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Review

miRNAs and their roles in KSHV pathogenesis

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ABSTRACT

Kaposi's sarcoma-associated herpesvirus (KSHV) is the etiological agent of Kaposi's sarcoma (KS), primary effusion lymphoma (PEL), and multicentric Castleman Disease (MCD). Recent mechanistic advances have discerned the importance of microRNAs in the virus–host relationship. KSHV has two modes of replication: lytic and latent phase. KSHV entry into permissive cells, establishment of infection, and maintenance of latency are contingent upon successful modulation of the host miRNA transcriptome. Apart from host cell miRNAs, KSHV also encodes viral miRNAs. Among various cellular and molecular targets, miRNAs are appearing to be key players in regulating viral pathogenesis. Therefore, the use of miRNAs as novel therapeutics has gained considerable attention as of late. This innovative approach relies on either mimicking miRNA species by identical oligonucleotides, or selective silencing of miRNA with specific oligonucleotide inhibitors. Here, we provide an overview of KSHV pathogenesis at the molecular level with special emphasis on the various roles miRNAs play during virus infection.

1. A brief introduction to Kaposi's sarcoma-associated herpesvirus

Kaposi's sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8), is an enveloped, double-stranded DNA virus originally discovered by Chang and Moore at Columbia University in Kaposi's Sarcoma (KS) tissues that were taken from acquired immunodeficiency syndrome (AIDS) patients (Bechtel et al., 2005; Chang et al., 1994; Jenner and Boshoff, 2002).

KSHV belongs to *Gammaherpesvirinae*, a sub-family of the *Herpesviridae* family, and the genus *rhadinovirus*, which is also known as *Rhadinoviridae* or *gamma-2 herpesviruses* (Taylor and Blackbourn, 2011; West and Damania, 2010; Zhu et al., 1999). KSHV is closely related to the primate *gamma-2 herpesvirus*, herpesvirus saimiri (HVS) and the human gamma-1 herpesvirus, Epstein–Barr virus (EBV; HHV-4) (Taylor and Blackbourn, 2011; Westmoreland and Mansfield, 2008). KSHV consists of ~165 kb dsDNA genome that encodes for more than 90 open reading frames (ORFs) as well as 25 microRNAs (miRNAs) (Arias et al., 2014; Bai et al., 2014). The majority of KSHV ORFs are conserved herpesvirus genes expressed by many other members of the family (Dourmishev et al., 2003). Additionally, the KSHV genome has its unique ORFs, known as K genes, that are specific to KSHV (Bai et al., 2014; Sharma-Walia et al., 2006). Both KSHV and EBV are oncoviruses, distinguished by their ability to establish a lifelong persistent infection in lymphocytes.

Owing to the absence of an appropriate experimental model for human γ-herpesviruses, *in vivo* studies on KSHV and EBV are limited (Cho et al., 2013). The murine gammaherpesvirus 68 (MHV-68), a member of the subfamily of *Gammaherpesvirinae* from wild rodents, has been developed as an experimental model for these studies (Simas and Efstathiou, 1998). Similar to KSHV and EBV, MHV-68 exhibits two distinct phases of life cycle; latent and lytic replication (Flano et al., 2000). Thus, MHV-68 is regarded as a substitute for the human γ-herpesvirus and has been widely used for *in vitro* and *in vivo* studies on KSHV and EBV (Cipkova-Jarcuskova et al., 2013; Wu et al., 2012).

KSHV is an oncogenic virus able to induce cellular transformation (Ganem, 2010; Jones et al., 2012). *In vitro* and *in vivo* studies have demonstrated that KSHV has a broad tropism and is able to infect a variety of cell types (Hertel, 2011). *In vivo*, KSHV can infect a variety of cell lineages including macrophages, keratinocytes, endothelial cells, and B-cells; the latter serving as its main reservoir (Ganem, 1998; Renwick et al., 2002). *In vitro*, KSHV can establish infection in a much broader range of cells, including human B cells, endothelial cells,

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epithelial cells, fibroblasts, mesenchymal stem cells, dendritic cells, and macrophages (Mesri et al., 1996; Rappocciolo et al., 2006; Wu et al., 2006).

2. KSHV pathogenesis: associated-diseases, epidemiology, and treatment

Studies strongly implicate KSHV as an etiological agent of KS and two other lymphoproliferative disorders: primary effusion lymphoma (PEL) and KSHV-associated Castleman Disease (KSHV-MCD) (Calabro and Sarid, 2018).

KSHV infection affects a wide range of the population with different geographical distributions; however, the prevalence of infection follows a very unusual geographical distribution (Mariggio et al., 2017). Sub-Saharan Africa has the greatest percentage of KSHV infection (seropositivity rates > 50%), where KSHV transmission is linked to horizontal transmission & intrafamilial/community spread *via* saliva (Cesarman et al., 2019). Such transmission modes have led KS to become the most prevalent cancer among men in Africa (Cao et al., 2014; Dedicoat et al., 2004; Mbulaiteye et al., 2004). Mediterranean, Middle Eastern, and Caribbean countries have intermediate prevalence (seropositivity 20–30%), while KSHV infection is less common in Europe, Asia, and the United States (seropositivity < 9%) (Dukers and Rezza, 2003; Uldrick and Whitby, 2011).

Therapeutic options include surgical excision, chemotherapy, radiotherapy, antiviral therapy, antibodies specific to cytokine receptors, or elimination of immunosuppressive therapy in case of transplant-associated KS (Hengge et al., 2002; Schwartz, 2004; Szajerka and Jablecki, 2007). Since the advent of the highly active antiretroviral therapy (HAART), there has been a sharp decline in the incidence of KS in AIDS patients (Franceschi et al., 2010; Gabarre and Bossi, 2003; Gantt et al., 2014). Other drugs that are commonly being used to treat KSHV-associated disease are ganciclovir (GCV) (Ocwieja et al., 2019) and foscarnet (Bossini et al., 2005).

3. KS: disease forms and geographic variation

KS is a multifocal malignancy originally described by Hungarian dermatologist Moritz Kaposi in 1872 (Stanescu et al., 2007). KS is the most prevalent cancer in HIV-infected patients, mainly affecting endothelial cells and manifesting as skin lesions (Park et al., 2019; Zhang et al., 2019). KS is characterized by three histological features: angiogenesis, inflammation, and proliferation (Li et al., 2019a; Thakker et al., 2018). KSHV DNA has been shown to be present in all four forms of KS: classical KS (CKS), epidemic KS (AIDS-KS), endemic-KS (EKS), and transplantation-associated KS (TKS) (Cesarman et al., 2019; Pugalagiri et al., 2013; Steuer et al., 2018).

4. KSHV has a biphasic life cycle

The KSHV life cycle is biphasic comprising two sequential phases of replication: latent and lytic (Li et al., 2019b; Zhang et al., 2019). Each phase of KSHV replication is characterized by its unique gene expression profile (Uppal et al., 2015). Shortly after KSHV infection, the virus replication switches to the latent phase with only a small percentage (< 3%) of infected cells supporting lytic replication (Steitz et al., 2011). A dynamic balance between latent and lytic phases of KSHV replication is critical to a successful virus infection, establishment of latency, and tumorigenesis (Frappier, 2015).

The KSHV latent phase of replication is characterized by a persistent virus infection with a restricted expression of viral genes. The key role of the latent phase is to keep the virus dormant to evade the immune system, yet maintaining replication of the viral genome (Nakayama et al., 2019). The few KSHV genes that are expressed during the latent phase are latency-associated nuclear antigen (LANA), vCyclin, vFLIP, and vIL-6. These genes are oncogenes and essential to maintaining the viral episome, promoting cell survival, and inhibiting apoptosis; all of which are a necessity to KSHV-induced pathogenesis (Choi et al., 2018; Li et al., 2019a; Zhi et al., 2015).

The molecular mechanisms by which KSHV reactivates from the latent phase and enters lytic replication are largely un-known (Traylen et al., 2011). However, a crucial role has been described for mitogen-activated protein kinase (MAPK) signaling in KSHV reactivation (Cohen et al., 2006; Ford et al., 2006). Recent studies determined retinoic acid-inducible gene (RIG)-I like receptors (RLRs) to restrict KSHV lytic reactivation and that this restriction was facilitated by the recognition of host-derived RNAs (Zhao et al., 2018). The authors concluded the existence of a direct correlation between RNA processing and virus reactivation. During the lytic phase, virus actively replicates with full viral gene expression and production of progeny virions (Toth et al., 2013). Once KSHV is reactivated, expression of lytic genes occurs in a sequential manner. Lytic genes can be divided into three groups: immediate early (IE), early (E), and late (L) genes (Uppal et al., 2014). Expression of IE genes occur immediately after reactivation and mainly encode transcription factors that are essential for the expression of viral and cellular genes. E genes encode for proteins that are required for viral DNA replication (viral polymerases, helicase, and primase) (Curreli et al., 2002). L genes encode for viral structural proteins and are expressed at the end of lytic replication. The final steps in the lytic phase are virus assembly and the release of mature virions (Chang and Kung, 2014). In summary, the presence of lytic cells is required for the production of angiogenic and anti-apoptotic viral products, which are essential to the tumorigenesis (Dunker et al., 2018; Staudt et al., 2004).

5. Virus entry: KSHV utilizes distinct receptors to successfully infect target cells

KSHV infects target cells in sequential steps (Akula et al., 2003; Kaleeba and Berger, 2006). Initially, the virus attaches to the host cell surface molecule, heparan sulfate (HS) (Bryan et al., 2005). Attachment of KSHV to target cells is critical for a successful virus infection as it allows envelope-associated proteins to make meaningful interactions with other cell surface receptor molecules which trigger the actual entry of the virus. The internalization of the virus is either by fusion or receptor-mediated endocytosis (Spear and Longnecker, 2003).

KSHV infects cells by different entry mechanisms in a cell type-dependent manner. Clathrin-mediated endocytosis seems to be one of the common mechanisms that KSHV utilizes to enter cells (Akula et al., 2003; Greene et al., 2007; Walker et al., 2016). KSHV utilizes different cell surface receptor molecules including Ephrin Receptor Tyrosine Kinase A2 (EphA2), dendritic cell-specific ICAM-3 grabbing nonintegrin (DC-SIGN), and different combinations of integrins such as α3β1, αVβ3, αVβ5, and α9β1 (Chakraborty et al., 2012; Chandran, 2010; Hensler et al., 2014; Hussein et al., 2015). Recent studies defined EphA4 as a novel entry receptor for KSHV in epithelial cells (Chen et al., 2019). These cell surface molecules are collectively referred to as entry receptors. Numerous studies have deemed a combination of these receptor molecules to be valuable for KSHV infection of cells (Akula et al., 2002; Hensler et al., 2014; Rappocciolo et al., 2008).

6. miRNAs: biogenesis and mechanism of action

MicroRNAs (miRNAs) are a class of highly conserved small non-coding RNAs of ~22 nucleotides in length. The first discovered miRNA is lin-4 which was identified by Ambros and Ruvkun labs in 1993 from *Caenorhabditis elegans* (*C. elegans*) (Lee et al., 1993; Wightman et al., 1993). miRNA lin-4 was described to regulate lin-14 mRNA translation during the early larval stage of the worm (Lee et al., 1993; Rougvie, 2001; Wightman et al., 1993). Subsequent studies revealed that the miRNAs act as post-transcriptional regulators of gene expression in many organisms (Chen, 2005; Cock et al., 2010; Cuperus et al., 2011; Ninova et al., 2016; Wienholds and Plasterk, 2005). The current release

Table 1
Numbers of pre-miRNA hairpins and mature miRNAs encoded by human herpesviruses.

Sub-Family	Viruses	Number of pre-miR Hairpins*	Number of mature miRNAs*	References
α-Herpesviruses	HSV-1 (Herpes simplex virus 1)	18	27	(Cui et al., 2006; Jurak et al., 2010)
	HSV-2 (Herpes simplex virus 2)	18	24	(Jurak et al., 2010; Tang et al., 2009; Umbach et al., 2010)
β-Herpesviruses	CMV (cytomegalovirus)	15	26	(Meshesha et al., 2012; Stark et al., 2012)
	Human herpesvirus 6B	4	8	(Tuddenham et al., 2012)
γ-Herpesviruse	EBV (Epstein Barr virus)	25	44	(Cai et al., 2006; Cosmopoulos et al., 2009; Landgraf et al., 2007; Pfeffer et al., 2004)
	KSHV (Kaposi's sarcoma-associated herpesvirus)	13	25	(Cai et al., 2005; Lin et al., 2010; Qin et al., 2017; Umbach and Cullen, 2010)

* Numbers of viral pre-miRNAs and mature RNAs based on the most recent release of miRBase (miRBase 21: http://www.mirbase.org/index.shtml).

of the miRBase database (miRBase release 21) contains 28,645 microRNA loci from 223 species which produce 35,828 mature microRNAs (Kozomara and Griffiths-Jones, 2014; Van Peer et al., 2014). The miRBase database is gradually increasing with over 2000 human miRNA sequences currently deposited in the most recent release of the mirBAse database (miRBAse 21) (Hammond, 2015; Kozomara and Griffiths-Jones, 2014).

Transcription of miRNA genes is mainly mediated by RNA polymerase II and to a lesser extent by RNA polymerase III (Ha and Kim, 2014; Ketting, 2010; Lee et al., 2004; Macfarlane and Murphy, 2010). In general, miRNA genes are transcribed as several kilobase long transcripts called primary miRNAs (Pri-miRNAs) (Cai et al., 2004). Pri-miRNAs are processed in the nucleus to ~60–70-nucleotide long miRNAs precursors (Pre-miRNAs) by the microprocessor, a complex of proteins composed of the RNAs III enzyme Drosha and its binding protein DGCR8 (Han et al., 2006). Subsequently, Pre-miRNAs are transported by Exportin-5 from the nucleus to the cytoplasm where they are trimmed by Dicer, another RNase III enzyme (Chendrimada et al., 2005; Okada et al., 2009). Dicer products are 19–25 nt long RNA duplexes with a 3′ 2-nt overhang. These miRNA duplexes are then loaded into the RNA-induced silencing complex (RISC) which includes the Ago proteins. The majority of miRNAs are produced by the canonical method described above, however, there are many alternative pathways for miRNAs biogenesis (Havens et al., 2012; Sibley et al., 2012; Yang and Lai, 2011). These include miRNAs that are generated in a microprocessor, or Dicer independent-ways (Coll et al., 2010; Eckenfelder et al., 2017; Herrera-Carrillo and Berkhout, 2017; Shapiro et al., 2010).

Once loaded to RISC, one strand of the miRNAs duplexes called the passenger strand gets ejected, while the other strand referred to as the guide strand directs the Ago proteins to the respective mRNA target(s) (Hutvagner and Zamore, 2002a,b; Khvorova et al., 2003). The seed region, positions 2–8 from the 5′ end of the guide strand is critical for miRNA binding to its target (Bartel, 2009). Mutations in the seed region of miRNAs have been shown to strongly impact the ability of miRNA to bind its targets (Kertesz et al., 2007; Mencia et al., 2009). The majority of miRNAs bind to 3′-UTR of mRNA targets, however, miRNAs can also bind to the coding region of a gene (CDS) and 5′-UTR of their targets (Gu et al., 2009).

The fate of miRNA targets depend on the level of complementarity between the miRNA and mRNA target. Low complementarity induces translational silencing, while high complementarity triggers degradation of mRNA (Bartel, 2004; Lewis et al., 2005). In both cases, miRNAs lead to a decrease in expression of respective proteins. A single miRNA can regulate hundreds of targets in an efficient way, conversely, multiple miRNAs can cooperatively regulate a single target (Zhou et al., 2013). Besides their role in the suppression of gene expression, miRNAs can also activate gene expression. The liver-specific miRNA, miR-122, has been shown to significantly enhance hepatitis C virus (HCV) infection and gene expression *via* binding to the 5′-UTR of the viral RNA and protecting it from exonuclease activity (Li et al., 2013). Similarly, miR-10a and miR-369-3p bind and activate expression of the ribosomal protein and TNF-α mRNAs respectively (Orom et al., 2008; Vasudevan and Steitz, 2007).

The accumulated evidence implicate miRNAs as gene regulators for about 60% of protein-coding genes. miRNA regulations have been shown to be critical for many vital mechanisms including maintenance of homeostasis, disease pathogenesis, and immunological responses to infection (Eulalio et al., 2012).

7. KSHV encodes miRNAs

Viruses have no miRNA processing machinery, yet many viruses encode miRNAs in their genomes including viruses from herpesviruses, adenovirus, polyomavirus, and retrovirus families (Cullen, 2011; Gourzones et al., 2012; Kincaid and Sullivan, 2012; Lieber and Haas, 2011; Nourse et al., 2012; Zhang et al., 2014). The first virus that was described to encode its own miRNA was Epstein–Barr virus (Pfeffer et al., 2004). In fact, majority of herpesviruses that infect humans encode their own miRNAs including viruses from Table 1 (Kincaid and Sullivan, 2012; Pfeffer et al., 2005; Wong et al., 2012).

One of the best examples of viruses that encode their own miRNA is KSHV. KSHV-encoded miRNAs have been described independently by several groups as early as 2005 (Cai et al., 2005; Pfeffer et al., 2005; Samols et al., 2005). Subsequent work revealed that the KSHV genome encodes 13 pre-miRNAs which are processed by cellular machinery to yield 25 mature miRNAs (Table 1) (Gottwein et al., 2011; Guo et al., 2017; Qin et al., 2017). The names, sequences, and locations of KSHV encoded miRNAs and their precursors are provided in Table 2 (Lin et al., 2010). Interestingly, KSHV-miRNAs have been shown to dominate the small RNA sequencing data generated from KSHV infected B-cell line BC-3 (Umbach and Cullen, 2010).

The majority of known KSHV-miRNAs are located in the latent locus and expressed during the latent phase of virus infection (Cai et al., 2005; Samols et al., 2005). KSHV-miR-K12-10 and KSHV-miR-K12-12 are expressed more during the lytic phase and located within ORF and 3′UTR of kaposin, respectively (Lin et al., 2010). The rest of KSHV-miRNAs are expressed strictly during the latent phase from a ~4-kb noncoding sequence located between the kaposin and ORF71 (v-FLIP) genes (Cai et al., 2005; Gottwein et al., 2006; Qin et al., 2017).

8. KSHV-encoded miRNAs promote virus latency and pathogenesis

Upon the discovery that KSHV encodes a considerable number of miRNAs, the initial focus has been to study the contributions of these miRNAs to KSHV infection and pathogenesis (Samols et al., 2007). Subsequent work revealed that KSHV-encoded miRNAs are able to regulate the expression of both viral and cellular genes that are essential to virus infection and the associated diseases (Dolken et al., 2010; Guo et al., 2017; Happel et al., 2016; Li et al., 2016a; Qin et al., 2017; Samols et al., 2007).

Table 2
Names and sequences of KSHV-encoded miRNAs and their precursors.*

Pre-miRNA	Mature miRNAs	Start	End	Strand
KSHV-miR-K12-1 CGAUUACAGGAAACUGGGUGUAAGCUGUACAUAAUCCCCGGCAGCACCUGUUUCCUGCAACCCUCGU	**KSHV-miR-K12-1-5p** AUUACAGGAAACUGGGUGUAAGC **KSHV-miR-K12-1-3p** GCAGCACCUGUUUCCUGCAACC	121847	121847	-
KSHV-miR-K12-2 GGGUCUACUUCGCUAACUGUAGUCCGGGUCGAUCUGAGCCAUUGAAGCAAGCUUCCAGAUCUUCCAGGGCUAGAGCUGCCGCGGUGACACC	**KSHV-miR-K12-2-5p** AACUGUAGUCCGGGUCGAUCUG **KSHV-miR-K12-2-3p** GAUCUUCCAGGGCUAGAGCUG	121674	121674	-
KSHV-miR-K12-3 GGCUAUCACAUUCUGAGGACGGCAGCGACGUGUGUCUAACGUCAACGUCGCGGUCACAGAAUGUGACACC	**KSHV-miR-K12-3-5p** UCACAUUCUGAGGACGGCAGCGA **KSHV-miR-K12-3-3p** UCGCGGUCACAGAAUGUGACA	121544	121613	–
KSHV-miR-K12-4 AUAACUAGCUAAACCGCAGUACUCUAGGGCAUUCAUUUGUUACAUAGAAUACUGAGGCCUAGCUGAUUAU	**KSHV-miR-K12-4-5p** AGCUAAACCGCAGUACUCUAGG **KSHV-miR-K12-4-3p** UAGAAUACUGAGGCCUAGCUGA	121413	121482	–
KSHV-miR-K12-5 UGACCUAGGUAGUCCCUGGUGCCCUAAGGGUCUACAUCAAGCACUUAGGAUGCCUGGAACUUGCCGGUCA	**KSHV-miR-K12-5-5p** AGGUAGUCCCUGGUGCCCUAAGG **KSHV-miR-K12-5-3p** UAGGAUGCCUGGAACUUGCCGGU	121263	121332	–
KSHV-miR-K12-6 CUUGUCCAGCAGCACCUAAUCCAUCGGCGGUCGGGCUGAUGGUUUUCGGGCUGUUGAGCGAG	**KSHV-miR-K12-6-5p** CCAGCAGCACCUAAUCCAUCGG **KSHV-miR-K12-6-3p** UGAUGGUUUUCGGGCUGUUGAG	120761	120822	–
KSHV-miR-K12-7 GCGUUGAGCGCCACCGGACGGGGAUUUAUGCUGUAUCUUACUACCAUGAUCCCAUGUUGCUGGCGCUCACGG	**KSHV-miR-K12-7-5p** AGCGCCACCGGACGGGGAUUUAUG **KSHV-miR-K12-7-3p** UGAUCCCAUGUUGCUGGCGC	120355	120426	–
KSHV-miR-K12-8 CGCGCACUCCCUCACUAACGCCCCGCUUUUGUCUGUUGGAAGCAGCUAGGCGCGACUGAGAGAGCACGCG	**KSHV-miR-K12-8-5p** ACUCCCUCACUAACGCCCCGCU **KSHV-miR-K12-8-3p** CUAGGCGCGACUGAGAGAGCA	119943	119943	–
KSHV-miR-K12-9 GGGUCUACCCAGCUGCGUAAACCCCGCUGCGUAAACACAGCUGGGUAUACGCAGCUGCGUAAACCC	**KSHV-miR-K12-9-5p** ACCCAGCUGCGUAAACCCCGCU **KSHV-miR-K12-9-3p** CUGGGUAUACGCAGCUGCGUAA	119300	119365	–
KSHV-miR-K12-10a CUGGAGGCUUGGGGCGAUACCACCACUCGUUUGUCUGUUGGCGAUUAGUGUUGUCCCCCCGAGUGGCCAG	**KSHV-miR-K12-10a-5p** GGCUUGGGGCGAUACCACCACU **KSHV-miR-K12-10a-3p** UAGUGUUGUCCCCCCGAGUGGC	117967	118036	–
KSHV-miR-K12-10b CUGGAGGCUUGGGGCGAUACCACCACUCGUUUGUCUGUUGGCGAUUGGUGUUGUCCCCCCGAGUGGCCAG	**KSHV-miR-K12-10b** UGGUGUUGUCCCCCCGAGUGGC			
KSHV-miR-K12-11 CGCUUUGGUCACAGCUUAAACAUUUCUAGGGCGGUGUUAUGAUCCUUAAUGCUUAGCCUGUGUCCGAUGCG	**KSHV-miR-K12-11-3p** GGUCACAGCUUAAACAUUUCUAGG **KSHV-miR-K12-11-5p** UUAAUGCUUAGCCUGUGUCCGA	120576	120576	–
KSHV-miR-K12-12 GAUGGCCGGCACGCGGUGUCAACCAGGCCACCAUUCCUCUCCGCAUUAAAGCACUCGGUGGGGGAGGGUGCCCUGGUUGACACAAUGUGCCGCGCAUC	**KSHV-miR-K12-12-5p** AACCAGGCCACCAUUCCUCUCCG **KSHV-miR-K12-12-3p** UGGGGGAGGGUGCCCUGGUUGA	117674	117771	–

* Name and sequences based on the most recent release of miRBase (miRBase 21: http://www.mirbase.org/index.shtml).

KSHV-encoded miRNAs are expressed abundantly during the latent phase of virus infection (Ueda, 2018). As latency is the default phase of KSHV infection, several studies have focussed their interests in determining the functions of these miRNAs in supporting viral latency (Chen et al., 2013; Gottwein, 2012; Lei et al., 2010). In 2009, Bellare and Ganem reported that the KSHV-miR-K12-9-5p inhibits virus reactivation by targeting the expression of replication and transcription activator (RTA), a KSHV immediate early gene, which is crucial for viral reactivation from latency (Bellare and Ganem, 2009). Moreover, elevated expression of RTA has been reported in cells infected with a mutant KSHV lacking 14 of the virus-encoded miRNAs (Lei et al., 2010). Similar studies conducted by Lu et al., using a mutant virus indicated that the KSHV miRNAs maintain virus latency *via* targeting many genes including RTA and cellular retinoblastoma (Rb)-like protein 2 (Rbl2) gene which regulate epigenetic reprogramming (Lu et al., 2010).

KSHV miRNAs inhibit apoptosis of latently-infected cells *via* targeting of apoptotic genes (Cai et al., 2005; Guo et al., 2017; Qin et al., 2017). Suffert et al., reported that the HEK293 epithelial cells and DG75 cells expressing KSHV miRNAs were protected from apoptosis (Suffert et al., 2011). Subsequently, they determined KSHV miRNAs, miR-K12-1, -3 and -4-3p targeted Casp3 and block apoptosis. Inhibition of these miRNAs with specific oligonucleotides directed to the seed regions enhances apoptosis of KSHV-infected cells (Suffert et al., 2011). Moreover, KSHV miRNAs modulate angiogenesis, signaling pathways, cell cycle, cell migration, and adhesion which are critical to KSHV dissemination and pathogenesis (Gallaher et al., 2013; Li et al., 2016a,b; Liu et al., 2017; Samols et al., 2007). By this way, KSHV miRNAs promote tumorigenesis.

KSHV miRNAs also enhance immune evasion and viral pathogenesis by regulating host immune responses. Several groups independently reported that the KSHV miRNAs impact the functions of immune effector cells and thus alter the secretion pattern of many cytokines including IL-6, IL-8, and IL-10 (Boss and Renne, 2010; Gallaher et al., 2013; Nachmani et al., 2009; Qin et al., 2010). The aberrent expression of these cytokines is a necessity for KSHV-associated diseases (Polizzotto et al., 2012; Tamburro et al., 2012).

9. Roles of cellular miRNAs in KSHV entry, replication, and pathogenesis

Beside encoding its own miRNAs, KSHV infection has been shown to significantly alter the expression of many cellular miRNAs. These miRNAs, in turn, regulate KSHV entry, replication, pathogenesis, and immune evasion (Choi et al., 2015; Qin et al., 2014). A miRNA microarray profiling of six paired KS and matched adjacent healthy tissues revealed that 170 cellular miRNAs that were differentially expressed in KS tissues compared to healthy tissues (Wu et al., 2015). A large number (n = 101) of these miRNAs including miR-125b-1-3p and miR-1183 were downregulated, while the rest (69 miRNAs) were upregulated and that included miR-126-3p, miR-199a-3p, and miR-16-5p (Wu et al., 2015). In a similar study, Catrina Ene et al., reported 185 differentially expressed miRNAs (76 were upregulated and 109 were downregulated) in KS tissues *versus* normal skin. The most significantly downregulated miRNAs in this study were cellular miRNAs: miR-99a, miR-200 family, miR-199b-5p, miR-100, and miR-335 (Catrina Ene et al., 2014). Similar studies reporting profiling of cellular miRNAs in KSHV-associated diseases has been conducted by several independent groups (Chugh et al., 2013; Lagos et al., 2010; O'Hara et al., 2008, 2009).

Similar to KSHV-encoded miRNAs, cellular miRNAs can also promote viral latency by inhibiting reactivation (Frappier, 2015). Many of the cellular miRNAs such as miR-498, miR-320d, miR-557, miR-766, miR-1227, miR-1258, and miR-1301 have been shown to target mRNA of viral lytic activator RTA (Murphy et al., 2008; Yan et al., 2013, 2014). HIV-1 viral protein R (Vpr) inhibits KSHV lytic cycle of replication *via* upregualting miR-942-5p and associated signaling that targets IκBα (Yan et al., 2016). Recent studies by the same group determined HIV-1 Vpr to upregulate another cellular miR-711 (Yan et al., 2018). Vpr targets Notch1 and thus inhibits NF-κB signaling which is required to support KSHV lytic replication. Such a Vpr-induced decline in NK-κB sinaling promotes expression of survival cytokines and proliferation. KSHV-induced cellular miRNAs are also involved in KSHV-induced angiogenesis. KSHV-K15, a viral oncoprotein has been shown to induce cell migration and angiogenesis *via* upregulation of cellular miR-21 and miR-31 (Tsai et al., 2009). Similarly, downregulation of miR-221/miR-222 cluster by KSHV infection has been reported to enhance the migration pattern of endothelial cells (Wu et al., 2011). Thus, KSHV-induced cellular miRNAs may function in unison with the KSHV-encoded miRNAs to promote latency and tumorigenesis.

The majority of the preceeding studies have investigated the induction and functions of miRNAs after KSHV has successfully established latency. For the first time, studies from our lab explored the ability of KSHV to alter expression of cellular miRNAs during early stages of infection; as early as 15 min post infection (PI) (Hussein and Akula, 2017b). We identified several cellular novel miRNAs which are upregulated during the initial stages of KSHV entry. One of these miRNAs, miR-36, was able to inhibit the entry of not only KSHV but also related viruses, EBV and HSV-2 (Hussein and Akula, 2017a). miR-36 inhibits virus entry *via* targeting the expression of interferon-inducible transmembrane 1 (IFITM1), that functions as non-specific antiviral protein. IFITM1 is a member of interferon-induced protein family including IFITM1, IFITM2, IFITM3, IFITM5, and IFITM10. Human IFITMs genes are located on chromosome 11 and are highly inducible by type I and II interferons (IFNs) (Friedman et al., 1984; Hickford et al., 2012; Reid et al., 1989). Based on IFITMs topologies, several mechanisms have been proposed to explain their role(s) in virus entry. However, the exact molecular mechanisms by which IFITMs inhibit or enhance virus entry remain to be determined.

10. Cellular miRNAs mediate immunity against viral pathogens

Several viruses have been shown to significantly alter the expression of cellular miRNAs in infected cells (Bruscella et al., 2017; Skalsky and Cullen, 2010). This could be in part due to the mechanism by which cells mount antiviral responses, or viral factors that inhibit cellular responses and change the intracellular milieu to support virus replication and infection (Bruscella et al., 2017; Cullen, 2013; Gottwein, 2013; Swaminathan et al., 2013; Trobaugh et al., 2014).

In general, the contributions of small RNAs to the antiviral response in chordates remains elusive compared to plants, arthropods, and nematodes (Cullen, 2010; tenOever, 2013). However, accumulating evidence indicates a crucial role for cellular miRNAs in antiviral immunity (Gantier et al., 2007; Skalsky and Cullen, 2010). Levels of miRNAs have been shown to correlate with the expression of interferons during virus infection (Lindsay, 2008; Pedersen et al., 2007). Pederson et al., have shown that interferon β induced by HCV rapidly modulates the expression of numerous cellular miRNAs. In turn, several of these miRNAs have been shown to target the HCV genome (Pedersen et al., 2007). Similarly, dicer-deficient mice are more susceptible to infection with cytomegalovirus and vesicular stomatitis virus (VSV) (Ostermann et al., 2012; Otsuka et al., 2007). These studies demonstrate that the miRNAs are critical to mounting rapid antiviral responses such as interferon and interferon-inducing genes.

Cellular miRNAs have been shown to directly target the genome and transcripts of many viruses including HIV, HCV, HBV, VSV, and KSHV viruses (Chen et al., 2011; Forster et al., 2015; Jopling et al., 2005; Nathans et al., 2009; Skalsky and Cullen, 2010). Kang et al., reported cellular miR-1293 to target KSHV encoded IL-6, an essential protein for KSHV-mediated diseases, especially in the inflammatory cytokine syndrome associated with KSHV infection in AIDS patients (Kang et al., 2011). Interestingly, KSHV has also evolved mechanisms to use cellular

miRNAs to evade antiviral innate immune responses. miR-123, a cellular miRNA induced by KSHV in endothelial cells target the p300 transcriptional co-activator which negatively regulate the expression of interferon-stimulated genes and enhance virus replication (Lagos et al., 2010; Qin et al., 2014).

Studies from our laboratory described a crucial role for the KSHV-induced cellular miR-36 to inhibit virus infection in both B and endothelial cells which are the main targets of KSHV infection *in vivo* (Hussein and Akula, 2017a). Interestingly, miR-36 was able to inhibit infection of not only KSHV, but also EBV, and HSV-2 viruses. We were able to detect up-regulation of miR-36 as early as 15 min post-KSHV infection (Hussein and Akula, 2017b). Subsequently, we found that miR-36 inhibits virus infection by targeting the expression of IFITM1 protein (Hussein and Akula, 2017a).

11. Targeting miRNAs for anti-viral and anti-cancer therapies

Cellular and viral miRNAs are attractive targets to design pathogen-specific antiviral therapies (Bofill-De Ros et al., 2017; Bruscella et al., 2017; Skalsky and Cullen, 2010). miRNA-based therapies could be formulated in two different forms: mimicking miRNA functions using miRNA-specific oligonucleotide mimics or silencing miRNA functions by miRNA-specific antisense oligonucleotide inhibitors (anti-miRNA) (Baigude and Rana, 2014; Reid et al., 2016; Tang and Tang, 2013).

There are several miRNA-based therapies currently being tested in human clinical trials (Christopher et al., 2016; Titze-de-Almeida et al., 2017). One of the most common examples of miRNA-based antiviral therapy is miR-122 antisense oligonucleotide inhibitor (miravirsen, Santaris Pharma, Hørsholm, Denmark). Miravirsen has been shown to be promising for treatment of HCV infection (de Jong and Jacobson, 2014; Janssen et al., 2013a,b). Interestingly, Miravirsen administration to 36 patients with chronic HCV genotype 1 infection resulted in a reduction of 1.2 to 3.0 log international units (IUs)/mL in HCV RNA levels in a dose-dependent manner without induction of virus resistance (Janssen et al., 2013b). In a recent and more promising study, Van der Ree et al., reported that the administration of 2 mg/kg or 4 mg/kg RG-101, a hepatocyte targeted N-acetylgalactosamine conjugated anti-miR-122 oligonucleotide, induced a significant reduction in HCV RNA levels (van der Ree et al., 2017).

As discussed above, miRNAs are able to directly target the viral genome, thus ubiquitously expressed miRNA can be harnessed to generate safe and effective live-attenuated vaccines (tenOever, 2013). Incorporation of tissue-specific miRNA target sequences into attenuated vaccines prevent the virus from replicating in this tissue (Drury et al., 2017; tenOever, 2013). Insertion of neuronal-specific miR-124 target sites into poliovirus genome inhibits the replication of the virus in the central nervous system. The engineered virus strain was able to elicit a strong protective immunity without producing neurovirulence in infected animals (Barnes et al., 2008). A similar approach has been applied to engineer safe and effective live attenuated vaccine strains for West Nile virus, dengue virus, influenza virus, VSV, and measles virus (Brostoff et al., 2016; Drury et al., 2017; Heiss et al., 2011; Kelly et al., 2010; Leber et al., 2011; Perez et al., 2009).

Similar to treating viral infections, miRNA-based therapies to treat for many cancers including that of lung cancer, pancreatic cancer, prostate cancer, colon cancer, ovarian cancer, and breast cancer are currently at preclinical and clinical phases of development (Christopher et al., 2016; Henry et al., 2011; Ibrahim et al., 2011; Liu et al., 2011; Pecot et al., 2013; Pramanik et al., 2011; Trang et al., 2011). miR-221 silencing using chol-anti-miR-221 blocks hepatocellular carcinoma and promote mouse survival. Chol-anti-miR-221 was able to inhibit tumor cell proliferation and increase the markers of apoptosis and cell-cycle arrest (Park et al., 2011). Targeting IFITM1 by employing mi-36-specific oligonucleotide mimics may yield anti-viral therapy to prevent KSHV and associated herpesvirus infections.

12. Conclusions

Modulation of gene expression is an integral part of the virus–host relationship. KSHV exploits the cellular transcriptional machinery to facilitate tissue invasion, establishment of infection, and maintenance of latency. Among the molecular targets of KSHV are small, noncoding miRNAs. These regulatory molecules are efficiently manipulated by KSHV to evade immune surveillance and promote virus survival. Accordingly, miRNAs have recently emerged as an attractive therapeutic alternative for KSHV as well as other infectious agents and diseases. Identification of the miRNA fingerprints of disease states and elucidating their various roles in pathogenesis is therefore of considerable interest. Our recent efforts have demonstrated that inhibiton of miR-36 effectively prevents KSHV lytic replication by down-regulating IFITM1; both *in vitro* and *in vivo*. Similarly, miRNA-based interventions have successfully been employed against HCV, poliovirus, and hepatocellular carcinoma with exceedingly encouraging results. Hence, targeting miRNAs holds great promise to expand on the scope of our existing arsenal of antiviral/cancer therapy and disease combating strategies.

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Conflict of interest

The authors declare no conflict of interest.

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