AMERICAN SOCIETY FOR MICROBIOLOGY Journal of Virology®

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Kaposi's Sarcoma-Associated Herpesvirus Latency-Associated Nuclear Antigen: Replicating and Shielding Viral DNA during Viral Persistence

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ABSTRACT Kaposi's sarcoma herpesvirus (KSHV) establishes lifelong latency. The viral latency-associated nuclear antigen (LANA) promotes viral persistence by tethering the viral genome to cellular chromosomes and by participating in latent DNA replication. Recently, the structure of the LANA C-terminal DNA binding domain was solved and new cytoplasmic variants of LANA were discovered. We discuss how these findings contribute to our current view of LANA structure and assembly and of its role during viral persistence.

KEYWORDS Kaposi's sarcoma-associated herpesvirus, LANA speckles, cytoplasmic DNA sensors, cytoplasmic variants, structure, virus persistence

Accepted manuscript posted online 26 April 2017

Citation Weidner-Glunde M, Mariggiò G, Schulz TF. 2017. Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen: replicating and shielding viral DNA during viral persistence. J Virol 91:e01083-16. https://doi.org/10.1128/JVI.01083-16.

Editor Michaela Ulrike Gack, University of Chicago

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Kaposi's sarcoma herpesvirus (KSHV) is the cause of three human malignancies—Kaposi's sarcoma (KS), primary effusion lymphoma (PEL), and the plasma cell variant of multicentric Castleman's disease (MCD). Like other herpesviruses, it establishes a lifelong infection of the host. KSHV persistence involves latency, during which no viral particles are produced, only a limited set of viral genes is expressed, and the circular latent genome is replicated and segregated to daughter cells as an episome by the host replication and cell division machinery. However, this mechanism of persistence is probably not very efficient as illustrated by the fact that, in cell culture, most KSHV-infected cells lose the viral genome rapidly (1). Notable exceptions to this rule are cultured cell lines established from PEL samples, which retain the viral genome indefinitely (2, 3). It is therefore possible that occasional low-level virus production and infection of new cells may be required for the persistence of KSHV in the infected host (1).

LANA DISCOVERY AND CHARACTERIZATION

One of the few proteins expressed during the latent phase of the viral life cycle, as well as in all KSHV-infected tumor cells, is the latency-associated nuclear antigen (LANA), which is essential for viral persistence. In this review, we focus on recently identified features of LANA that relate to its role in both the latent and lytic replication cycles during viral persistence. For a more comprehensive overview of LANA and its functions, we refer the reader to several excellent recent reviews (4–7).

LANA was initially identified as a "speckled" nuclear fluorescence staining pattern (see Fig. 1A) recognized by serum antibodies from KSHV-infected patients (8–11). The size of the LANA protein is heterogeneous, and multiple protein bands in the range of 150 to 230 kDa, thought to be mostly the result of posttranslational modifications, can be seen on Western blots of lysates of infected cells (12–17). LANA is encoded by KSHV ORF73, and ORF73 and the neighboring genes ORF72/vcyc (viral cyclin), ORF71/vFLIP (viral FLICE inhibitory protein), and K12/kaposin and a transcript encoding 12 micro-

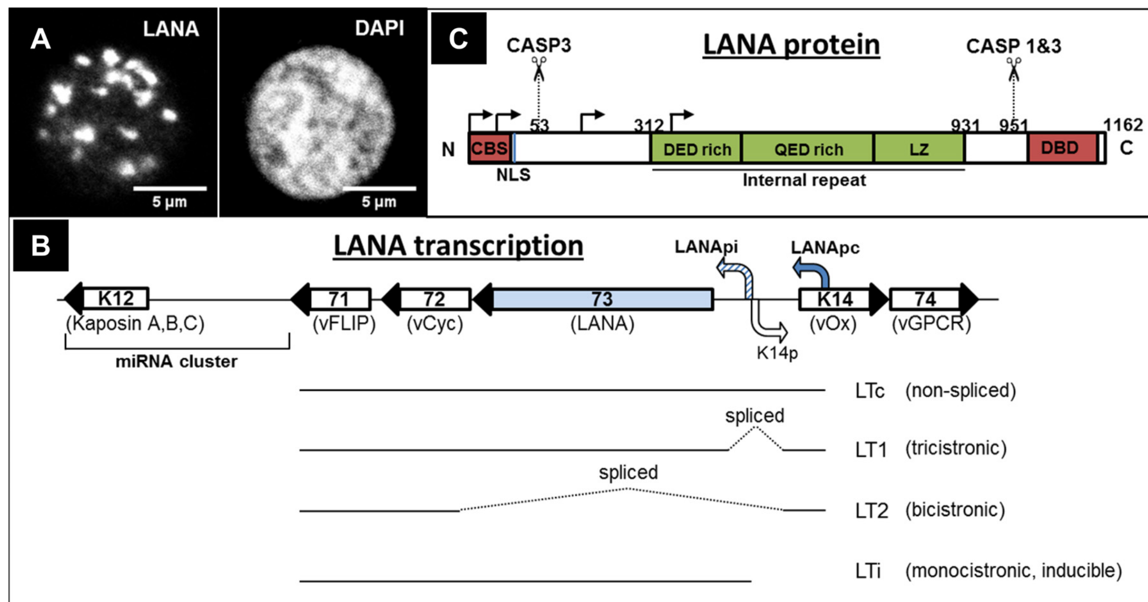

FIG 1 (A) Immunofluorescence staining of LANA speckles in PEL cells. (Left panel) LANA staining. (Right panel) DAPI (4′,6-diamidino-2-phenylindole) staining of the nucleus. (B) Simplified structure of KSHV latency locus, indicating the LANA constitutive promoter (Lana pc) and the bidirectional lytic LANA inducible (LANA pi)/K14 promoter, as well as transcripts produced from the latency locus (20, 22, 26, 27). Viral open reading frame (ORF) numbers are indicated inside the respective genes, and the customary names are given below. ORF71 (vFLIP—viral FLICE inhibitory protein), ORF72 (vCyc—viral cyclin), ORF73 (LANA), ORF K14 (vOx—viral homologue of OX2), ORF74 (vGPCR—viral G protein coupled receptor) are indicated. (C) Schematic representation of LANA domains and important motifs. Caspase 1 and 3 cleavage sites (CASP1/3) (13) are also indicated. Arrows indicate canonical and alternative translation initiation sites (17). CBS, chromatin binding site; NLS, nuclear localization signal; DBD, DNA binding domain; LZ, leucine zipper.

RNAs (miRNAs) make up the major latency locus of KSHV (16, 18–21). LANA is translated from a spliced mRNA (LT1), whose transcription is directed by the constitutively active latency promoter (Fig. 1B) (22–25). In addition, a bidirectional promoter, located in the intron of the latent LANA transcript and activated by the KSHV lytic regulator RTA (replication and transcription activator), directs the expression of a "lytic" or "inducible" LANA transcript following the activation of the lytic replication cycle, as well as the expression of a bicistronic mRNA for the neighboring ORFK14/vOX2 (viral homolog of CD200 glycoprotein) and ORF74/vGPCR (viral G protein-coupled receptor) genes (Fig. 1B) (20, 26, 27). This transcriptional arrangement suggests a role for LANA during both latency and lytic reactivation.

ROLE OF LANA IN VIRAL PERSISTENCE

LANA speckles (Fig. 1A) contain latent viral DNA and are attached to mitotic chromosomes during cell division (28–30). As mentioned above, LANA is essential for latent persistence: experiments using small interfering RNA (siRNA) to silence LANA expression in PEL cells harboring latent KSHV, or deleting LANA from a recombinant KSHV genome, showed that LANA is necessary for persistence of the viral genome in an episomal state (31–35). The presence of LANA is also sufficient to mediate the replication and maintenance of a plasmid containing the KSHV latent origin of replication in transfected cells (28, 36–38). These observations suggested a model of LANA replicating and tethering the KSHV episome to host chromosomes during cell division.

In order to perform these two functions—latent replication and tethering of viral episomes to mitotic chromosomes—LANA associates with cellular histones H2A and H2B via a domain at its N-terminal end (chromatin binding sequence [CBS; Fig. 1C]), binds to the viral latent origin of replication, which is located in each of the multiple terminal repeat (TR) subunits flanking the viral genome (29, 36, 39, 40), and recruits the cellular replication machinery. LANA was shown to colocalize and interact with ORC (origin recognition complex) (41, 42) and RFC (replication factor C) (43). Additionally, the MCM (minichromosome maintenance) complex, TopoIIβ (topoisomerase 2 β), and

PCNA were shown to be recruited to the TR (41, 43, 44). LANA is also known to recruit a member of the replication fork protection complex, the Tim protein, to TR in order to regulate the formation of recombination structures that arise at the TR during replication and to promote the stability of TR elements (45).

LANA-MEDIATED CHROMATIN ASSOCIATION AND TRANSCRIPTIONAL REGULATION

LANA binds to the viral genome directly at the terminal repeat region (see below) but can also associate with it indirectly through protein-protein interactions. On the other hand, LANA associates with cellular DNA or chromatin, mostly through protein-protein interactions, but has also been suggested to bind directly to LANA binding site (LBS)-like sequences in the human genome (46–48). In the cellular chromatin/DNA, LANA associates preferentially with active promoters and was found to bind at locations close to transcriptional start sites (TSS) of H3K4me3-decorated promoters (46–48). Specific LBSs within the human genome seem to differ in different cell types (46–48). LANA was previously observed to associate with transcriptional activators and repressors (49–55) and may regulate the transcription of both viral and cellular genes. LANA activates its own promoter and represses the promoter of the lytic switch protein—RTA (replication and transcription activator) (47, 49, 56, 57). With regard to cellular genes, ectopic expression of LANA leads to both activation and repression of transcription (54, 57–59). However, the mechanism of LANA-mediated regulation of promoter activity has been identified only in the case of a few cellular genes (46, 60, 61). Additionally, a recent study in LEC (lymphatic endothelial cells) showed no correlation between LANA binding sites in the cellular promoters and their transcriptional activity (48). This suggests that mere binding of LANA to host regulatory sequences is, at least in the majority of cases, not sufficient for the control of cellular gene transcription.

LANA was also observed to associate with chromatin-modifying complexes, including the H3K9 methyltransferase SUV39H, H3K4 methyltransferase hSET1, a H3K9 demethylase, the histone acetyltransferase CBP, the histone deacetylase mSin3, and chromatin remodelers (FACT, CBP, and BET proteins) (46, 50, 62–65). Therefore, a role for LANA in the epigenetic modification of the KSHV or cellular genome has recently been suggested. The deposition of histones on the viral genome and their epigenetic modification, as well as the methylation of KSHV DNA, occur after entry of the virus into the cell and upon circularization of the viral genome (66–69). KSHV latency is associated with deposition of H3K27me3, a bivalent mark representing "poised" heterochromatin that can repress transcription despite the presence of activating modifications, on the promoters of lytic genes (67). LANA has been shown to be involved in the establishment of this epigenetic modification by directly recruiting PRC2 (polycomb repressive complex 2), which contains EZH2 (enhancer of zeste homolog 2), an H3K27me3 histone methyltransferase, or by mediating the redistribution of Sp100, a negative regulator of PRC2 recruitment, into different chromatin compartments (69, 70). LANA was also found to interact with hSET1, an H3K4-specific lysine methyltransferase, thereby inducing transcriptional activation of H3K4me3-decorated promoters (46). LANA has also been reported to promote lytic gene expression by recruiting JMJD1A (Jumonji domain-containing protein 1A)/KDM3 (lysine demethylase 3), an H3K9me1/2 histone demethylase, to the viral genome, resulting in an increase of viral gene expression (63). The balance between repressive H3K27me3 and activating H3K4me3 marks at both KSHV latent promoters as well as at promoters essential for reactivation may affect the switch between latency and lytic replication.

LANA STRUCTURE AND BINDING TO THE VIRAL LATENT ORIGIN OF REPLICATION

The prototypical LANA protein in the KSHV BC-1 strain consists of 1,162 amino acids (aa) (71) and can be divided into an N-terminal domain, a C-terminal domain, and the internal repeat region (Fig. 1C). The N-terminal domain contains the nuclear localization signal (NLS) responsible for the nuclear localization of the full-length LANA protein (72),

as well as the motif responsible for the tethering of LANA speckles to mitotic chromatin (the CBS described above) (29, 39, 73). The N-terminal domain of LANA was also shown to play a role in replication and transcriptional regulation (29, 74, 75) and contains a motif for the recruitment of E3-type ubiquitin ligases (76). The internal repeat region consists of three sections, two of which are of a very acidic nature (DED rich and QED rich) and one that contains a leucine zipper (16, 18, 19, 71). This internal repeat region is required for KSHV genome persistence and contributes to immune evasion by preventing the presentation of antigenic peptides on MHC-I (major histocompatibility complex class I) molecules (31, 32, 77). The C-terminal domain contains a region responsible for the binding to the latent replication origin in the terminal repeat (TR) region of the viral genome (DNA binding domain [DBD]), contributes to the association of LANA with interphase chromatin, and is essential for latent replication (40, 78–82). The interaction with the interphase chromatin may involve binding to one or more candidates from a long list of cellular proteins, including, e.g., MeCP2 (methyl CpG binding protein 2), DEK, and Brd2/4 (bromodomain- and ET domain-containing protein 2/4) (53, 55, 82–86).

We and others have determined the structure of the LANA DNA binding domain (DBD) by X-ray crystallography (83, 87, 88). The purified LANA DBD forms dimers and multimers of dimers in solution. Some of the crystals obtained consisted of LANA DBD tetramers or pentamers of dimers arranged in a ring; in one crystal form, the pentamers appeared to be arranged in what looked like the beginning of a right-handed spiral of dimers (83, 88).

The basic LANA DBD dimer is formed by an antiparallel β-barrel structure at the dimerization interface and has three α-helices on each side of the β-barrel (Fig. 2A) (83, 87, 88). The bottom face of the dimer contains a specific binding site for the three LANA binding sites (LBS1 to LBS3) that are located in each of the 801-bp terminal repeat (TR) subunits flanking the KSHV genome in various numbers (40, 78–80, 87, 88). We recently also solved the structure of the LANA DBD dimer in complex with LBS1 (88). Unlike the latent origin binding proteins of Epstein-Barr virus (EBNA-1 [Epstein-Barr nuclear antigen 1]) and bovine papillomavirus (E2), the LANA DBD dimer binds asymmetrically to LBS1.

A LANA DBD dimer binds to LBS1 with approximately 100-fold-higher affinity than to LBS2 and LBS3, and the binding to LBS1, LBS2, and LBS3 is cooperative (88). The three LBSs are spaced apart by 22 bp and are therefore positioned on the same face of DNA, with one (LBS3) being located on the DNA strand opposite LBS1 and LBS2. This allows the three LANA DBD dimers binding to these three adjacent LBSs to interact with each other via a lateral alpha helical domain (88). Taking the data together, the asymmetric binding of three LANA DBD dimers to three adjacent LBS motifs was shown to induce a bend in the TR subunit DNA (Fig. 2B) (88–90).

The LANA DBD dimer face located opposite the sequence-specific DNA binding site features a characteristic "basic patch," which was shown to be the binding site for the bromodomain and ET domain (BET) proteins but also to represent a sequence-independent DNA binding site (Fig. 2B) (83, 87, 88). We found that, *in vitro*, a LANA DBD mutant devoid of its specific binding site for LBS1 to LBS3 is able to coat DNA molecules, regardless of their sequence, by arranging a spiral of dimers around them (88). We postulated that a combination of these features, i.e., the sequence-specific interaction of LANA with the three LBSs (via the bottom face of the LANA DBD), together with the sequence-independent interaction with any DNA (host or viral) through the basic patch, as well as the ability of LANA to form different oligomer arrangements and to interact with other proteins, provides the basis for the assembly of the typical LANA speckles (Fig. 1A and 2B). These features may also allow LANA to assemble viral DNA structures as a first step in viral latent DNA replication (Fig. 2B). Latent replication could initiate at the TR region but also in other areas of the viral genome, including the long unique region (LUR) of the viral genome (91).

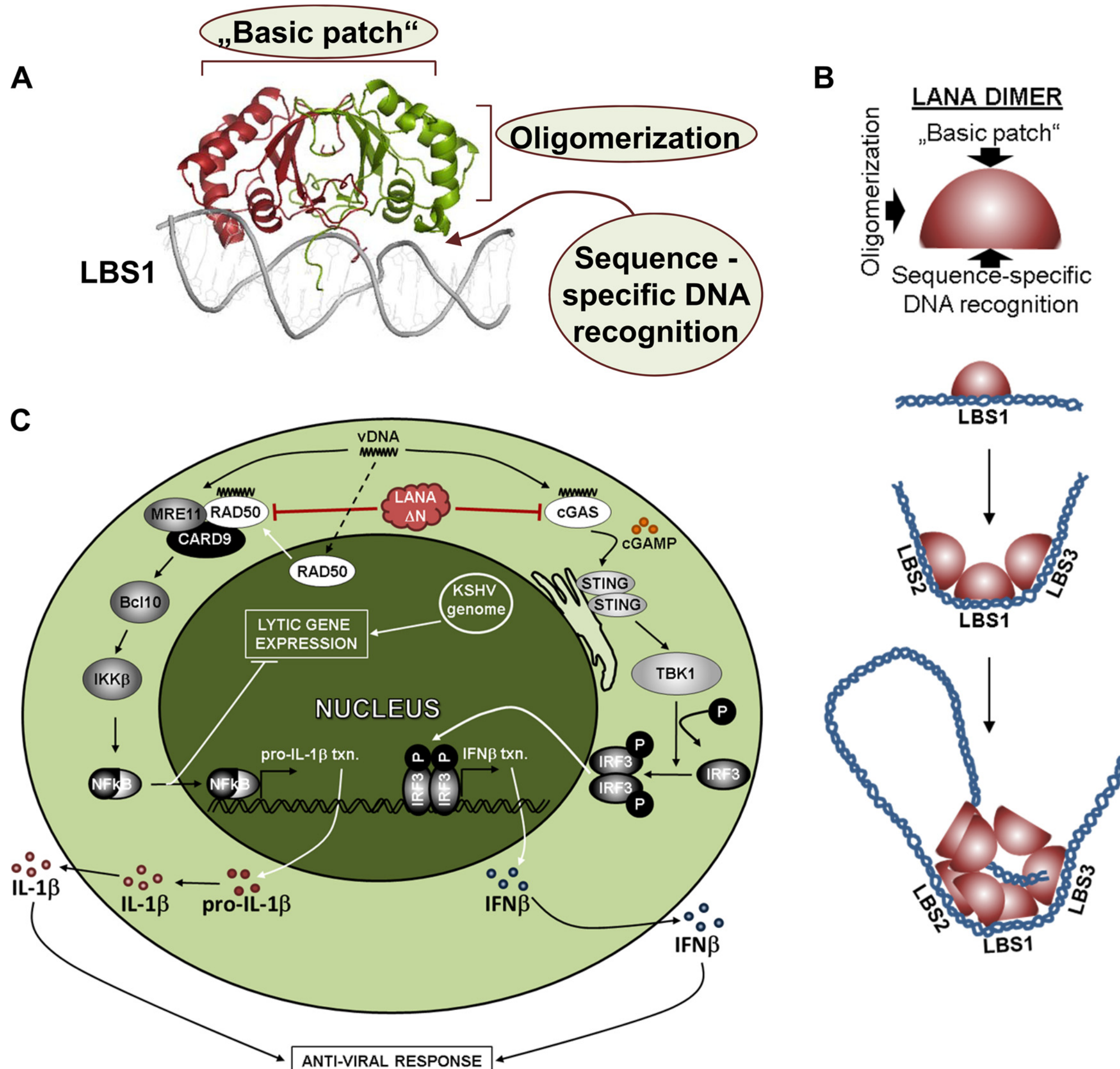

FIG 2 (A) Structure of KSHV LANA dimer bound to LBS1. Functionally important surfaces are indicated. (B) Model showing how sequence-specific binding of LANA dimers to LBS1, LBS2, and LBS3 in combination with oligomerization and sequence-independent binding of LANA to the long unique region of the viral genome may lead to the assembly of larger structures that could form the basis of LANA speckles (Fig. 1A). (C) Diagram of N-terminally truncated LANA (LANAΔN) antagonizing viral DNA sensing by cGAS and the double-strand break repair machinery in the cytoplasm. A simplified version of the affected signaling pathways is shown. IL-1β, interleukin-1 beta; vDNA, viral DNA; IFNβ, beta interferon.

LANA ISOFORMS

As mentioned above, LANA is detectable on SDS-PAGE/Western blots as several bands with different molecular weights. While posttranslational modifications explain some of these multiple protein bands, there is currently also evidence of alternative translation initiation, alternative stop codons, internal frameshifting, and proteolytic cleavage contributing to the complexity of LANA isoforms (12, 13, 15, 17). Transfection of LANA expression vectors encoding a mutated start codon generates LANA variants by initiating translation at downstream translation initiation sites (dTIS); consequently, these lack the main nuclear localization signal located within the first 30 amino acids of full-length LANA (Fig. 1C) and are therefore located in the cytoplasm rather than the nucleus (17). In addition, frameshifting within the LANA internal repeat region results in shortened LANA variants with an alternative C-terminal domain translated from a different reading frame (15). Furthermore, the presence of proteolytic cleavage sites targeted by caspase 1 and 3 has been noted in the N- and C-terminal LANA domains (Fig. 1C) and caspase-mediated cleavage could therefore conceivably contribute to the generation of novel LANA isoforms (13).

ROLE OF CYTOPLASMIC LANA IN ANTAGONIZING INNATE IMMUNITY

The existence of N-terminally truncated LANA variants in the cytoplasm can be observed in KSHV-infected cells (17, 92). We recently showed that these play a role in the regulation of latency and in counteracting innate immune responses triggered by the presence of viral DNA in the cytosol. In particular, cytoplasmic LANA variants interact with and antagonize the innate DNA sensor cGAS (cyclic GMP-AMP synthase) (Fig. 2C) (92). The physiological role of cGAS is to synthesize the cyclic dinucleotide cGAMP upon recognizing cytoplasmic foreign DNA. cGAMP then binds to and activates STING (stimulator of interferon [IFN] genes), which, following relocation to the endoplasmic reticulum, induces the phosphorylation and activation of the cellular kinase TBK1 (TANK binding kinase 1) and thereby TBK1-mediated phosphorylation of IRF3 and subsequent increased expression from type I interferon gene promoters (93–98). Like other herpesviruses, KSHV is known to activate the cGAS-IRF3-IFN pathway during lytic replication (92, 99), presumably in response to viral DNA that may be inappropriately released from leaky capsids in the cytoplasm, as shown for herpes simplex virus 1 (HSV1) (100). For both HSV and KSHV, cGAS-dependent activation of interferon gene expression has been shown to restrict viral lytic replication (92, 101, 102). By binding to cGAS, cytoplasmic LANA variants inhibit the phosphorylation of TBK1 and IRF3 that occurs in response to the presence of transfected or viral DNA and may therefore antagonize the restriction on lytic KSHV replication imposed by cGAS and thus promote KSHV reactivation from latency, as well as—in an experimental heterologous system—lytic HSV1 replication (92). Thus, by promoting KSHV lytic replication, cytoplasmic LANA variants appear to exert a role that is opposed to that of full-length LANA, which, as reviewed above, promotes the establishment and maintenance of latency.

Antagonizing the cGAS-dependent activation of the IFN pathway clearly plays an important role in the KSHV lytic replication cycle, as illustrated by the fact that several other KSHV proteins antagonize either cGAS directly (e.g., orf52) (103) or the downstream STING protein (vIRF1) (99). In addition, multiple other KSHV proteins have been shown to downregulate the IFN response induced by transfected DNA (99), but their mode of action has not yet been clarified. The relative importance of cytoplasmic LANA versus these other KSHV proteins in antagonizing cGAS also needs to be investigated in more depth.

The role of cytoplasmic LANA as an antagonist of the innate immune response may go beyond its ability to inhibit cGAS-dependent IFN activation. By the use of coimmunoprecipitation and mass spectrometry, we and others have shown the interaction of LANA with Mre11 and RAD50, members of the MRN (Mre11, RAD50, NBS1) complex involved in the repair of the DNA double-strand breaks (92, 104). We found that, in concert with RAD50 and CARD9 (caspase recruitment domain-containing protein 9), cytoplasmic LANA variants can inhibit the previously reported (105) ability of Mre11 to activate the NF-κB pathway in response to foreign DNA (Fig. 2C) (106). The NF-κB pathway plays an important role in suppressing the lytic replication of KSHV and MHV68 and promoting latency (107–109). Several latent KSHV proteins, including full-length LANA and vFLIP, are potent activators of NF-κB (109–113). The ability of cytoplasmic LANA variants to antagonize Mre11-dependent NF-κB activation reinforces the notion that cytoplasmic LANA can oppose the effects of full-length LANA. It also provides an interesting example of the connection between DNA damage response (DDR) pathways and the innate immune response to foreign or damaged "self" DNA and the need for KSHV to restrain these cellular responses.

OUTLOOK

Our model of how LANA may assemble latent viral DNA into the typical nuclear speckles (Fig. 1A and 2B) and the observation that cytoplasmic LANA isoforms may play a role in the modulation of innate immune response pathways (Fig. 2C) suggest several questions:

- If cytoplasmic LANA isoforms do indeed play a role in promoting the reactivation

from latency by antagonizing the innate immune response, is their generation linked to the use of the alternative lytic LANA promoter (Fig. 1B)?

- If so, does the shorter 5′ untranslated region (UTR) of the lytic LANA transcript (Fig. 1B) favor the use of alternative translation initiation codons?
- If LANA has a role in antagonizing the innate immune response, initiated by either cGAS or the double-strand-break (DSB) repair machinery, is it conceivable that not just latent replication but also "shielding" of nuclear viral DNA from the innate immune response is an important role of LANA speckles?
- If so, where does latent viral replication happen and could it be mediated by LANA molecules that are not packaged in the typical speckles?

Answering these and other questions will help our understanding of how KSHV, in spite of not being very efficient with regard to the latent replication/maintenance of its episomes, manages to persist in infected individuals throughout their lives.

ACKNOWLEDGMENTS

This work was supported by a grant to T.F.S. from the Deutsche Forschungsgemeinschaft (DFG) (Collaborative Research Centre SFB900 "Chronic Infections: Microbial Persistence and its Control," Project C1). G.M. is a recipient of PhD fellowship IRTG 1273, funded by the DFG.

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