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Review

# Activation and counteraction of antiviral innate immunity by KSHV: an update

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ABSTRACT

The innate immune responses triggering production of type I interferons and inflammatory cytokines constitute a nonspecific innate resistance that eliminates invading pathogens including viruses. The activation of innate immune signaling through pattern recognition receptors (PRRs) is by sensing pathogen-associated molecular patterns derived from viruses. According to their distribution within cells, PRRs are classified into three types of receptors: membrane, cytoplasmic, and nuclear. Kaposi's sarcoma-associated herpesvirus (KSHV), a large DNA virus, replicates in the nucleus. Its genome is protected by capsid proteins during transport in the cytosol. Multiple PRRs are involved in KSHV recognition. To successfully establish latent infection, KSHV has evolved to manipulate different aspects of the host antiviral innate immune responses. This review presents recent advances in our understanding about the activation of the innate immune signaling in response to infection of KSHV. It also reviews the evasion strategies used by KSHV to subvert host innate immune detection for establishing a persistent infection.



## 1. Introduction

Kaposi's sarcoma-associated herpesvirus (KSHV), a γ2 herpesvirus, is etiologically associated with Kaposi's sarcoma (KS) and two other rare lymphoproliferative disorders: a variant of multicentric Castleman disease (MCD) and primary effusion lymphoma (PEL) [1–4]. Like all other herpesviruses, KSHV displays two distinct life modes, latent and lytic replication. Following primary infection, both lytic and latent genes are expressed. After abortive lytic replication, latent cycle is founded. Latency is the default state that maintains KSHV genome as a multicopy, circular episomal DNA with only a small portion of latent genes expressed [5,6]. Viruses undergo lytic replication under certain circumstances such as hypoxia or immune suppression, leading to a complete panel of viral genes expression and production of infectious progeny virus [7–10].

The innate immune response is a relatively nonspecific response that is the host first line to defense against invading pathogens before they establish full infection in cells. Induction of inflammatory cytokines and type I interferon (IFN) response is critical for host innate defense mechanisms. Host cells employ an array of constitutively expressed, germline-encoded pattern-recognition receptors (PRRs) to recognize pathogen-derived and conserved pathogen associated molecular patterns (PAMPs). Recognition subsequently evokes PRR-adaptor-transcriptional factor signaling cascades to induce inflammatory cytokines and type I IFN production [11,12]. Six types of PRRs have been identified including toll-like receptors (TLRs), retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs), absent in melanoma 2 (AIM2)-like receptors (ALRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), cytosolic DNA-sensing receptors and nuclear DNA sensors [13].

Data suggest that most host innate immune systems can be activated by KSHV infection. However, KSHV has evolved a variety of sophisticated countermeasures, encoding numerous genes and microRNAs that interfere with the host innate immune response. These countermeasures are critical for establishing persistent infection [13]. This brief review covers the up-to-data advances in understanding the cellular sensing of KSHV infection and KSHV strategies for escaping host innate immune signaling pathways.

## 2. Kaposi's sarcoma-associated herpesvirus

KSHV (also called human herpesvirus type 8) is a member of the human γ-herpesvirus family, which was discovered in 1994 from KS tissue by Chang and Moore using representational difference analysis [1]. By 1996, the Chang and Moore groups had sequenced and cloned the entire viral genome [14].

### 2.1. Virion structure

Similar to the other members of the rhadinovirus genus of herpesviruses, KSHV virions exhibit an icosahedral capsid protecting

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the KSHV genome. The capsid is surrounded by lipid-containing envelope. A highly organized and dense proteinaceous layer localizes between the capsid and the envelope, is called the tegument layer (Fig. 1a).

The KSHV envelope is studded with glycoproteins that have key functions in mediating viral entry and viral recognition by host cell surface receptors. Seven viral glycoproteins have been identified, including gB (ORF8), K8.1, gH (ORF22), gM (ORF39), gL (ORF47), gN (ORF53), and ORF68 [15–20].

The tegument layer is a morphologically amorphous structure that remains largely undefined. Based on the specific biochemical criteria of tegument components and mass spectrometry analysis of mature KSHV virions, several tegument proteins were identified: ORF11, ORF21, ORF33, ORF38, ORF45, ORF50, ORF52, ORF55, ORF63, ORF64 and ORF75 [5,20,21]; more would be characterized in the future. Tegument proteins have key roles at various stages of the KSHV life cycle. They are involving virion tegumentation, assembly, trafficking, replication and egress processes, and mediate host innate immunity to facilitate the persistent infection [22].

The KSHV capsid is a triangulation number of 16 icosahedral lattice with 12 pentons, 150 hexons, and 320 triplexes. Five capsid proteins have been identified [23]: ORF25 encoded major capsid

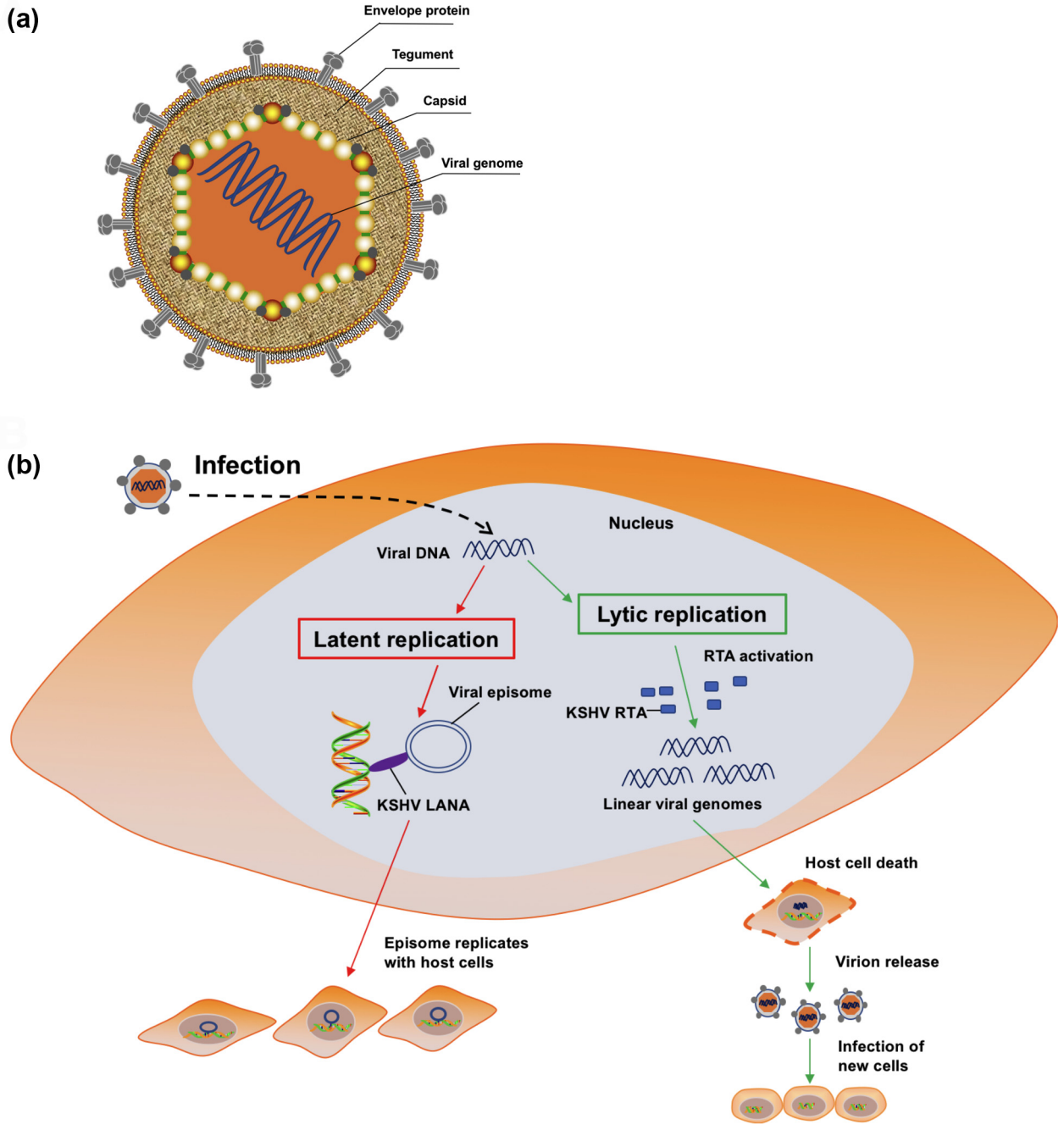


**Fig. 1.** (Color online) (a) Schematic presentation of KSHV structure. KSHV virions exhibit an icosahedral nucleocapsid surrounded by a lipid bilayer envelope, and a tegument layer between the capsid and envelope. (b) Schematic representation of KSHV life cycle in infected cells. KSHV life cycle contains two phases of infection: a short lytic replication and a persistent latent replication. During latency, LANA protein tethers KSHV episome to host cell chromosome. KSHV episome replicates along with host cell dividing during KSHV latent infection. Upon exogenous stimuli, e.g. cellular stress, valproate, butyrate etc., KSHV can be induced to switch from latency to lytic replication. During this phase, the RTA promoter is activated and most viral genes are expressed. During lytic replication, the KSHV genome replicates in a rolling cycle mechanism. Linear genomes are packaged into capsids, and then host cell are destroyed, leading to release of new virions to infect new host cells.

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