Front. Biol. 2010, 5(2): 105–115
DOI 10.1007/s11515-010-0021-x

REVIEW

The replication and transcription activator (RTA) of Kaposi's sarcoma-associated herpesvirus/human herpesvirus-8

Zhilong YANG (✉)[1,2], Charles WOOD (✉)[1]

1 Nebraska Center for Virology and School of Biological Sciences, 102C Morrison Life Sciences Research Center, 4240 Fair Street, East Campus, University of Nebraska-Lincoln, Lincoln, NE 68583, USA
2 Current address: National Institutes of Health, 33 North Drive, Bethesda, MD, 20892, USA

Abstract Kaposi's sarcoma-associated herpesvirus (KSHV) is γ-2 herpesvirus with latency and lytic replication stages in its life-cycle. The viral replication and transcription activator (RTA) is the key protein for triggering KSHV lytic gene expression and replication from latency. In this review, we will discuss the gene expression program in KSHV lytic replication and latency, the regulation of the RTA expression, the RTA protein and the mechanisms that RTA utilizes to transactivate its target genes. We will focus on the RTA-mediated transactivation mechanisms, including DNA-binding, interacting with cellular co-factors and promoting repressor degradation.

Keywords Kaposi's sarcoma-associated herpesvirus (KSHV), replication and transcription activator (RTA), transactivation

1 Introduction

Kaposi's sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus-8 (HHV-8), is the latest identified human herpesvirus and the etiologic agent of Kaposi's sarcoma (KS), which is the most common neoplasm in AIDS patients (Chang et al., 1994; Goedert, 2000). KSHV is also associated with two other neoplastic disorders: primary effusion lymphoma (PEL) and Multi-centric Castleman's Disease (MCD) (Cesarman et al., 1995a; Soulier et al., 1995).

KSHV belongs to γ-2 herpesvirus genus. The closest human herpesvirus relative of KSHV is Epstein-Barr virus (EBV), which is the prototype of γ-1 herpesvirus (Chang et al., 1994; Russo et al., 1996). KSHV contains a large double-stranded DNA genome approximately 165 kb in size with approximately 90 open reading frames (ORFs) (Dourmishev et al., 2003). Like other herpesviruses, KSHV can establish latent infection in infected cells and be reactivated to lytic replication (Cohrs and Gilden, 2001). According to the gene expression pattern, KSHV genes are classified into two categories: latent genes and lytic genes (Renne et al., 1996; Sarid et al., 1998; Zhong et al., 1996). During latency, the KSHV genome exists as a closed circular episome with only a limited number of genes expressed, including latency-associated nuclear antigen (LANA), v-cyclin, vFLIP, Kaposin and LANA2 (vIRF2) (Burysek and Pitha, 2001; Dittmer et al., 1998; Kedes et al., 1997; Muralidhar et al., 2000; Rainbow et al., 1997; Sadler et al., 1999; Saveliev et al., 2002). A number of KSHV-encoded microRNAs are also expressed during latency (Cai et al., 2005; Pfeffer et al., 2005; Samols et al., 2005). These proteins and microRNAs expressed during latency were thought to function in viral episome maintenance, viral genome replication, viral immune evasion and viral latency (Cotter and Robertson, 1999; Friborg et al., 1999; Komatsu et al., 2001; Kwun et al., 2007; Lim et al., 2000; Liu et al., 2007; Samols et al., 2005; Skalsky et al., 2007; Verma et al., 2006). They regulate cell growth, transformation and tumorigenesis during disease progression (Cai et al., 2006b; Friborg et al., 1999; Katano et al., 2001; Si and Robertson, 2006). Lytic genes are expressed during lytic replication or reactivation. The lytic genes can be further divided into three subcategories based on the expression kinetics: immediate early (IE), early and late genes. The IE gene expression upon induction or after primary infection does not require *de novo* protein synthesis and occurs in the presence of protein synthesis inhibitor cycloheximide (Ye et al., 2007; Zhu et al., 1999). The proteins encoded by IE genes in herpesviruses usually function as regulatory factors in viral and cellular gene expression. Several genes have been identified as IE genes

Received December 28, 2009; accepted January 25, 2010

E-mail: yangzh@mail.nih.gov, cwood1@unl.edu

in KSHV including ORF50, ORF45, ORFK4.2 and a 4.5 kb mRNA (Gradoville et al., 2000; Haque et al., 2000; Lukac et al., 1999; Sarid et al., 1998; Sun et al., 1999; Zhu et al., 1999). The most extensively studied IE gene in KSHV is open reading frame 50 (ORF50), which encodes the RTA protein. Its expression is sufficient and necessary to induce the lytic replication program of KSHV. The early genes and late genes are under the control of IE genes (Sun et al., 1999; Zhu et al., 1999). The lytic gene products can facilitate virus spread and create a tumor cell growth-friendly microenvironment through the production of viral and cellular cytokines induced during lytic replication (Staskus et al., 1997; Sun et al., 1999).

The switch from latency to lytic replication of KSHV can be initiated by the KSHV IE protein RTA (Lukac et al., 1998; Sun et al., 1998). This is different from EBV, with which the reactivation needs the expression of two EBV IE genes: BZLF1 (ZTA) and BRLF1 (RTA) (Amon and Farrell, 2005). A number of studies have shown that the RTA is the key for KSHV transition from latency to lytic replication. They demonstrated that: (1) ORF50 is one of the IE genes induced upon the lytic replication inducer 12-O-tetradecanoylphorbol-13-acetate (TPA) induction. The ORF50 mRNA can be detected at 1 h post TPA treatment (Sarid et al., 1998; Sun et al., 1999). (2) The expression of ORF50 mRNA is resistant to protein synthesis inhibitor cycloheximide (Ye et al., 2007). (3) Ectopic expression of RTA alone in KSHV latent PEL cells is able to disrupt latency and drive the virus into lytic replication cycle, while interference of RTA function reduces the level of viral lytic replication. The C-terminal activation domain deletion of dominant-negative mutant RTA could reduce the spontaneous reactivation of KSHV (Lukac et al., 1999). (4) RTA expression stimulates KSHV DNA replication directly evidenced by the amplification of the KSHV lytic origin in a plasmid-based replication assay (AuCoin et al., 2004; Wang et al., 2004). (5) Knockdown of RTA expression using the specific ribozyme substantially decreased the reactivation rate in KSHV infected PEL cells (Zhu et al., 2004). (6) Using a KSHV bacterial artificial chromosome (BAC) system in which the ORF50 locus was disrupted, KSHV does not enter lytic replication unless an ectopic RTA is expressed (Xu et al., 2005). RTA was also found to be incorporated into KSHV virions (Bechtel et al., 2005; Lan et al., 2005b), suggesting an immediate role of RTA after primary infection.

2 The induction of ORF50/RTA expression

The reactivation of KSHV from latency can be triggered by a number of stimuli. These stimuli can be classified into three groups: (1) chemical agents, including phorbol ester such as TPA, sodium butyrate, 5'-azacytidine, glycyrrhizic and trichostatin A (TSA)(Cesarman et al., 1995b; Chen et al., 2001; Curreli et al., 2005; Miller et al., 1996; Renne et al., 1996); (2) natural products, such as *Euphorbia kansui* (*E. kansui*), *Croton tiglium* (*C. tiglium*), and *Aconitum carmichaeli* (*A. Carmichaeli*) (Cho et al., 2008); (3) physiological stimuli, such as hypoxia. Hypoxia is a shortage of oxygen in the body. Acute and chronic exposure of KSHV infected PEL cells to hypoxia (1% O_2) induced KSHV lytic replication (Haque et al., 2003). Two compounds, desferoxamine and cobalt chloride, that increase the levels of intracellular hypoxia-inducible factor 1, are also able to reactivate KSHV in PEL cells (Davis et al., 2001). Other physiological stimuli include several neuron transmitters, such as epinephrine and norepinephrine (Chang et al., 2005) and inflammatory cytokines, such as interferon (IFN)-γ (Chang et al., 2000; Varthakavi et al., 1999). The induction of reactivation of KSHV by stimuli involves many different signaling pathways. The pathways presently identified include: cyclic AMP/protein kinase A (PKA) pathway (Chang et al., 2005), protein kinase C (PKC) pathway (Castagna et al., 1982), dopamine receptor-mediated signaling pathways (Lee et al., 2008), MEK/ERK pathway, JNK and p38 MAPK pathways (Xie et al., 2008), and Raf/MEK/ERK/Ets-1 signaling pathway (Yu et al., 2007). However, different stimuli may activate different signaling pathways.

No matter what pathways are involved, the induction of KSHV lytic replication involves either the expression of RTA through activation of its promoter, or by regulating RTA at the translational level via the KSHV microRNA, such as miR K9*, which targets the 3'-UTR of RTA mRNA (Bellare and Ganem, 2009). The 3 kb promoter sequence upstream of the ORF50 start codon are most susceptible to transcriptional regulation and was found to be silenced during latency (Deng et al., 2000). Treatment by chemical inducers such as sodium butyrate, 5'-azacytidine or TSA treatment causes changes in the chromatin structure in the ORF50 promoter region, inducing the expression of RTA (Chen et al., 2001; Lu et al., 2003). It is well established that the DNA methylation status and histone acetylation status play pivotal roles in gene expression via chromatin remodeling (Wu and Grunstein, 2000). In KSHV latently infected cells, the ORF50 promoter DNA is heavily methylated. The reactivation of KSHV in BCBL-1 cells by DNA methyltransferase inhibitor 5'-azacytidine correlates with the methylation defect of the ORF50 promoter DNA (Chen et al., 2001). The ORF50 promoter in KSHV latently infected cells is also associated with multiple histone deacetylases (HDACs), which remove acetyl groups from histones and are the negative regulators of transcription (Marks et al., 2003). Upon treatment with HDACs inhibitor sodium butyrate or TSA, the HDACs are inhibited and the SWI/SNF chromatin remodeling complex binds to the promoter of ORF50. The SWI/SNF remodeling complex destabilizes histone-DNA interaction and positively regulates transcription, thus inducing RTA expression. Consistent with these findings, cyclic AMP-response element binding protein (CREB)-binding protein

(CBP), which harbors histone acetylase activity, was found to induce RTA transcription in a plasmid-based assay (Lu et al., 2005; Lu et al., 2003).

Another cellular factor that positively regulates RTA expression is Oct-1. The binding of Oct-1 to ORF50 promoter was found to significantly enhance RTA expression (Sakakibara et al., 2001), while Oct-2 binding to ORF50 promoter suppresses RTA expression (Di Bartolo et al., 2009). The reactivation of KSHV by hypoxia may be related to the hypoxia response elements in the promoter of ORF50 (Haque et al., 2003). LANA, which is a repressor of the ORF50 promoter in normal conditions (Lan et al., 2004), can upregulate ORF50 promoter with hypoxia-inducible factor 1 during hypoxia (Cai et al., 2006a). Under hypoxia, cellular transcription factor X-box binding protein-1 (XBP-1) is upregulated and enhances RTA expression through the XBP-1 binding element in ORF50 promoter. Given that there are several kilobases of DNA sequence between the putative RTA promoter element and the transcription initiation site, this region may contain a number of transcriptional factor binding sites, it is likely that more cellular factors that regulate ORF50 promoter will be identified.

3 The KSHV RTA protein

KSHV RTA is the homologue of EBV RTA (Wu et al., 2000). The protein is 691 amino acids in size with a predicted molecular mass of 73.7 kDa. However, the expressed protein from mammalian cells is about 110 kDa as determined by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and suggests that RTA is modified by post-translational mechanisms (Lukac et al., 1999). Indeed, RTA has been found to be phosphorylated (Lukac et al., 1999). The RTA protein contains an N-terminal (1–530 aa) DNA-binding and oligomerization domain, a C-terminal acidic activation domain and two nuclear localization signals (NLS) (Duan et al., 2001; Lukac et al., 1999). The self-oligomerization domain of RTA lies at the proline-rich, N-terminal leucine heptapeptide repeat (LR) (Bu et al., 2007). The truncated RTA protein containing only the DNA-binding domain has a much higher DNA-binding affinity as compared to wild-type RTA, suggesting the presence of an inhibitory element for DNA-binding in the wild-type RTA protein (Chang and Miller, 2004). The mutant containing only the DNA-binding domain can serve as the dominant-negative mutant of RTA since it competes with the wild-type RTA for DNA binding but cannot activate gene expression (Lukac et al., 1999). The activation domain is highly acidic and similar to HSV-1 transcriptional activator VP16 activation domain. It contains four hydrophobic domains known as activation domains 1–4 (AD1–AD4) (Lukac et al., 1999). A schematic of the RTA protein is shown in Fig. 1.

4 Mechanisms of RTA-mediated transactivation

RTA activates a number of KSHV promoters, including both lytic and latent promoters. The known KSHV promoters that respond to RTA include polyadenylated nuclear (PAN) RNA, ORFK8, ORF57, vIRF1, K1, gB, K5, K9, ORF6, ORF59, ORF21, K12, K14/vGPCR, K15, LANA, vIL-2, vMIP1, ORF50, and others (Byun et al., 2002; Chang and Ganem, 2000; Chang et al., 2002; Chen et al., 2000; Deng et al., 2002a; Duan et al., 2001; Haque et al., 2000; Jeong et al., 2001; Lan et al., 2005b; Lukac et al., 2001; Lukac et al., 1999; Matsumura et al., 2005; Sakakibara et al., 2001; Song et al., 2002; Ueda et al., 2002; Wong and Damania, 2006; Zhang et al., 1998; Ziegelbauer et al., 2006). The transactivation of promoters by RTA involves the binding of RTA to DNA, interaction with other proteins and promoting the degradation of transcriptional repressors.

4.1 Direct DNA binding by RTA

The transactivation of many promoters by RTA involves direct binding of RTA to specific DNA sequences. The DNA sequences in the promoters that are critical for RTA-mediated transactivation are known as RTA response elements (RREs). RTA strongly transactivates two delayed-early promoters, ORF57 and K8 promoters. RTA directly binds to the RREs in these two promoter regions (Duan et al., 2001; Lukac et al., 2001; Song et al., 2002). Initially, using *in vitro* electrophoretic mobility shift assay (EMSA), RTA was found to bind a 12-bp DNA sequence, 5'-AACAATAATGTT-3', shared by ORF57 and K8 promoters. Deletion of the 12 bp DNA sequence impaired the ability of RTA to transactivate these two promoters. More than one RTA binding sites are in the ORF57 promoter. RTA also binds an interferon regulatory factor-7 (IRF-7) binding site on the ORF57 promoter, 5'-ATTTTTCGTTTG-3', and the binding is important for RTA-mediated transactivation (Wang et al., 2005). Recently, a study identified an additional RRE in ORF57 promoter in a GC-rich manner (Wen et al., 2009). RTA transactivates the PAN and K12 promoters (Chang et al., 2002; Song et al., 2001). The transactivation of these two promoters also involves the direct binding of RTA to the DNA elements within the promoters (Chang et al., 2002). However, the RREs found within the PAN and K12 promoters (5'-AAATGGGTGGCTAACCCCIACATAA-3') are different in sequence to those found in the ORF57 and K8 promoters. There are other RTA responsive promoters with different RREs. The KSHV K14 RRE is an IFN-stimulated response element (ISRE)-like sequence and can be bound directly by RTA (Zhang et al., 2005). The vIL-6 promoter contains a 26-bp RRE, 5'-AAACCCCGCCCCCTGGTGCTCACTTT-3', which has

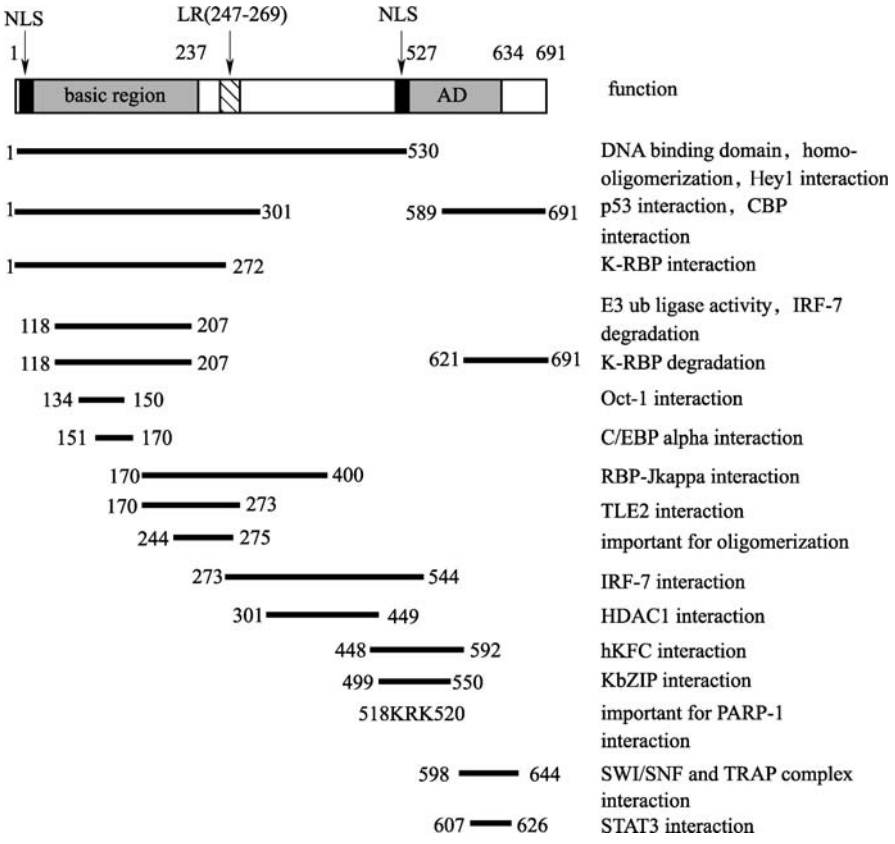

Fig. 1 Primary structure-function map of KSHV RTA. The structural motifs and the location of each functional domain of the RTA protein are shown in the protein or shown as black bars, with amino acid boundaries indicated by numbers. The corresponding functions are shown on the right. LR: leucine repeats; AD: activation domain; NLS: nuclear localization signal.

no significant homology to other RREs (Deng et al., 2002b).

Several studies aimed to identify the common sequence bound by RTA. Liao et al. suggest that an RTA oligomer can form multiple contacts with a tandem array of phased A/T triplets in the configuration of $(A/T)_3$ $(G/C)_7$ repeats (Liao et al., 2003a). However, some RREs do not fall into this consensus. Ziegelbauer et al. have performed repeated cycles of *in vitro* binding followed by amplification of bound sequences to identify direct RTA binding sequences from synthetic oligonucleotide pools and KSHV genomic libraries. The result indicates that there is only a weak consensus sequence that can be bound by RTA (Ziegelbauer et al., 2006). Chen et al. investigated RTA binding targets on KSHV genome through a chromatin immunoprecipitation assay followed by a KSHV genome-wide tiling microarray (ChIP-on-chip) approach (Chen et al., 2009). By this approach, the authors identified 19 RTA binding sites in the KSHV genome from a KSHV-infected cell line. Chen et al. further suggest that the RTA consensus binding motif is $TTCCAGGAT(N)_{0-16}TTCCTGGGA$ and half or part of this motif is sufficient. These findings suggest the complexity of RTA binding *in vivo* and *in vitro*. These results also suggest that the DNA-binding is not the sole mechanism for RTA-mediated transactivation.

4.2 Interaction with cellular cofactors

The direct DNA binding by RTA is not the only mechanism for RTA-mediated transactivation. This is evidenced from a number of studies demonstrating that alternative mechanisms may be involved. First, some of the bindings were found to be non-functional since RTA cannot transactivate luciferase reporter constructs containing such binding elements alone (Ziegelbauer et al., 2006). In addition, a study of the ORF57 promoter suggests that the ability of RTA to mediate transcriptional activation is not solely coupled to its DNA binding ability (Wen et al., 2009). Second, deletion of amino acids 521–534 or mutation of a basic motif (KKRK) at amino acids 527–530 in RTA dramatically enhances the DNA binding ability of RTA, but its transactivation ability was impaired (Chang and Miller, 2004). Third, a study by conditional nuclear localization of RTA suggests that the induction of many KSHV lytic genes requires viral proteins other than RTA (Bu et al., 2008). In fact, RTA was found to interact with other cellular

proteins to define its targets and regulate its transactivation.

4.2.1 Interaction with RBP-Jκ

RBP-Jκ (also called CSL or CBF-l) is a sequence-specific DNA binding protein and is the effector protein of the Notch signaling pathway (Mumm and Kopan, 2000). RBP-Jκ was identified as an RTA-interacting protein through a yeast two-hybrid screening for possible cellular binding proteins of RTA (Liang et al., 2002). Notably, RTA and the physiological effector protein of RBP-Jκ, Notch, share the same binding region of RBP-Jκ central repressor domain, suggesting that RTA may replace Notch during KSHV lytic reactivation. Mutation of RBP-Jκ binding site in the ORF57 promoter dramatically impairs RTA responsiveness. In addition, ORF57 promoter cannot be activated by RTA in RBP-Jκ (-/-) fibroblasts, but the defect can be complemented by ectopic expression of RBP-Jκ. These studies suggest that the RTA-RBP-Jκ complex targets RTA to RBP-Jκ recognition sites within the promoter to mediate transactivation (Liang et al., 2002). Further studies showed that KSHV could establish latency but could not be reactivated in RBP-Jκ (-/-) fibroblasts suggesting that RBP-Jκ is important for KSHV lytic replication (Liang and Ganem, 2003). In addition to ORF57 promoter, the requirement of RBP-Jκ has also been demonstrated with KSHV ORF6, K8, K14, K6, and LANA LTi promoters (Lan et al., 2005b; Liang et al., 2002; Liang and Ganem, 2003, 2004; Matsumura et al., 2005; Staudt and Dittmer, 2006; Wang and Yuan, 2007). In fact, there are at least 260 RBP-Jκ recognition sites located within the KSHV genome and many of them may be functional binding sites (Persson and Wilson, 2009). These studies suggest the critical role of RBP-Jκ in facilitating RTA-mediated transactivation.

4.2.2 Interaction with other cellular cofactors

RTA also interacts with chromatin remodeling-related proteins such as CREB-binding protein (CBP) to enhance its transactivation. CBP is a transcriptional coactivator that contains intrinsic histone acetyltransferase (HAT) activity and interacts with RTA (Gwack et al., 2001). This interaction is thought to relax nucleosomal structures on chromosome and the tightly packed DNA regions for the access of transcriptional machinery. The cellular transcription factor CBP has been shown to increase the ability of RTA to transactivate viral promoters (Gwack et al., 2001). The other cellular transcriptional cofactors, including SWI/SNF and TRAP/Mediator complexes, also interact with RTA (Gwack et al., 2003a). These cofactors presumably modulate chromatin organization on viral promoters and facilitate viral gene expression. The high mobility group box 1 (HMGB1) protein enhances the ability of RTA transactivation even though direct protein-protein interaction was not detected (Song et al., 2004). HMGB1 belongs to a family of large chromosomal proteins that promote chromatin remodeling by which transcriptional machinery can access DNA more easily.

The other RTA-interacting proteins that are important for RTA transactivation include CCAAT/enhancer-binding protein-alpha (C/EBPα) (Wang et al., 2003a, b) and Octamer-1 (Oct-1) (Carroll et al., 2007; Sakakibara et al., 2001). C/EBPα is a transcriptional factor belonging to the leucine zipper family. Multiple C/EBPα-binding sites are found in the PAN, K8, ORF57 and RTA promoters. The activation of these promoters can be cooperatively activated by RTA and C/EBPα (Wang et al., 2003a). An Oct-1 binding site was found in the K8 promoter which overlaps with the RTA binding site. Carroll et al. found that direct interactions of RTA with the Oct-1 protein and K8 promoter DNA sequence are critical for maximal transactivation of this promoter by RTA (Carroll et al., 2007).

4.3 Promotion of repressors degradation

There are a number of cellular and viral proteins which were found to suppress RTA-mediated transactivation. The cellular factors include histone deacetylase 1 (HDAC1), IRF-7, poly(ADP-ribose) polymerase 1 (PARP-1), Ste20-like kinase hKFC, nuclear factor-κB (NF-κB), Hey 1, KSHV-RTA binding protein (K-RBP), transducin-like enhancer of split 2 (TLE2) (Brown et al., 2003; Gould et al., 2009; Gwack et al., 2001; Gwack et al., 2003b; He et al., 2010; Wang et al., 2005; Yada et al., 2006; Yang and Wood, 2007).

K-RBP is a KRAB-containing zinc finger protein and represses RTA-mediated transactivation. The repression may involve both the KRAB repression domain and the DNA-binding zinc finger domain of K-RBP (Yang et al., 2009; Yang and Wood, 2007). HDAC1 interacts with RTA to downregulate RTA-mediated transactivation of KSHV promoters. This is likely due to the removal of the acetyl groups from histones by HDAC1, which results in the chromatin structure not accessible to the transcriptional machinery (Gwack et al., 2001). The cellular PARP-1 and hKFC physically interact with the serine/threonine-rich region of KSHV RTA. More importantly, the interactions can transfer poly (ADP-ribose) and phosphate groups to the RTA protein, therefore strongly repress its transactivation activity by inhibiting RTA interactions with viral promoters (Gwack et al., 2003b). Another RTA-interacting protein, IRF-7, was found to repress transactivation of the ORF57 promoter by inhibiting RTA binding to its RRE on the ORF57 promoter (Wang et al., 2005). NF-κB is another potent repressor of RTA (Brown et al., 2003). Recently, two other cellular proteins, Hey 1 and TLE2 (Gould et al., 2009; He et al., 2010), were found to be induced by RTA expression and repress RTA-mediated activation (Yada et al., 2006).

In addition to cellular proteins, several KSHV viral proteins were also found to repress RTA-mediated transactivation. The IE protein K8 interacts with RTA and represses RTA's ability to transactivate the ORF57 and K8 but not the PAN RNA promoters (Izumiya et al., 2003; Liao et al., 2003b). The repression involves the sumoylation of KbZIP (Izumiya et al., 2005). LANA is the major latent protein of KSHV and plays a critical role in maintaining KSHV latency. It interacts with RTA and represses transcription of the RTA promoter (Lan et al., 2004). The repression is dependent on the presence of the RBP-Jκ binding element in the ORF50 promoter (Lan et al., 2005a, b). This repression is one of the mechanisms by which LANA maintains KSHV latency. This is not unprecedented since Rhesus Monkey Rhadinovirus (RRV) LANA (R-LANA) represses the transactivation potential of RRV RTA (DeWire and Damania, 2005), and HVS C488 LANA suppresses the function of herpesvirus saimiri (HVS) RTA (Schafer et al., 2003). Recently, the vFLIP (K13) protein of KSHV was also found to block RTA-mediated KSHV reactivation (Zhao et al., 2007).

Study on KSHV-RTA binding protein (K-RBP) and RTA has revealed that RTA can promote the repressor, K-RBP, degradation in a proteasome-dependent manner (Yang et al., 2008). The degradation involves in the promotion of K-RBP ubiqitination by RTA. Two regions in RTA, the Cys/His-rich domain and C terminus of RTA, are required to induce K-RBP degradation. The degradation of K-RBP correlates with the transactivation ability of RTA. In the same study (Yang et al., 2008), RTA was found to promote the degradation of K8, LANA and NF-κB, though the detailed mechanism remains to be elucidated. In another study, RTA was found to promote IRF-7 degradation through the ubiquitin-proteasome pathway and serve as an intrinsic E3 ubiquitin ligase (Yu et al., 2005). Since IRF-7 is an RTA transcriptional repressor as well (Wang et al., 2005), the degradation of IRF-7 may help the virus to escape the innate immunity as well as enhance RTA-mediated transactivation. Recently, the RTA repressor, Hey1, was added on the list of cellular proteins that can be degraded by RTA via the proteasome pathway (Gould et al., 2009). However, the studies on Hey1 and K-RBP could not determine whether RTA has an intrinsic E3 ligase activity. It is possible that RTA may also recruit cellular E3 ligase to promote its substrate ubiquitination or promote degradation through other pathway(s). These studies also suggest that the RTA and its repressors form a regulatory loop to fine-tune the balance between KSHV latency and lytic replication. Given that herpes simplex virus type 1 transactivator ICP0 and human cytomegalovirus transactivator pp71 also stimulate the degradation of their cellular repressors (Everett, 2000; Kalejta and Shenk, 2003), the promotion of repressor degradation by viral transactivators may be a common feature for regulating herpesvirus lytic gene expression and replication.

5 Conclusion remarks

KSHV RTA plays a central role in regulating KSHV latency and lytic replication. It is a multiple function protein involving several mechanisms to activate its target promoters. The multiple mechanisms ensure that the transcriptional factor RTA can target different promoters, overcome repression and modulate its own activity to serve as the initiator of KSHV lytic replication. The mechanisms of RTA-mediated transactivation may also be utilized by other herpesvirus transactiviators and other transcriptional factors, thus the study of RTA transactivation will be useful for understanding how other transcriptional factors function.

The detailed mechanisms of RTA DNA-binding, protein interaction and promoting degradation remain to be fully elucidated. It is also possible that RTA may employ other novel mechanism(s) in mediating transactivation. The modulation of RTA function ultimately regulates the lytic and latent programs of KSHV. Further understanding the function of RTA may yield novel strategy to prevent KSHV replication and the development of associated diseases.

References

Amon W, Farrell P J (2005). Reactivation of Epstein-Barr virus from latency. Rev Med Virol, 15(3), 149–156

AuCoin D P, Colletti K S, Cei S A, Papouskova I, Tarrant M, Pari G S (2004). Amplification of the Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8 lytic origin of DNA replication is dependent upon a cis-acting AT-rich region and an ORF50 response element and the trans-acting factors ORF50 (K-Rta) and K8 (K-bZIP). Virology, 318(2), 542–555

Bechtel J T, Winant R C, Ganem D (2005). Host and viral proteins in the virion of Kaposi's sarcoma-associated herpesvirus. J Virol, 79(8), 4952–4964

Bellare B, Ganem D (2009). Regulation of KSHV lytic switch protein expression by a virus-encoded microRNA: An evolutionary adaptation that fine-tunes lytic reactivation. Cell Host & Microbe, 6(6), 570–575

Brown H J, Song M J, Deng H, Wu T T, Cheng G, Sun R (2003). NF-kappaB inhibits gammaherpesvirus lytic replication. J Virol, 77(15), 8532–8540

Bu W, Carroll K D, Palmeri D, Lukac D M (2007). Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8 ORF50/Rta lytic switch protein functions as a tetramer. J Virol, 81(11), 5788–5806

Bu W, Palmeri D, Krishnan R, Marin R, Aris V M, Soteropoulos P, Lukac D M (2008). Identification of direct transcriptional targets of the Kaposi's sarcoma-associated herpesvirus Rta lytic switch protein by conditional nuclear localization. J Virol, 82(21), 10709–10723

Burysek L, Pitha P M (2001). Latently expressed Human herpesvirus 8-encoded interferon regulatory factor 2 inhibits double-stranded RNA-activated protein kinase. J Virol, 75(5), 2345–2352

Byun H, Gwack Y, Hwang S, Choe J (2002). Kaposi's sarcoma-associated herpesvirus open reading frame (ORF) 50 transactivates K8 and ORF57 promoters via heterogeneous response elements. Mol Cells, 14(2), 185–191

Cai Q, Lan K, Verma S C, Si H, Lin D, Robertson E S (2006a). Kaposi's sarcoma-associated herpesvirus latent protein LANA interacts with HIF-1 alpha to upregulate RTA expression during hypoxia: Latency control under low oxygen conditions. J Virol, 80(16), 7965–7975

Cai Q L, Knight J S, Verma S C, Zald P, Robertson E S (2006b). EC5S ubiquitin complex is recruited by KSHV latent antigen LANA for degradation of the VHL and p53 tumor suppressors. PLoS Pathog, 2 (10), e116

Cai X, Lu S, Zhang Z, Gonzalez C M, Damania B, Cullen B R (2005). Kaposi's sarcoma-associated herpesvirus expresses an array of viral microRNAs in latently infected cells. Proc Natl Acad Sci U S A, 102 (15), 5570–5575

Carroll K D, Khadim F, Spadavecchia S, Palmeri D, Lukac D M (2007). Direct interactions of Kaposi's sarcoma-associated herpesvirus/ human herpesvirus 8 ORF50/Rta protein with the cellular protein Octamer-1 and DNA are critical for specifying transactivation of a delayed-early promoter and stimulating viral reactivation. J Virol, 81 (16), 8451–8467

Castagna M, Takai Y, Kaibuchi K, Sano K, Kikkawa U, Nishizuka Y (1982). Direct activation of calcium-activated, phospholipid-dependent protein kinase by tumor-promoting phorbol esters. J Biol Chem, 257(13), 7847–7851

Cesarman E, Chang Y, Moore P S, Said J W, Knowles D M (1995a). Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. New Engl J Med, 332 (18), 1186–1191

Cesarman E, Moore P S, Rao P H, Inghirami G, Knowles D M, Chang Y (1995b). In vitro establishment and characterization of two acquired immunodeficiency syndrome-related lymphoma cell lines (BC-1 and BC-2) containing Kaposi's sarcoma-associated herpesvirus-like (KSHV) DNA sequences. Blood, 86(7), 2708–2714

Chang J, Ganem D (2000). On the control of late gene expression in Kaposi's sarcoma-associated herpesvirus (human herpesvirus-8). J Gen Virol, 81(Pt 8), 2039–2047

Chang J, Renne R, Dittmer D, Ganem D (2000). Inflammatory cytokines and the reactivation of Kaposi's sarcoma-associated herpesvirus lytic replication. Virology, 266(1), 17–25.

Chang M, Brown H J, Collado-Hidalgo A, Arevalo J M, Galic Z, Symensma T L, Tanaka L, Deng H, Zack J A, Sun R, Cole S W (2005). beta-Adrenoreceptors reactivate Kaposi's sarcoma-associated herpesvirus lytic replication via PKA-dependent control of viral RTA. J Virol, 79(21), 13538–13547

Chang P J, Miller G (2004). Autoregulation of DNA binding and protein stability of Kaposi's sarcoma-associated herpesvirus ORF50 protein. J Virol, 78(19), 10657–10673

Chang P J, Shedd D, Gradoville L, Cho M S, Chen L W, Chang J, Miller G (2002). Open reading frame 50 protein of Kaposi's sarcoma-associated herpesvirus directly activates the viral PAN and K12 genes by binding to related response elements. J Virol, 76(7), 3168–3178

Chang Y, Cesarman E, Pessin M S, Lee F, Culpepper J, Knowles D M, Moore P S (1994). Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science, 266(5192), 1865–1869

Chen J, Ueda K, Sakakibara S, Okuno T, Parravicini C, Corbellino M, Yamanishi K (2001). Activation of latent Kaposi's sarcoma-associated herpesvirus by demethylation of the promoter of the lytic transactivator. Proc Natl Acad Sci U S A, 98(7), 4119–4124

Chen J, Ueda K, Sakakibara S, Okuno T, Yamanishi K (2000). Transcriptional regulation of the Kaposi's sarcoma-associated herpesvirus viral interferon regulatory factor gene. J Virol, 74(18), 8623–8634

Chen J, Ye F, Xie J, Kuhne K, Gao S J (2009). Genome-wide identification of binding sites for Kaposi's sarcoma-associated herpesvirus lytic switch protein, RTA. Virology, 386(2), 290–302

Cho H J, Yu F, Sun R, Lee D, Song M J(2008). Lytic induction of Kaposi's sarcoma-associated herpesvirus in primary effusion lymphoma cells with natural products identified by a cell-based fluorescence moderate-throughput screening. Arch Virol, 153(8), 1517–1525

Cohrs R J, Gilden D H (2001). Human herpesvirus latency. Brain Pathol, 11(4), 465–474

Cotter M A 2nd, Robertson E S (1999). The latency-associated nuclear antigen tethers the Kaposi's sarcoma-associated herpesvirus genome to host chromosomes in body cavity-based lymphoma cells. Virology, 264(2), 254–264

Curreli F, Friedman-Kien A E, Flore O (2005). Glycyrrhizic acid alters Kaposi sarcoma-associated herpesvirus latency, triggering p53-mediated apoptosis in transformed B lymphocytes. J Clin Invest, 115(3), 642–652

Davis D A, Rinderknecht A S, Zoeteweij J P, Aoki Y, Read-Connole E L, Tosato G, Blauvelt A, Yarchoan R (2001). Hypoxia induces lytic replication of Kaposi sarcoma-associated herpesvirus. Blood, 97(10), 3244–3250

Deng H, Chu J T, Rettig M B, Martinez-Maza O, Sun R (2002a). Rta of the human herpesvirus 8/Kaposi sarcoma-associated herpesvirus up-regulates human interleukin-6 gene expression. Blood, 100(5), 1919–1921

Deng H, Song M J, Chu J T, Sun R (2002b). Transcriptional regulation of the interleukin-6 gene of human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus). J Virol, 76(16), 8252–8264

Deng H, Young A, Sun R (2000). Auto-activation of the rta gene of human herpesvirus-8/Kaposi's sarcoma-associated herpesvirus. J Gen Virol, 81(Pt 12), 3043–3048

DeWire S M, Damania B (2005). The Latency-Associated Nuclear Antigen of Rhesus Monkey Rhadinovirus Inhibits Viral Replication through Repression of Orf50/Rta Transcriptional Activation. J Virol, 79(5), 3127–3138

Di Bartolo D L, Hyjek E, Keller S, Guasparri I, Deng H, Sun R, Chadburn A, Knowles D M, Cesarman E (2009). Role of defective Oct-2 and OCA-B expression in immunoglobulin production and Kaposi's sarcoma-associated herpesvirus lytic reactivation in primary effusion lymphoma. J Virol, 83(9), 4308–4315

Dittmer D, Lagunoff M, Renne R, Staskus K, Haase A, Ganem D (1998). A cluster of latently expressed genes in Kaposi's sarcoma-associated herpesvirus. J Virol, 72(10), 8309–8315

Dourmishev L A, Dourmishev A L, Palmeri D, Schwartz R A, Lukac D M (2003). Molecular genetics of Kaposi's sarcoma-associated herpesvirus (human herpesvirus-8) epidemiology and pathogenesis.

Microbiol Mol Biol Rev, 67(2), 175–212

Duan W, Wang S, Liu S, Wood C (2001). Characterization of Kaposi's sarcoma-associated herpesvirus/human herpesvirus-8 ORF57 promoter. Arch Virol, 146(2), 403–413

Everett R D (2000). ICP0, a regulator of herpes simplex virus during lytic and latent infection. Bioessays, 22(8), 761–770

Friborg J Jr, Kong W, Hottiger M O, Nabel G J (1999). p53 inhibition by the LANA protein of KSHV protects against cell death. Nature, 402 (6764), 889–894

Goedert J J (2000). The epidemiology of acquired immunodeficiency syndrome malignancies. Semin Oncol, 27(4), 390–401

Gould F, Harrison S M, Hewitt E W, Whitehouse A (2009). Kaposi's sarcoma-associated herpesvirus RTA promotes degradation of the Hey1 repressor protein through the ubiquitin proteasome pathway. J Virol, 83(13), 6727–6738

Gradoville L, Gerlach J, Grogan E, Shedd D, Nikiforow S, Metroka C, Miller G (2000). Kaposi's sarcoma-associated herpesvirus open reading frame 50/Rta protein activates the entire viral lytic cycle in the HH-B2 primary effusion lymphoma cell line. J Virol, 74(13), 6207–6212

Gwack Y, Baek H J, Nakamura H, Lee S H, Meisterernst M, Roeder R G, Jung J U (2003a). Principal role of TRAP/mediator and SWI/SNF complexes in Kaposi's sarcoma-associated herpesvirus RTA-mediated lytic reactivation. Mol Cell Biol, 23(6), 2055–2067

Gwack Y, Byun H, Hwang S, Lim C, Choe J (2001). CREB-binding protein and histone deacetylase regulate the transcriptional activity of Kaposi's sarcoma-associated herpesvirus open reading frame 50. J Virol, 75(4), 1909–1917

Gwack Y, Nakamura H, Lee S H, Souvlis J, Yustein J T, Gygi S, Kung H-J, Jung J U (2003b). Poly(ADP-Ribose)polymerase 1 and ste20-like kinase hKFC act as transcriptional repressors for gamma-2 herpesvirus lytic replication. Mol Cell Biol, 23(22), 8282–8294

Haque M, Chen J, Ueda K, Mori Y, Nakano K, Hirata Y, Kanamori S, Uchiyama Y, Inagi R, Okuno T, Yamanishi K (2000). Identification and analysis of the K5 gene of Kaposi's sarcoma-associated herpesvirus. J Virol, 74(6), 2867–2875

Haque M, Davis D A, Wang V, Widmer I, Yarchoan R (2003). Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) contains hypoxia response elements: relevance to lytic induction by hypoxia. J Virol, 77(12), 6761–6768

He Z, Liu Y, Liang D, Wang Z, Robertson E S, Lan K (2010). Cellular corepressor TLE2 inhibits replication-and-transcription-activator-mediated transactivation and lytic reactivation of Kaposi's sarcoma-associated herpesvirus. J Virol, 84(4): 2047–2062

Izumiya Y, Ellison T J, Yeh E T, Jung J U, Luciw P A, Kung H J (2005). Kaposi's sarcoma-associated herpesvirus K-bZIP represses gene transcription via SUMO modification. J Virol, 79(15), 9912–9925

Izumiya Y, Lin S F, Ellison T, Chen L Y, Izumiya C, Luciw P, Kung H J (2003). Kaposi's sarcoma-associated herpesvirus K-bZIP is a coregulator of K-Rta: physical association and promoter-dependent transcriptional repression. J Virol, 77(2), 1441–1451

Jeong J, Papin J, Dittmer D (2001). Differential regulation of the overlapping Kaposi's sarcoma-associated herpesvirus vGCR (orf74) and LANA (orf73) promoters. J Virol, 75(4), 1798–1807

Kalejta R F, Shenk T (2003). Proteasome-dependent, ubiquitin-independent degradation of the Rb family of tumor suppressors by the human cytomegalovirus pp71 protein. Proc Nation Acad Sci, 100 (6), 3263–3268

Katano H, Sato Y, Sata T (2001). Expression of p53 and human herpesvirus-8 (HHV-8)-encoded latency-associated nuclear antigen with inhibition of apoptosis in HHV-8-associated malignancies. Cancer, 92(12), 3076–3084

Kedes D H, Lagunoff M, Renne R, Ganem D (1997). Identification of the gene encoding the major latency-associated nuclear antigen of the Kaposi's sarcoma-associated herpesvirus. J Clin Invest, 100(10), 2606–2610

Komatsu T, Barbera A J, Ballestas M E, Kaye K M (2001). The Kaposi' s sarcoma-associated herpesvirus latency-associated nuclear antigen. Viral Immunol, 14(4), 311–317

Kwun H J, da Silva S R, Shah I M, Blake N, Moore P S, Chang Y (2007). Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen 1 mimics Epstein-Barr virus EBNA1 immune evasion through central repeat domain effects on protein processing. J Virol, 81(15), 8225–8235

Lan K, Kuppers D A, Robertson E S (2005). Kaposi's sarcoma-associated herpesvirus reactivation is regulated by interaction of latency-associated nuclear antigen with recombination signal sequence-binding protein Jkappa, the major downstream effector of the Notch signaling pathway. J Virol, 79(6), 3468–3478

Lan K, Kuppers D A, Verma S C, Robertson E S (2004). Kaposi's sarcoma-associated herpesvirus-encoded latency-associated nuclear antigen inhibits lytic replication by targeting Rta: a potential mechanism for virus-mediated control of latency. J Virol, 78(12), 6585–6594

Lan K, Kuppers D A, Verma S C, Sharma N, Murakami M, Robertson E S (2005). Induction of Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen by the lytic transactivator RTA: a novel mechanism for establishment of latency. J Virol, 79(12), 7453–7465

Lee S, Deng H, Yu F, Melega W P, Damoiseaux R, Bradley K A, Sun R (2008). Regulation of Kaposi's sarcoma-associated herpesvirus reactivation by dopamine receptor-mediated signaling pathways. J Acquir Immune Defic Syndr, 48(5), 531–540

Liang Y, Chang J, Lynch S J, Lukac D M, Ganem D (2002). The lytic switch protein of KSHV activates gene expression via functional interaction with RBP-Jkappa (CSL), the target of the Notch signaling pathway. Genes Dev, 16(15), 1977–1989

Liang Y, Ganem, D. (2003). Lytic but not latent infection by Kaposi's sarcoma-associated herpesvirus requires host CSL protein, the mediator of Notch signaling. Proc Natl Acad Sci U S A, 100(14), 8490–8495

Liang Y, Ganem D (2004). RBP-J (CSL) is essential for activation of the K14/vGPCR promoter of Kaposi's sarcoma-associated herpesvirus by the lytic switch protein RTA. J Virol, 78(13), 6818–6826

Liao W, Tang Y, Kuo Y L, Liu B Y, Xu C J, Giam C Z (2003a). Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8 transcriptional activator Rta is an oligomeric DNA-binding protein that interacts with tandem arrays of phased A/T-trinucleotide motifs. J Virol, 77 (17), 9399–9411

Liao W, Tang Y, Lin S F, Kung H J, Giam C Z (2003b). K-bZIP of Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8 (KSHV/HHV-8) binds KSHV/HHV-8 Rta and represses Rta-

mediated transactivation. J Virol, 77(6), 3809–3815

Lim C, Sohn H, Gwack Y, Choe J (2000). Latency-associated nuclear antigen of Kaposi's sarcoma-associated herpesvirus (human herpesvirus-8) binds ATF4/CREB2 and inhibits its transcriptional activation activity. J Gen Virol, 81(Pt 11), 2645–2652

Liu J, Martin H J, Liao G, Hayward S D (2007). The Kaposi sarcoma-associated herpesvirus LANA protein stabilizes and activates c-Myc. J Virol, 81(19), 10451–10459

Lu F, Day L, Lieberman P M (2005). Kaposi's sarcoma-associated herpesvirus virion-induced transcription activation of the ORF50 immediate-early promoter. J Virol, 79(20), 13180–13185

Lu F, Zhou J, Wiedmer A, Madden K, Yuan Y, Lieberman P M (2003). Chromatin Remodeling of the Kaposi's Sarcoma-Associated Herpesvirus ORF50 Promoter Correlates with Reactivation from Latency. J Virol77(21), 11425–11435

Lukac D M, Garibyan L, Kirshner J R, Palmeri D, Ganem D (2001). DNA binding by Kaposi's sarcoma-associated herpesvirus lytic switch protein is necessary for transcriptional activation of two viral delayed early promoters. J Virol, 75(15), 6786–6799

Lukac D M, Kirshner J R, Ganem D (1999). Transcriptional activation by the product of open reading frame 50 of Kaposi's sarcoma-associated herpesvirus is required for lytic viral reactivation in B cells. J Virol, 73(11), 9348–9361

Lukac D M, Renne R, Kirshner J R, Ganem D (1998). Reactivation of Kaposi's sarcoma-associated herpesvirus infection from latency by expression of the ORF 50 transactivator, a homolog of the EBV R protein. Virology, 252(2), 304–312

Marks P A, Miller T, Richon V M (2003). Histone deacetylases. Curr Opin Pharmacol, 3(4), 344–351

Matsumura S, Fujita Y, Gomez E, Tanese N, Wilson A C (2005). Activation of the Kaposi's sarcoma-associated herpesvirus major latency locus by the lytic switch protein RTA (ORF50). J Virol, 79 (13), 8493–8505

Miller G, Rigsby M O, Heston L, Grogan E, Sun R, Metroka C, Levy J A, Gao S J, Chang Y, Moore P (1996). Antibodies to butyrate-inducible antigens of Kaposi's sarcoma-associated herpesvirus in patients with HIV-1 infection. N Engl J Med, 334(20), 1292–1297

Mumm J S, Kopan R (2000). Notch signaling: from the outside in. Dev Biol, 228(2), 151–165

Muralidhar S, Veytsmann G, Chandran B, Ablashi D, Doniger J, Rosenthal L J (2000). Characterization of the human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus) oncogene, kaposin (ORF K12). J Clin Virol, 16(3), 203–213

Persson L M, Wilson A C (2009). Wide-scale use of Notch-signaling factor CSL/RBP-J{kappa} in RTA-mediated KSHV lytic gene activation. J Virol. doi:10.1128/JVI.01301-09

Pfeffer S, Sewer A, Lagos-Quintana M, Sheridan R, Sander C, Grasser F A, van Dyk L F, Ho C K, Shuman S, Chien M, Russo J J, Ju J, Randall G, Lindenbach B D, Rice C M, Simon V, Ho D D, Zavolan M, Tuschl T (2005). Identification of microRNAs of the herpesvirus family. Nat Methods, 2(4), 269–276

Rainbow L, Platt G M, Simpson G R, Sarid R, Gao S J, Stoiber H, Herrington C S, Moore P S, Schulz T F (1997). The 222- to 234-kilodalton latent nuclear protein (LNA) of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) is encoded by orf73 and is a component of the latency-associated nuclear antigen. J Virol, 71(8), 5915–5921

Renne R, Zhong W, Herndier B, McGrath M, Abbey N, Kedes D, Ganem D (1996). Lytic growth of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) in culture. Nat Med, 2(3), 342–346

Russo J J, Bohenzky R A, Chien M C, Chen J, Yan M, Maddalena D, Parry J P, Peruzzi D, Edelman I S, Chang Y, Moore P S (1996). Nucleotide sequence of the Kaposi sarcoma-associated herpesvirus (HHV8). Proc Natl Acad Sci U S A, 93(25), 14862–14867

Sadler R, Wu L, Forghani B, Renne R, Zhong W, Herndier B, Ganem D (1999). A complex translational program generates multiple novel proteins from the latently expressedkaposin (K12) locus of Kaposi's sarcoma-associated herpesvirus. J Virol, 73(7), 5722–5730

Sakakibara S, Ueda K, Chen J, Okuno T, Yamanishi K (2001). Octamer-binding sequence is a key element for the autoregulation of Kaposi's sarcoma-associated herpesvirus ORF50/Lyta gene expression. J Virol, 75(15), 6894–6900

Samols M A, Hu J, Skalsky R L, Renne R (2005). Cloning and identification of a microRNA cluster within the latency-associated region of Kaposi's sarcoma-associated herpesvirus. J Virol, 79(14), 9301–9305

Sarid R, Flore O, Bohenzky R A, Chang Y, Moore P S (1998). Transcription mapping of the Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) genome in a body cavity-based lymphoma cell line (BC-1). J Virol, 72(2), 1005–1012

Saveliev A, Zhu F, Yuan Y (2002). Transcription mapping and expression patterns of genes in the major immediate-early region of Kaposi's sarcoma-associated herpesvirus. Virology, 299(2), 301–314

Schafer A, Lengenfelder D, Grillhosl C, Wieser C, Fleckenstein B, Ensser A (2003). The latency-associated nuclear antigen homolog of herpesvirus saimiri inhibits lytic virus replication. J Virol, 77(10), 5911–5925

Si H, Robertson E S (2006). Kaposi's sarcoma-associated herpesvirus-encoded latency-associated nuclear antigen induces chromosomal instability through inhibition of p53 function. J Virol, 80(2), 697–709

Skalsky R L, Hu J, Renne R (2007). Analysis of viral cis-elements conferring Kshv Episome partitioning and maintenance. J Virol, doi:10.1128/JVI.00842-07

Song M J, Brown H J, Wu T T, Sun R (2001). Transcription activation of polyadenylated nuclear rna by rta in human herpesvirus 8/Kaposi's sarcoma-associated herpesvirus. J Virol, 75(7), 3129–3140

Song M J, Hwang S, Wong W, Round J, Martinez-Guzman D, Turpaz Y, Liang J, Wong B, Johnson R C, Carey M, Sun R (2004). The DNA architectural protein HMGB1 facilitates RTA-mediated viral gene expression in gamma-2 herpesviruses. J Virol, 78(23), 12940–12950

Song M J, Li X, Brown H J, Sun R (2002). Characterization of interactions between RTA and the promoter of polyadenylated nuclear RNA in Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8. J Virol, 76(10), 5000–5013

Soulier J, Grollet L, Oksenhendler E, Cacoub P, Cazals-Hatem D, Babinet P, d'Agay M F, Clauvel J P, Raphael M, Degos L. (1995). Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood, 86(4), 1276–1280

Staskus K A, Zhong W, Gebhard K, Herndier B, Wang H, Renne R, Beneke J, Pudney J, Anderson D J, Ganem D, Haase A T (1997).

Kaposi's sarcoma-associated herpesvirus gene expression in endothelial (spindle) tumor cells. J Virol, 71(1), 715–719

Staudt M R, Dittmer D P (2006). Promoter switching allows simultaneous transcription of LANA and K14/vGPCR of Kaposi's sarcoma-associated herpesvirus. Virology, 350(1), 192–205

Sun R, Lin S F, Gradoville L, Yuan Y, Zhu F, Miller G (1998). A viral gene that activates lytic cycle expression of Kaposi's sarcoma-associated herpesvirus. Proc Natl Acad Sci U S A, 95(18), 10866–10871

Sun R, Lin S F, Staskus K, Gradoville L, Grogan E, Haase A, Miller G (1999). Kinetics of Kaposi's sarcoma-associated herpesvirus gene expression. J Virol, 73(3), 2232–2242

Ueda K, Ishikawa K, Nishimura K, Sakakibara S, Do E, Yamanishi K (2002). Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) replication and transcription factor activates the K9 (vIRF) gene through two distinct cis elements by a non-DNA-binding mechanism. J Virol, 76(23), 12044–12054

Varthakavi V, Browning P J, Spearman P (1999). Human immunodeficiency virus replication in a primary effusion lymphoma cell line stimulates lytic-phase replication of Kaposi's sarcoma-associated herpesvirus. J Virol, 73(12), 10329–10338

Verma S C, Choudhuri T, Kaul R, Robertson E S (2006). Latency-associated nuclear antigen (LANA) of Kaposi's sarcoma-associated herpesvirus interacts with origin recognition complexes at the LANA binding sequence within the terminal repeats. J Virol, 80(5), 2243–2256

Wang J, Zhang J, Zhang L, Harrington W Jr, West J T, Wood C (2005). Modulation of human herpesvirus 8/Kaposi's sarcoma-associated herpesvirus replication and transcription activator transactivation by interferon regulatory factor 7. J Virol, 79(4), 2420–2431

Wang S E, Wu F Y, Fujimuro M, Zong J, Hayward S D, Hayward G S (2003a). Role of CCAAT/enhancer-binding protein alpha (C/EBPalpha) in activation of the Kaposi's sarcoma-associated herpesvirus (KSHV) lytic-cycle replication-associated protein (RAP) promoter in cooperation with the KSHV replication and transcription activator (RTA) and RAP. J Virol, 77(1), 600–623

Wang S E, Wu F Y, Yu Y, Hayward G S (2003b). CCAAT/enhancer-binding protein-alpha is induced during the early stages of Kaposi's sarcoma-associated herpesvirus (KSHV) lytic cycle reactivation and together with the KSHV replication and transcription activator (RTA) cooperatively stimulates the viral RTA, MTA, and PAN promoters. J Virol, 77(17), 9590–9612

Wang Y, Li H, Chan M Y, Zhu F X, Lukac D M, Yuan Y (2004). Kaposi's sarcoma-associated herpesvirus ori-Lyt-dependent DNA replication: cis-acting requirements for replication and ori-Lyt-associated RNA transcription. J Virol, 78(16), 8615–8629

Wang Y, Yuan Y (2007). Essential role of RBP-Jkappa in activation of the K8 delayed-early promoter of Kaposi's sarcoma-associated herpesvirus by ORF50/RTA. Virology, 359(1), 19–27

Wen H J, Minhas V, Wood C (2009). Identification and characterization of a new Kaposi's sarcoma-associated herpesvirus replication and transcription activator (RTA)-responsive element involved in RTA-mediated transactivation. J Gen Virol, 90(Pt 4), 944–953

Wong E L, Damania B (2006). Transcriptional regulation of the Kaposi's sarcoma-associated herpesvirus K15 gene. J Virol, 80(3), 1385–1392

Wu J, Grunstein M (2000). 25 years after the nucleosome model: chromatin modifications. Trends Biochem Sci, 25(12), 619–623

Wu T T, Usherwood E J, Stewart J P, Nash A A, Sun R (2000). Rta of murine gammaherpesvirus 68 reactivates the complete lytic cycle from latency. J Virol, 74(8), 3659–3667

Xie J, Ajibade A O, Ye F, Kuhne K, Gao S J (2008). Reactivation of Kaposi's sarcoma-associated herpesvirus from latency requires MEK/ERK, JNK and p38 multiple mitogen-activated protein kinase pathways. Virology, 371(1), 139–154

Xu Y, AuCoin D P, Huete A R, Cei S A, Hanson L J, Pari G S (2005). A Kaposi's sarcoma-associated herpesvirus/Human herpesvirus 8 ORF50 deletion mutant Is defective for reactivation of latent virus and DNA replication. J Virol, 79(6), 3479–3487

Yada K, Do E, Sakakibara S, Ohsaki E, Ito E, Watanabe S, Ueda K (2006). KSHV RTA induces a transcriptional repressor, HEY1 that represses rta promoter. Biochem Biophys Res Commun, 345(1), 410–418

Yang Z, Wen H J, Minhas V, Wood C (2009). The zinc finger DNA-binding domain of K-RBP plays an important role in regulating Kaposi's sarcoma-associated herpesvirus RTA-mediated gene expression. Virology, 391(2), 221–231

Yang Z, Wood C (2007). The transcriptional repressor K-RBP modulates RTA-mediated transactivation and lytic replication of Kaposi's sarcoma-associated herpesvirus. J Virol, 81(12), 6294–6306

Yang Z, Yan Z, Wood C (2008). Kaposi's sarcoma-associated herpesvirus transactivator RTA promotes degradation of the repressors to regulate viral lytic replication. J Virol, 82(7), 3590–3603

Ye J, Gradoville L, Daigle D, Miller G (2007). De novo protein synthesis is required for lytic cycle reactivation of Epstein-Barr virus, but not Kaposi's sarcoma-associated herpesvirus, in response to histone deacetylase inhibitors and protein kinase C agonists. J Virol, 81(17), 9279–9291

Yu F, Harada J N, Brown H J, Deng H, Song M J, Wu T T, Kato-Stankiewicz J, Nelson C G, Vieira J, Tamanoi F, Chanda S K, Sun R (2007). Systematic identification of cellular signals reactivating Kaposi sarcoma-associated herpesvirus. PLoS Pathog, 3(3), e44

Yu Y, Wang S E, Hayward G S (2005). The KSHV immediate-early transcription factor RTA encodes ubiquitin E3 ligase activity that targets IRF7 for proteosome-mediated degradation. Immunity, 22(1), 59–70

Zhang J, Wang J, Wood C, Xu D, Zhang L (2005). Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8 replication and transcription activator regulates viral and cellular genes via interferon-stimulated response elements. J Virol, 79(9), 5640–5652

Zhang L, Chiu J, Lin J C (1998). Activation of human herpesvirus 8 (HHV-8) thymidine kinase (TK) TATAA-less promoter by HHV-8 ORF50 gene product is SP1 dependent. DNA Cell Biol, 17(9), 735–742

Zhao J, Punj V, Matta H, Mazzacurati L, Schamus S, Yang Y, Yang T, Hong Y, Chaudhary P M (2007). K13 blocks KSHV lytic replication and deregulates vIL6 and hIL6 expression: A model of lytic replication induced clonal selection in viral oncogenesis. PLoS ONE, 2(10), e1067

Zhong W, Wang H, Herndier B, Ganem D (1996). Restricted expression of Kaposi sarcoma-associated herpesvirus (human herpesvirus 8) genes in Kaposi sarcoma. Proc Natl Acad Sci U S A, 93(13), 6641–

6646

Zhu F X, Cusano T, Yuan Y (1999). Identification of the immediate-early transcripts of Kaposi's sarcoma-associated herpesvirus. J Virol, 73 (7), 5556–5567

Zhu J, Trang P, Kim K, Zhou T, Deng H, Liu F (2004). Effective inhibition of Rta expression and lytic replication of Kaposi's sarcoma-associated herpesvirus by human RNase P. Proc Natl Acad Sci U S A, 101(24), 9073–9078

Ziegelbauer J, Grundhoff A, Ganem D (2006). Exploring the DNA binding interactions of the Kaposi's sarcoma-associated herpesvirus lytic switch protein by selective amplification of bound sequences in vitro. J Virol, 80(6), 2958–2967