transcription factors IRF3 or IRF7 of host IFN pathway. Although vIRF4 shares the partial structural similarity with cellular IRFs, it has not been shown to regulate host innate immune IFN signaling.

RTA (ORF50)

RTA is the key regulator for switching KSHV latency to lytic replication (Sun et al., 1998). An early study shows that RTA leads to the proteasome-dependent degradation of IRF7, subsequently blocking type 1 IFN production. Moreover, RTA also enhances the K48-linked polyubiquitination of IRF7 *in vitro*, suggesting that RTA acts as a viral ubiquitin E3 ligase (Yu et al., 2005). The further study detailed the molecular mechanism of RTA-mediated IFN shutdown. The data suggested that RTA cooperates with cellular RTA-associated ubiquitin E3 ligase (RAUL or UBE3C) to promote the proteasome-dependent degradation of IRF3 and IRF7 (Yu and Hayward, 2010).

ORF45

KSHV *ORF45* is a tegument protein and characterized as an immediate early gene in KSHV lytic replication (Zhu and Yuan, 2003). ORF45 blocks the phosphorylation and nuclear translocation of IRF7, resulting in a inhibition of IFN signaling transactivation (Zhu et al., 2002; Liang et al., 2012). Interestingly, ORF45 specifically and directly targets IRF7 inhibitory domain (ID) but not the close homolog IRF3, maintains IRF7 in a close form, and prevents it from being activated by KSHV infection (Sathish et al., 2011; Liang et al., 2012). Furthermore, KSHV ORF45 also binds to IRF7's upstream kinase TBK1 and IKKε to form a complex with IRF7/TBK1 or IKKε. Within this complex, ORF45 competes with IRF7 to be phosphorylated by TBK1/IKKε on serine 41 and serine 162, and consequently serves as a decoy substrate of TBK1/IKKε (Liang et al., 2012). Deletion of ORF45 results in a lower viral replication and higher host anti-viral type 1 IFN responses (Zhu et al., 2010).

ORF52

KSHV *ORF52* is a late gene and a tegument protein abundantly present in extracellular virions (Li et al., 2016). ORF52 is conserved within gammaherpesvirus and subverts cytosolic DNA sensing signaling by directly blocking cGAS enzymatic activity and cGAMP production. ORF52 is also associated with DNA and both cGAS-binding and DNA-binding activities are required for ORF52 inhibitory function on cGAS. Genetically knocking out ORF52 results in reduced progeny virus production of KSHV and a further defect in virus infectivity. Therefore, ORF52-null mutant KSHV infection stimulates an increased IFNβ signaling response (Wu et al., 2015; Li et al., 2016).

K-bZIP (K8)

K-bZIP is a leucine zipper-containing transcription factor, which is immediately expressed upon lytic reactivation. K-bZIP could block IRF3 occupancy on IFNβ promoter region, impairing the formation of p300/CBP-IRF3 enhanceosome, leading to the inhibition of IFNβ production (Lefort et al., 2007).

PART TWO: EVASION OF AUTOPHAGY PATHWAY

Autophagy is an important homeostatic mechanism involving the formation of double-membrane vesicles, called autophagosome, which sequester cytoplasmic damaged organelles, protein aggregates, or invading intracellular pathogens for degradation (Klionsky, 2005; Rodgers et al., 2014). Conserved from yeast to humans,

autophagy takes place through a series of steps that include initiation, elongation, and formation of autophagosomes, followed by fusion with lysosomes for the cargo degradation (Rodgers et al., 2014). Since autophagy functions in diverse cellular processes, it undergoes delicate regulations on each step. For examples, mTOR phosphorylates ULK1 to block autophagy initiation (Kim et al., 2011); Bcl2 constitutively binds to Beclin1 and blocks autophagosome nucleation (Pattingre et al., 2005); FLIP targets Atg3 E2 enzyme to block autophagosome elongation (Lee et al., 2009); and finally, Rubicon interacts with Beclin-1/UVRAG/Vps34 complex to block autophagosome maturation (Matsunaga et al., 2009; Zhong et al., 2009).

Besides its homeostatic role, autophagy also serves as an ancient innate immune response from the single-celled organisms to mammalians, which not only packages and depredates the invading pathogens, but also promotes the antigen presentation to adaptive immune response (Rodgers et al., 2014). Therefore, autophagy is an important anti-viral immunity and is blocked by certain viruses such as KSHV. To establish the persistent infection, KSHV has evolved its viral proteins to target almost every stage of the autophagy pathway (Figure 1).

vBcl2 (ORF16)

Virus-encoded homologs of Bcl2 (vBcl2) contribute to immune evasion of all gammaherpesviruses, including EBV, KSHV, HVS and MHV68. vBcl2 of KSHV is encoded by *ORF16* gene and expressed as an early gene during lytic reactivation (Cheng et al., 1997). However, vBcl2 of MHV68 is encoded by its *M11* gene and expressed during latent infection. Similar as cellular Bcl2 homologs, both KSHV vBcl2 and MHV68 M11 bind to Beclin-1 to prevent autophagosome formation. The binding affinity between Beclin-1 and vBcl2 is much higher than other pro-apoptotic Bcl2 family members such as BAX or BAK, suggesting Beclin-1 may be the major target of vBcl2 during infection. Loss of M11 in MHV68 does not affect acute infection but instead severely impairs chronic infection in mice, suggesting the critical virulent role of M11 during infection. Unlike MHV68 M11, KSHV vBcl2 is essential for KSHV lytic replication in cell culture system and surprisingly, the anti-autophagic and anti-apoptotic roles of vBcl2 are dispensable for KSHV lytic replication, suggesting the novel crucial role of vBcl2 for KSHV life cycle. Further mutagenesis analysis indicates that the glutamic acid 14 (E14) in the α1 helix is important for KSHV lytic replication, which is apart from the central hydrophobic BH3-peptidebinding groove for Beclin-1 interaction in the crystal structure, explaining how vBcl2 of KSHV genetically separates its multiple functions (Gelgor et al., 2015; Liang et al., 2015). It is very interesting to further explore how vBcl2 affect KSHV lytic replication through the discovery of novel protein-protein interactions.

vFLIP (K13)

KSHV vFLIP is encoded by ORF71 gene and characterized as a latent gene. vFLIP of KSHV contains two death effector domains and is reported to induce the NF-κB signaling pathway but block apoptosis as well as autophagy elongation step (Grossmann et al., 2006; Lee et al., 2009; Graham et al., 2013). Autophagosome elongation involves two ubiquitin-like conjugation reactions, leading to the covalent linking of Atg5-Atg12 and LC3-phosphatidylethanolamine, respectively. Conjugation of LC3 to phosphatidylethanolamine is sequentially processed by E1-like enzyme Atg7 and E2-like enzyme Atg3 (Noda and inagaki, 2015). Both KSHV vFLIP and cellular FLIP compete with LC3 for the interaction to Atg3, and overexpression of vFLIP blocks rapamycin-induced autophagic cell death of KSHV-infected B lymphocytes (BCBL1 cells). Two vFLIP-derived peptides strikingly induce autophagy and autophagic cell death by binding to vFLIP itself and therefore preventing the vFLIP-Atg3 association (Lee et al., 2009). Although vFLIP strongly blocks autophagy, genetically knockout of *vFLIP* from KSHV genome shows little effect in KSHV lytic replication and progeny virus production in cell culture model (Liang et al., 2015).

K7

KSHV *K7* gene is expressed during lytic replication and localized on mitochondria in infected cells (Feng et al., 2002). It has been shown to inhibit both apoptosis and autophagy maturation step upon several stimuli (Feng et al., 2002; Liang et al., 2013). Autophagosome matures by fusion with the late endosome and the lysosome, which is controlled by Beclin-1/UVRAG/PI3KC3/Rubicon complex. Rubicon is a negative regulator of this step and is dissociated from the Beclin-1 complex during autophagosome maturation, allowing the formation of autolysosome and subsequent cargo degradation (Matsunaga et al., 2009; Zhong et al., 2009). KSHV K7 directly interacts with Rubicon and promotes the interaction between Rubicon and Beclin-1 complex, resulting in a robust blockage in autophagosome maturation stage. As a result, knocking out of K7 from KSHV genome leads to impaired lytic gene expression during KSHV lytic cycle (Liang et al., 2013).

In summary, the involvement of different viral anti-interferon and anti-autophagic genes during infection suggests that interference with these cellular processes is a common strategy used by viral pathogens. Therefore, the several genes could be potential therapeutic targets for the treatment of KSHV-associated malignancies in future.

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COMPLIANCE WITH ETHICS GUIDELINES

The authors declare that they have no conflict of interest. This article does not contain any studies with human or animal subjects performed by any of the authors.

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