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Multi-step regulation of innate immune signaling by Kaposi's sarcoma-associated herpesvirus

Hye-Ra Lee[a,*], Rina Amatya[a], Jae U. Jung[a,b]

[a] Department of Molecular Microbiology and Immunology, Keck School of Medicine, University of Southern California, Harlyne J. Norris Cancer Research Tower, 1450 Biggy Street, Los Angeles, CA 90033, USA
[b] Department of Pharmacology and Pharmaceutical Sciences, School of Pharmacy, University of Southern California, HMR Rm 401, 2011 Zonal Avenue, Los Angeles, CA 90033, USA

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ABSTRACT

The innate immune system provides an immediate and relatively non-specific response to infection with the aim of eliminating the pathogen before an infection can be fully established. Activation of innate immune response is achieved by production of pro-inflammatory cytokines and type I interferon (IFN). The IFN response in particular is one of the primary defenses utilized by the host innate immune system to control pathogen infection, like virus infection. Hence, viruses have learned to manipulate host immune control mechanisms to facilitate their propagation. Due to this, much work has been dedicated to the elucidation of the Kaposi's sarcoma-associated herpesvirus (KSHV)-mediated immune evasion tactics that antagonize a host's immune system. This review presents our current knowledge of the immune evasion strategies employed by KSHV at distinct stages of its life cycle to control a host's immune system with a focus on interferon signaling.

1. Introduction

Kaposi's sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8, is a DNA tumor virus that has been identified as the etiological agent of Kaposi's sarcoma (KS) (Chang et al., 1994) as well as B-cell associated lymphoproliferative disorders, namely, primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD) (Cesarman et al., 1995; Soulier et al., 1995). In order to efficiently establish life-long persistency as well as their life cycle, KSHV display latent and lytic cycles. Once KSHV infects the host, it maintains its genome as a multicopy circular episomal DNA and only a minimal number of viral genes are expressed (Zhong et al., 1996). Upon certain circumstances, the virus switch into lytic replication, leading to a temporally regulated cascade of viral gene expression accompanied by replication of the viral genomic DNA (Renne et al., 1996). Importantly, mounting data indicates that modulation of host immune response is critical for these life cycles of KSHV. Thereby, KSHV encodes numerous genes for immunomodulatory proteins that subvert the host immune system (Lee et al., 2012).

Viral infection of host cells gives rise to type I interferon (IFN) and pro-inflammatory cytokines, which are essential for host immunity to viruses. Thus, innate immune signaling plays a key role in immune surveillance by sensing pathogens and initiating protective immune responses. Notably, the responsible receptors/sensors belong to one of five types of pattern-recognition receptors (PRRs): Toll-like receptors (TLRs), C-type lectin receptors (CLRs), Retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and the AIM2-like receptors (ALRs) (Hoffmann and Akira, 2013; Brubaker et al., 2015; Brennan and Bowie, 2010). These PRRs recognize conserved molecular structures of pathogens called pathogen-associated molecular patterns (PAMPs) and trigger production of proinflammatory cytokines and IFNs for host defense (Hoffmann and Akira, 2013; Brubaker et al., 2015; Brennan and Bowie, 2010). Such molecules are involved in direct inhibition of viral replication, elimination of viral components from infected cells, or induction of apoptosis in infected cells. Additionally, these innate immune signals can activate host adaptive immunity, therefore, are fundamental for clearance of pathogens (Nie and Wang, 2013).

To evade elimination *via* host immune response, KSHV thus targets key regulatory steps of the host innate immune responses, including IFN-mediated anti-viral immunity. Here, we present our field's current knowledge of the immune evasion strategies employed by KSHV to control the type I IFN signaling cascade, with a specific focus on how KSHV modulates IFNs production (Fig. 1).

* Corresponding author. Tel.: +1 323 442 1713; fax: +1 323 442 1721.
E-mail address: hyelee@usc.edu (H.-R. Lee).

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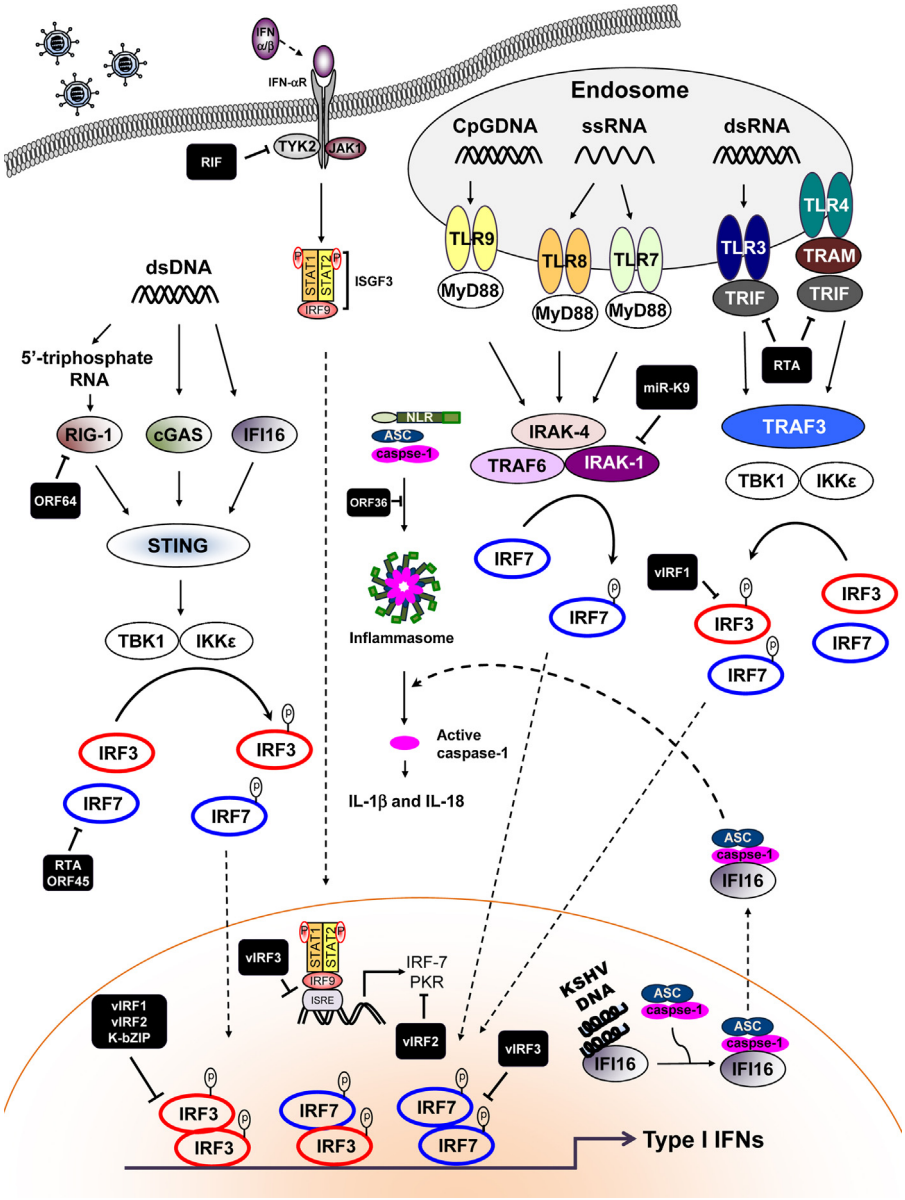

Fig. 1. An outline of the inhibition of type I IFN signaling pathways by viral proteins of KSHV. Following KSHV infection of cells, specific TLRs are activated, initiating the recruitment of adaptor proteins, MyD88 and TRIF. Subsequently, it leads to the activation of TBK1 and IKKε, which phosphorylate IRF3. IRF3 then dimerizes and translocates to the nucleus and participates in the transcriptional activation of the IFN-β promoter. Binding of newly secreted IFN-β to the type I IFN receptor (IFNAR1) leads to the activation of the JAK-STAT, resulting in forming thee ISGF3 complex. ISGF3 binds to ISRE found in numerous IFN-induced gene promoters, like IRF7. Newly synthesized IRF7 is phosphorylated by TBK1 and IKKε, which can then homodimerize or heterodimerize with IRF3 before binding to the promoters of the genes that encode IFN-α/β. Moreover, dsDNA accumulates in the cytoplasm after infection by KSHV. The intracellular DNA recognized by cytoplasmic receptor, IFI16 and cGAS. Alternatively, dsDNA is transcribed into dsRNA by polymerase III in cell-type specific manner. Generated dsRNA is recognized by RIG-1 and production of type I IFNs are induced. Following DNA stimulation, an ER protein STING translocates from the ER to the cytoplasmic punctate structure and subsequently it recruits TBK1 and IKKε. Among the KSHV-encoded proteins, numerous proteins target this pathway. Black squares indicate KSHV proteins.

2. IFN pathway

As we described above, one of the primary cellular responses to viral infection is expression of the type I IFNs (IFN-α and IFN-β) that result in the expression of genes that suppress cell growth, promote apoptosis, enhance antigen presentation, and modulate several signal transduction pathways. These genes are upregulated by interferon regulatory factors (IRFs), a family of transcription factors that are activated by IFN signaling through their cognate type I receptor (IFNAR). All IRFs share homology in the C-terminal region, which contains the IRF-association domain (IAD), and the N-terminal region has the DNA-binding domain (DBD), which is characterized by the presence of five tryptophan repeats. In brief, activation of IFN by viral infection leads to phosphorylation, dimerization, and translocation of IRFs, thereby it produces type I IFNs (IFN-α and IFN-β). Hence, it is not surprising that several KSHV proteins, in the form of viral IRFs (vIRFs), have evolutionarily developed various tactics to subvert these pathways to the advantage of their life cycles.

2.1. vIRF1 (K9)

vIRF1 was the first vIRF found to effectively repress cellular type I and type II IFN responses (Gao et al., 1997; Zimring et al., 1998). One of its known mechanisms is by inhibiting IRF1 transactivation independently of competition with IRF1 for DNA binding (Zimring

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