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miRNAs in the pathogenesis of oncogenic human viruses

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Abstract

Tumor viruses are a class of pathogens with well established roles in the development of malignant diseases. Numerous bodies of work have highlighted miRNAs (microRNAs) as critical regulators of tumor pathways and it is clear that the dysregulation of cellular miRNA expression can promote tumor formation. Tumor viruses encode their own miRNAs and/or manipulate the expression of cellular miRNAs to modulate their host cell environment, thereby facilitating their respective infection cycles. The modulation of these miRNA responsive pathways, however, often influences certain signal transduction cascades in ways that favor tumorigenesis. In this review, we discuss the roles of virally-encoded and virally-regulated cellular miRNAs in the respective viral life-cycles and in virus associated pathogenesis.

1. Introduction

MiRNAs (microRNAs) are a newly-discovered class of gene regulators that are single-stranded non-protein-coding RNAs with an average length of 21-22 nucleotides. The first characterized miRNA, lin-4, was originally discovered in roundworm (*Caenorhabditis elegans*) by Lee and colleagues in 1993 [1]. Lin-4 was shown to regulate roundworm development and was predicted to function through an RNA-RNA interaction [1]. At that time, however, lin-4 was only viewed as a unique regulator in worms and the importance of this discovery did not receive broad recognition. The dawn of the miRNA era occurred approximately eight years later when three groups simultaneously reported the identification of miRNAs as a class of regulators in the journal *Science* [2;3;4]. Since this time, the list of identified miRNAs has grown rapidly and miRNAs are now appreciated as a highly conserved and evolutionarily important component of living organisms [3]. Currently, miRNAs have been identified in almost all studied multi-cellular eukaryotes in the plant and animal Kingdoms. Recent studies demonstrated that miRNAs can also be encoded by certain single-cell eukaryotes and by viruses [5;6]. The current total number of identified miRNA genes is ~14197 including ~940 human miRNAs (according to the Sanger miRBase 2010 Release 15). A much higher number of miRNAs is predicted by computational approaches [7] and it is estimated that miRNAs account for 1-5% of expressed genes in animal genomes [8;9]. At this level, miRNAs would become one of the most abundant classes of gene regulators in higher eukaryotes [8;9].

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Conflicts of Interest Statement

None Declared

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Since the discovery of miRNAs, the way in which they execute their function has been the subject of intense study. The central dogma states that miRNAs regulate their targets primarily through base complementary interactions. Under the guidance of the “seed” region (the 5' nucleotides 2-8 of the mature miRNA), miRNAs typically interact with the 3'-UTR (**un**translated region) of their mRNA targets and less frequently through target sites within the coding region or the 5'-UTR. This interaction occurs in the context of a protein nucleic acid complex referred to as miRISC (miRNA induced silencing complexes) and the formation of this complex on target mRNAs results in the inhibition of protein production through a number of mechanisms including degradation of the target mRNA and inhibition of translation [7;8].

Genetically, miRNA genes are located within introns of protein-coding or non-protein-coding genes or in intergenic regions as stand alone genes. MiRNAs can be found as either a single unit or as clusters of more than one miRNA. Clustered miRNAs are usually expressed together as polycistronic transcripts and their targets are often predicted to have similar functions. Based on the similarity of the 5' seed sequence, some miRNAs are separated into families, such as the miR-200 family of miRNAs which includes miR-200a/b/c, miR-141, and miR-429 which are transcribed from two distinct genomic loci.

Although there is only a small percentage of human miRNAs that are currently being investigated, miRNAs are predicted to regulate approximately one third of human mRNAs [7;10]. Each miRNA can have multiple target transcripts, and each transcript can be silenced by multiple miRNAs leading to an extremely complicated regulatory system. Due in part to the pleiotropic nature of miRNA targeting, it is likely that they are involved in the regulation of nearly every signal transduction pathway utilized by the cell. To date, miRNAs have already been shown to exhibit regulatory functions in numerous cellular pathways and cellular processes including proliferation, differentiation, and apoptosis [10].

The development of cancer is a multi-factorial and multi-step process. As widespread regulators of many if not all signaling pathways, it is not a stretch to expect miRNAs to be involved in the regulation of oncogenic pathways. In fact, accumulating evidence indicates that disruption of miRNA expression correlates with most types of human malignancies including breast cancer [11], ovarian cancer [12], cervical cancer [13], prostate cancer [14], colorectal cancer [15], gastric cancer [16], nasopharyngeal carcinoma [17], lung cancer [18], renal cancer [19], and hematopoietic malignancies [20]. Human miRNAs are frequently located in genomic regions linked to cancer such as fragile sites, minimal regions of loss of heterozygosity, minimal regions of amplification, and common breakpoint regions, further implicating them in tumorigenesis [21]. MiRNAs can function as either oncogenes (oncomirs) or tumor suppressors through the inhibition of critical protein-coding genes involved in tumorigenesis. Informatics studies have suggested the possibility that miRNAs may also regulate the development of certain cancers by targeting non-protein-coding RNAs such as those transcribed from ultraconserved regions (UCRs) [22]. While these studies may have important implications in cancer biology, experimental validation of this concept is nevertheless pending. Overall, the study of detailed mechanisms through which miRNAs contribute to cancer is in its nascent stages, yet it is clear that the discovery of miRNAs has created a new dimension for us to understand the mechanism of tumorigenesis.

2. Viruses, miRNAs and cancer

A hallmark of viruses is their incredible mastery of the art of cellular hijacking to achieve their own tenets of self-preservation and proliferation. With their limited genetic capacity, they rely exquisitely on a wide range of host functions to achieve these tenets. Nevertheless, they seem never content to simply utilize existing cellular functions in their natural state but

instead modulate and fine-tune each of these pathways/functions in ways that provide a greater advantage for the virus. Given the now well established role of miRNAs in regulating almost every aspect of the cellular regulatory machinery, it is not surprising to find viruses interacting with these pathways as a means of modulating the host environment to suit their needs. Although the study of how viruses utilize miRNA pathways in their life cycle is in its infancy, we know that this intersection with miRNA pathways occurs through virus-mediated modulation of existing cellular miRNA expression and/or through the evolution of a virus-encoded repertoire of miRNAs.

From an evolutionary standpoint, the genesis of a virus-encoded miRNA seems quite tractable since there are only a handful of nucleotides that are needed to confer an appropriately processed functional miRNA molecule. Yet this relatively simple evolutionary process can potentially capacitate virus mediated regulation of hundreds of cellular (and/or viral) genes. This in part, may explain the high relative abundance of virus-encoded miRNAs for some viruses such as the Epstein-Barr virus which encodes at least 44 mature miRNAs in a genome that is more than 16,000 times smaller than the human genome. This de novo evolution of functional virus-encoded miRNAs is a little more difficult than it may seem, because, in addition to the presence of seed complementarity of the target mRNAs, there are flanking sequence and secondary structure constraints on the target RNAs that determine whether the respective site is potentially susceptible to miRNA targeting. Therefore, finding targetable sequences common to a repertoire of cellular mRNAs whose inhibition provides an advantage to the virus may be a challenge. Although many viruses have, in fact, evolved with their own functional miRNA genes, they also utilize the mechanism of modulating cellular miRNAs to influence a repertoire of mRNA targets.

There is a third situation which is a hybrid of the two scenarios mentioned above. In this case, the virus appears to have evolved to encode miRNAs that target an already existing miRNA/targetome pathway. Salient examples of this is the Kaposi's sarcoma herpes virus (KSHV) encoded miR-K12-11 and Marek's disease virus (MDV-1) encoded miR-M4 which have the identical seed sequence as that of the cellular miRNA, miR-155. Having identical seed sequences, these virus-encoded miRNAs target a highly overlapping set of genes with that of miR-155 [23;24;25]. This scenario is even more interesting, however, because another herpesvirus, the Epstein-Barr virus, has evolved with a mechanism to simply modulate the host miR-155 expression to suit its life cycle.

It appears, then, that the miR-155 pathway is particularly well suited to the life cycle needs of these three herpesviruses but these viruses have intersected with this pathway in two different ways. Notably, all three of these herpesviruses are oncogenic while the inappropriate expression of cellular miR-155 is similarly known to be oncogenic outside of any viral context. It is not too hard to imagine then, that while a miR-155-like function is integral to some aspect of the life cycle of these viruses, the inappropriate activation of a miR-155 function during the virus life cycle may partly explain the oncogenic tendency of these viruses.

Of all the viruses studied to date, herpesviruses are the hands down winners in terms of the number of miRNAs encoded, with herpes viral miRNAs accounting for more than 97% of all known virus encoded miRNAs. The explanation for this extreme bias may lie at least partly in a defining characteristic of herpesviruses: their ability to exist in a latent phase. In this state, herpesviruses need to remain relatively undetectable to the immune system in order to avoid total virus clearance. They cannot, therefore, express foreign viral proteins that can potentially be processed and presented on the cell surface to attract an immune response. Nevertheless, herpesviruses still need to control/regulate themselves as well as the cellular host during latency. MiRNAs may be a particularly well suited means for

herpesviruses to regulate themselves as well as their host cell environments during latency when they need to exist in an immunologically transparent state.

Viruses integrate into the cellular miRNA machinery in a variety of ways to achieve pathogenic success. As miRNAs regulate pathways that are such critical mediators of cellular signaling and cancer, pathogenic success is not always that far away from oncogenesis. In conjunction with host cell genetic abnormalities and/or other exogenous agents, the balance between pathogenic success and cancer can be tipped towards the latter. Below we have outlined many of the known miRNAs and affected pathways that are influenced by viruses and we discuss their possible relevance in the genesis of virus induced cancers.

3. Epstein-Barr virus

Epstein-Barr virus (EBV, Human Herpesvirus 4 (HHV-4)) is closely associated with a number of human tumors including Burkitt's lymphoma, Hodgkin's disease, lymphoproliferative disease in immuno-suppressed patients, nasopharyngeal carcinoma, gastric carcinoma, and renal cell carcinoma [26]. EBV is a member of the human herpesviridae family, of which Herpes Simplex virus (HSV), Cytomegalovirus (CMV), and Kaposi's sarcoma herpes virus (KSHV) are also members. After initial infection, EBV, like other herpesviruses, exhibits life-long latency in its host during which the viral genome exists as an episomal closed circular plasmid DNA and only a restricted set of viral genes are expressed. Viral reactivation (the lytic cycle) is initiated periodically in response to a variety of physiological signals. Reactivation leads to the expression of ~100 viral genes and culminates in the production of infectious virions that are released and available to infect new host cells. The virus is transmitted mainly through salivary exchange and currently, more than 90% of the world's adult population are persistent carriers of EBV [27]. Although the exact mechanism for EBV primary infection is still not clear, current theory holds that during primary infection, EBV initially infects the oropharyngeal epithelial cells which are permissive for viral lytic infection. Productive replication in this epithelial cell population leads to the latent infection of nearby B-cells in which the full complement of EBV latency proteins are expressed (referred to as type III latency) [28]. Expression of this full repertoire of latency genes induces B-cell activation/proliferation and facilitates a transient virus driven expansion of the latently infected B-cell pool. In a small population of circulating B-cells, EBV establishes a more restricted form of latent infection in which either one (type I latency) or no (type O latency) viral protein is expressed. Once an immune response is mounted, the lytic infected epithelial cells, as well as the expanding type III latency B-cell population, are mostly eliminated. The remaining small population of infected circulating B-cells, exhibiting restricted latency gene expression, will then persist for the lifetime of the host. It is thought that there are occasional transitions to type III latency in some B-cells, as well as sporadic reactivation events in epithelial tissue, whereby EBV is produced and secreted into the saliva for transmission to a new host.

EBV encodes its own repertoire of miRNAs and it modulates the expression of cellular miRNAs in a concerted effort to regulate its life cycle. While EBV uses miRNAs to regulate pathways in ways that promote its life cycle, virus survival has many of the same needs as tumor survival. In conjunction with additional factors including host genetic alterations and/or a compromised host immune system, the expression of EBV encoded miRNAs and/or the dysregulation of cellular miRNAs can lead to virus associated tumors through the miRNA dependent modulation of cancer pathways.

3.1. EBV-encoded miRNAs

Due to the non-immunogenic property of these tiny RNA molecules, viral miRNAs are good candidates to execute various latency associated tasks once an immune response to viral antigens has been mounted by the host. This may partly explain the common occurrence of virus-encoded miRNAs among the herpesvirus family. In addition, however, the biosynthesis cascade involved in the production of miRNAs is preferentially suited to nuclear DNA viruses (although miRNAs generated by RNA retrovirus (e.g. HIV-1) have also been identified (although this assertion remains controversial) [29]). To date, virus-encoded miRNAs have been found in the genomes of a number of human and non-human viruses including EBV, KSHV, CMV, HSV, SV40, rLCV, rhesus monkey rhadinovirus, herpes B virus, MHV68, mouse CMV, MDV, and HIV-1. As shown in Table 1, the herpesvirus family encodes most of the currently identified viral miRNAs and EBV, the first human virus reported to express its own miRNAs [6], is one of the leading viral miRNA encoders.

EBV encoded miRNAs are derived from two different clusters within the viral genome. Three viral miRNAs are encoded within the BamHI H rightward open reading frame (BHRF) region and the remaining miRNAs are found within the BamHI A rightward transcript (BART) region. The EBV BART gene was originally identified by Hitt and colleagues in the EBV-infected nasopharyngeal carcinoma cell line, C15 [30]. In the years following, BART transcripts were detected in both healthy viral carriers and in many other EBV-associated diseases including oral hairy leukoplakia, Burkitt's lymphoma, Hodgkin's lymphoma, gastric carcinoma, as well as nasal natural killer/T-cell lymphomas, [31;32;33;34;35]. BART sequences are largely conserved between EBV strains with the exception of a large 12-kb deletion spanning most of the BART locus which was identified in the B95-8 laboratory EBV strain [36]. For many years, BART transcripts were thought to function primarily through open reading frames within the spliced forms of these transcripts. Ectopic expression of open reading frames encoding two of these proteins, RPMS1 and A73, has been shown to modulate cellular signaling pathways relevant to tumorigenesis [37;38]. To date, however, the endogenous expression of neither of these proteins has been observed in virus infected cells [37;38;39].

EBV BART miRNAs are derived from a large intron within BART transcripts prior to splicing [40]. The identification of BART miRNAs was first accomplished by Pfeffer and colleagues [6] in the EBV B95-8 strain. This group successfully cloned five mature EBV encoded miRNAs, including miR-BART1 and miR-BART2, from the BART locus, and the three BHRF miRNAs, miR-BHRF1-1, miR-BHRF1-2, and miR-BHRF1-3, located 5'- and 3' of the BHRF1 (BamHI H Rightward ORF1) open reading frame [6]. Later, using wild-type EBV infected cell lines, another group extended the number of EBV encoded miRNAs to seventeen, including fourteen BART miRNAs and all three of the previously identified BHRF1 miRNAs [41]. Interestingly, the identification of miRNAs from the rhesus lymphocryptovirus (rLCV), an evolutionarily distant relative of EBV (~23 million years evolutionary divergence or ~13 million years ago), revealed a number of miRNAs that show strong conservation in terms of both miRNA sequence and genomic positions [41;42;43]. This intimates an evolutionarily conserved role for these miRNAs in the life cycles of these viruses.

In a separate study, Grundhoff and colleagues [44] identified a total of twenty-two mature miRNAs in wild-type EBV infected cell lines through a combination of computational bioinformatics, microarray, and northern blot approaches. Recently, an additional three miRNAs, miR-BART21-5p, BART21-3p, and miR-BART22, were identified by other groups [45;46] bringing the total number of EBV encoded mature miRNAs to ~40.

3.2. Regulation of EBV-encoded miRNA expression

EBV exhibits tissue-specific expression of its miRNAs. By studying nasopharyngeal carcinoma (NPC) tissues, Zhu and colleagues found that EBV-miR-BARTs were expressed in all NPC tissues examined, but EBV-miR-BHRF1s were not [45]. Similarly, in another epithelial cell model system, Kim et al. [47] found that EBV-miR-BARTs, but not EBV-miR-BHRF1s were expressed in EBV-associated gastric carcinoma cell lines and gastric carcinoma tumor tissues.

In B-cells, the pattern of EBV miRNA expression appears to be somewhat dependent on the latency type. In one report, expression of miR-BART2 but not miR-BHRF1-3 was detected in some primary Burkitt's lymphoma samples (which exhibit type I latency), whereas miR-BHRF1-3 expression was found to be high in type III latency cell lines and AIDS-related large B-cell lymphoma samples (which typically exhibit type III latency gene expression) [48]. Consistently, another study has demonstrated that BHRF1 miRNAs are expressed at high levels in type III latency cells but are undetectable in cells displaying a viral type I/II latent infection [41].

In addition to an apparent latency type dependency of EBV miRNA expression, induction of the EBV lytic cycle has been shown to correlate with the induction of certain EBV miRNAs (such as miR-BART1-3p, miR-BART3-3p, miR-BART7, miR-BART10-3p, and miR-BHRF1-2, and to a lesser extent miR-BHRF1-1) in the type I latency Burkitt's lymphoma cell line Mutu I [41]. These observed expression differences between different stages of the EBV life cycle may reflect stage specific miRNA function. Nevertheless, future studies will be needed to assess this contention.

Theoretically, expression of miRNAs can be regulated at every step within its biosynthesis pathway (e.g. in the transcriptional initiation step or during the processing of miRNA precursors). Currently, the mechanisms involved in regulating EBV miRNA expression are not all that clear. Some studies have demonstrated that all the miR-BARTs are derived from the same transcript [40] and there is a coordinate expression of the BART mRNAs and the miR-BARTs [41]. Therefore, it is likely that the activity of the BART promoter is a primary determinant of the overall expression levels of miR-BARTs. Despite this, however, it is clear that different BART miRNAs are expressed at different levels within the same cell, probably due to varying accessibility of individual BART miRNA sequences to the microprocessor machinery [49]. Since nucleotide polymorphisms can affect the processing of miRNAs, variable relative abundances of individual miR-BARTs from one cell to another may result from sequence variations of miR-BARTs precursors [40;50].

In contrast to miR-BARTs, miR-BHRF1s appear to be processed from two different precursors with miR-BHRF1-1 being derived from EBNA (Epstein-Barr nuclear antigen) transcripts and miR-BHRF1-2 and 1-3 being generated from BHRF1 transcripts [41]. The expression of miR-BHRF1-1 is therefore regulated largely independently from the expression of BHRF1-2 and BHRF1-3.

3.3. Biological roles of EBV-encoded miRNAs

The evolutionary conservation of a number of EBV miRNAs with miRNAs encoded by the rhesus lymphocryptovirus implies that these miR-BARTs play critical roles in EBV's life cycle. In addition, there is accumulating evidence that some EBV encoded miRNAs may contribute to the oncogenic properties of the virus such as: (1) the induction of epithelial cell proliferation; (2) providing survival signals for virus infected cells in vivo (e.g. under hypoxic conditions inside the tumor); and (3) escaping host immune surveillance.

Choy and colleagues [51] have shown that miR-BART5 targets the transcript encoding the cellular factor PUMA (p53 up-regulated modulator of apoptosis) and they propose a role of miR-BART5 in the inhibition of apoptosis. MiR-BART5 may improve the overall survival of infected cells during the natural infection course of the virus and it may contribute to cell survival in virus associated cancers. Interestingly, miR-BART5's seed sequence contains significant homology with the cellular miRNAs, miR-18a and miR-18b, which display elevated expression in a number of cancers including liver cancer [52].

Like other members of the herpesvirus family (human CMV, HSV-1, and KSHV), EBV encoded miRNAs are also predicted to suppress virus immediate early (IE) lytic genes [53]. For instance, miR-BART15 is predicted (through computational methods) to down-regulate the EBV immediate-early transactivators, Zta and Rta [53]. Since these transactivators are the molecular switches controlling the transition into the lytic cycle, targeting Zta and Rta transcripts would represent a cost efficient means of suppressing the entire repertoire of lytic genes during latency.

MiR-BART2 has been shown to down-regulate the EBV encoded DNA polymerase gene, BALF5 [54], which is expressed during the lytic phase of the virus life cycle. Strikingly, miR-BART2 has perfect complementarity to the 3'-UTR of BALF5, and miR-BART2 thereby causes degradation of the BALF5 mRNA [54]. During the transition from viral latency to lytic reactivation, miR-BART2 is downregulated and enforced expression of miR-BART2 impairs EBV lytic replication [54]. These experiments support a model in which miR-BART2 functions to enforce viral latency thereby maintaining expression of the oncogenic viral latency genes [54]. At another level, the down-regulation of BALF5 by miR-BART2 may also help to reduce the amount of this antigenic viral protein to facilitate evasion of host immune surveillance. EBV miR-BART2 has also recently been shown to inhibit expression of the stress-induced immune molecule MICB to prevent Natural Killer (NK) cell mediated cell killing and facilitate immuno-evasion during EBV infection [55].

In addition to inhibiting entry into the lytic cycle, viral miRNAs also appear to be involved in regulating the expression of certain latency genes. For instance, EBV BARTs Cluster1 miRNAs (namely, miR-BART1, miR-BART16, and miR-BART-17) have been shown to target the 3'-UTR of the viral latent membrane protein LMP1 [56]. Although LMP1 is generally viewed as a key oncogene in the development of EBV-associated malignancies, when expressed inappropriately and/or at high levels, it can also cause growth arrest and induce apoptosis. The adjusting/fine-tuning of LMP1's expression levels by miR-BARTs may help to attenuate the inhibitory properties associated with high level or inappropriate expression of LMP1. On the other hand, the downregulation of LMP1 may also be part of an immuno-evasion strategy during certain parts of the viral life cycle. In the same vein, the mRNA of another viral latent membrane protein, LMP2A, was shown to be targeted by miR-BART22 [57]. LMP2A is a potent immunogen that is capable of inducing a cytotoxic T-cell response. The modulation of LMP2A levels may similarly help alleviate host immune surveillance.

MiR-BHRF1-3 has been shown to down-regulate expression of the interferon-inducible T-cell attracting chemokine, CXCL11/I-TAC, in B-cells [48]. Inhibition probably occurs by targeting the transcripts for degradation since the 3' UTR of *CXCL11* transcripts have perfect complementarity to miR-BHRF1-3. CXCL11 functions through binding to the chemokine receptor CXCR3, which is found predominantly on T-cells. CXCL11 is an important effector of Cytotoxic T-Lymphocyte (CTL) activation and is reported to be a potent anti-tumor factor in animal models [58;59]. Through this mechanism, miR-BHRF1-3 may help suppress immunosurveillance to EBV antigens [48]. MiR-BHRF1-3 is also

predicted to target the transcripts encoding the EBV immediate-early transactivators, Zta and Rta, and may therefore represent additional viral miRNAs that help enforce latency [53].

3.4. EBV-regulated cellular miRNAs

In addition to utilizing its own repertoire of miRNAs, EBV has tapped into existing cellular miRNA pathways to facilitate its complex life cycle. A number of studies have reported a correlation between EBV type III latency (which drives B-cell activation/proliferation) and expression of the oncogenic cellular miRNA, miR-155 [60;61], and we have shown that type III latency genes drive miR-155 expression [62]. We have also shown that the cellular miRNA, miR-146a, is similarly induced by EBV type III latency gene expression and that this occurs at least in part through the viral latent protein, LMP1 [63;64]. A number of other cellular miRNAs are also differentially expressed (although typically more moderately) in type I and type III latently infected cells including miR-15a, miR-21, miR-28, miR-34a, members of the miR-23a cluster [miR-23a, miR-24, and miR-27a], and miR-146b [64]. Similarly, Mrazek and colleagues [65] showed that EBV regulates miR-155 and miR-146a as well as other cellular miRNAs. Below, we will focus on a number of EBV-regulated cellular miRNAs, particularly those showing larger magnitudes of induction by EBV.

3.4.1. MiR-155—MiR-155 is encoded within the *BIC* (B cell integration cluster) gene which was originally identified as a frequent integration site in avian leukosis virus induced-B cell lymphomas [66;67;68]. Although *BIC* transcripts were shown many years ago to play a critical role in lymphomagenesis [66;67;68], the mechanism through which the *BIC* gene elicited a tumor phenotype remained a mystery since there were no discernable open reading frames encoded by these transcripts. In 2005, Eis et al. [69] demonstrated that *BIC* transcripts were processed into the functional miRNA, miR-155. Since this time, elevated miR-155 expression has been shown to correlate with an array of different tumor types and is now considered one of the most highly implicated miRNAs in cancer.

3.4.1.1. Regulation of miR-155 expression by EBV: Cellular miR-155 appears to be regulated by multiple signaling pathways. For instance, miR-155 can be transcriptionally induced by B-cell receptor (BCR) activation through an AP-1 element located near the transcription start site of its promoter region [70]. As mentioned above, EBV type III latency genes facilitate high level miR-155 expression [62], but the mechanism through which this occurs is still under investigation. Nevertheless, two studies implicated the viral latent protein, LMP1, as playing a role in the transcriptional up-regulation of miR-155 in B-cells through an NF- κ B mediated mechanism [71;72]. We similarly observed LMP1 mediated induction of miR-155 but at a comparatively low level. We proposed that other EBV latency gene(s) may provide unique and essential cooperative functions necessary to sustain the robust miR-155 expression observed in type III latency cells [62]. In line with this hypothesis, Lu et al. [72] demonstrated that the EBV latency protein, EBNA-2, can also induce *BIC*/miR-155 expression in B-cells.

3.4.1.2. MiR-155's function: MiR-155 is involved in immunological processes in normal tissues such as immunity, haematopoiesis, and inflammation. The dysregulation of miR-155 expression plays a role in the development of a number of diseases including cancers, viral infections, and cardiovascular diseases.

Accumulating studies have identified a wide array of miR-155 targets that may contribute to the modulation of cell proliferation, differentiation and apoptosis pathways. Our group reported that miR-155 can target the 3'UTRs of numerous transcription factor transcripts [62;73;74]. For example, we and others demonstrated that miR-155 directly targets the transcript encoding the transcriptional repressor, BACH1 [23;24;62], which binds to

consensus AP-1 promoter elements [75]. Considering the known activation of AP-1 by EBV latency proteins as well as the role of AP-1 in the activation of lymphocytes during immune responses, it is reasonable to believe that the suppression of AP-1 inhibitors such as *BACH1* may de-repress AP-1 promoter elements and increase their accessibility to activating AP-1 factors.

Through microarray studies and 3' UTR reporter studies, we also identified *DET1* as a miR-155 target [62]. Since *DET1* mediates ubiquitin dependent degradation of the AP-1 family member, c-Jun [76], the inhibition of *DET1* expression may further support increased AP-1 signaling through an increase in c-Jun levels.

In addition to *BACH1*, we also showed that miR-155 can target two other transcriptional repressor gene transcripts, *HIVEP2* and *ZNF652* [62]. Like *BACH1*, *ZNF652* and *HIVEP2* repress transcription through the direct binding to promoter/enhancer elements [77;78]. *HIVEP2* is downregulated in breast cancers [79] and, mechanistically, *HIVEP2* inhibits the expression of *MYC* through binding to an NF- κ B element in the *MYC* intron 1 regulatory element [78]. The suppression of *HIVEP2* may support cell survival and proliferation by increasing the expression of NF- κ B responsive promoters such as the promoter driving expression of the *MYC* gene. *ZNF652* binds DNA and recruits the ETO family member *CBFA2T3* [77]. *CBFA2T3* is a transcriptional repressor that functions as a putative breast tumor suppressor. By inference, the inhibition of *ZNF652* expression by miR-155 is expected to mitigate the impact of *CBFA2T3*'s inhibitory influences on *ZNF652* binding sites and contribute to tumor development.

As alluded to above, while EBV has evolved with mechanisms to facilitate high level expression of cellular miR-155, two other oncogenic herpesviruses, KSHV and MDV-1, have been found to encode their own miR-155 functional homologues. Although it has yet to be proven, the well established link between miR-155 and cancer leads to the obvious extension that the miR-155 functions of these viruses contribute to their respective oncogenic nature. In support of this contention, it is intriguing that the non-oncogenic strain of Marek's Disease virus, MDV-2, does not encode any miR-155 ortholog [80]. It seems that EBV, KSHV and MDV-1 all utilize miR-155 function to facilitate signaling cascades that presumably support their life style but which also may partly explain their oncogenic propensity. Notably, the utilization of miR-155 in the virus life cycle is not unique to herpesviruses, as the oncogenic retrovirus REV-T (reticuloendotheliosis virus strain T) has recently been shown to up-regulate miR-155 expression in both REV-T-infected chicken embryo fibroblasts and REV-T-induced B-cell lymphomas [81]. In this setting, miR-155 was found to play a critical pro-survival/anti-apoptotic role by targeting transcripts of the cell-cycle regulatory gene, *JARID2* [81].

Outside of a viral context, many studies have reported that miR-155 induces tumorigenesis through an interplay with multiple cancer-related pathways. For instance, miR-155/*BIC* cooperates with *MYC* to induce Burkitts lymphoma [82]. A recent report demonstrated that miR-155 is involved in tumor metastasis through the enhancement of TGF- β mediated Epithelial-Mesenchymal Transition (EMT) and cell migration [83]. MiR-155 may also be responsible for the dysregulation of certain ncRNA that are transcribed from ultraconserved regions (UCRs), a class of sequences that are commonly disrupted in cancers [22]. Lastly, miR-155 is implicated in facilitating tumorigenesis by modulation of the NF- κ B pathway and evasion of host innate immunity [72].

3.4.2. MiR-146—In humans, there are two miR-146 genes that are located on chromosomes 5q33 and 10q24 and encode miR-146a and miR-146b, respectively. MiR-146a and miR-146b are predicted to have similar target repertoires since they share a

high homology (with only a two-nucleotide difference in their 3' non-seed sequence). In response to various immune-mediators such as LPS, IL-1b, and TNFa, miR-146a expression can be transcriptionally activated through an NF-kB dependent mechanism [84]. The upregulation of miR-146a can be achieved by the EBV encoded LMP1 and this induction similarly occurs through NF-kB signaling [63;85].

3.4.2.1. Role of miR-146 in tumorigenesis: Previously, a number of studies have demonstrated the dysregulation of miR-146 expression in human cancers, such as thyroid carcinomas [86;87], cervical cancers [88], breast cancers [89], pancreatic cancers [89], and prostate cancers [89;90]. Nevertheless, the link between miR-146 and cancer is a little murky since there is both evidence that miR-146 promotes a cancer phenotype and there is evidence that miR-146 suppresses the tumor phenotype.

Like miR-155, there is evidence that miR-146 mediates cancer development by targeting key genes involved in proliferation, apoptosis, inflammation, and immunity. For example, over-expression of miR-146a in cervical cancer cell lines significantly enhances cell proliferation rate [88]. A recent study has demonstrated that miR-146a can prevent cytokine-induced apoptosis in human bronchial epithelial cells (HBECS), probably through a mechanism involving the upregulation of *BCL2L1* (Bcl-XL) and phosphorylation of STAT3 [91]. In addition, miR-146 is involved in modulating immune responses. MiR-146 targets transcripts encoding factors in the NF-kB signaling pathway, such as IRAK1 (IL-1 receptor associated kinase 1) and TRAF6 (TNF receptor associated factor 6). By extension, miR-146 may function as a negative feedback regulator to fine-tune the immune response [84]. It is also predicted that the dysregulated expression of miR-146a could lead to inhibition of the interferon response pathway in tumors, therefore helping to suppress host immune surveillance through interferon signaling. In the context of EBV infection, induction of miR-146a could result in the suppression of the interferon-mediated antiviral response, protecting the virus from host immunity and facilitating the development of EBV-associated tumors [63].

Evidence that miR-146a also functions as a tumor suppressor is derived from studies showing a down-regulation of miR-146a levels in androgen-independent prostate cancers [90]. The loss of miR-146a function may contribute to this transformation, probably due to the loss of miR-146a mediated suppression of ROCK1, a key factor promoting the androgen-dependent to androgen-independent transformation of prostate cancer [90].

Constitutively active NF-kB signaling is often utilized by tumor cells to promote proliferation, survival, and metastasis. Studies in human breast cancer cell lines have shown that miR-146a/b acts as a negative regulator of NF-kB activity to inhibit tumor cell invasion and migration [92]. Breast cancer metastasis suppressor 1 (*BRMS1*) plays an important role in the suppression of metastasis in multiple human cancer cells. *BRMS1* significantly induces miR-146a and miR-146b levels which, in turn, downregulate the expression of epidermal growth factor receptors and inhibit invasion and migration of tumor cells [93].

A recent study demonstrated that a single nucleotide polymorphism (SNP rs2910164) in the pre-miR-146a shows a close association with papillary thyroid cancer [86]. This common G/C polymorphism is located at position +60 of pre-miR-146a and somatic mutations to a C are commonly found in papillary thyroid tumors. Functionally, this mutation affects the processing of miR-146a and leads to an impact on the overall level of mature miR-146a (the G allele generally gives rise to a higher level of mature miRNAs than the C allele). The reduction in mature miR-146a in papillary thyroid cancers due to G → C mutation leads to a weaker inhibition of target genes involved in the NF-kB signaling pathway (e.g. *TRAF6* and *IRAK1*), and *CCDC6* (a gene frequently rearranged with *RET* proto-oncogene in papillary

thyroid cancer). In these settings it appears that miR-146a suppresses tumorigenesis. This suppression is alleviated by the G → C transversion, mitigating the miR-146a mediated negative feedback regulation of the NF-κB signaling pathway [86;94].

3.4.3. Other EBV-regulated cellular miRNAs—Besides miR-155 and miR-146, miR-127 is induced by EBV infection [95;96] and miR-21, -23a, -24, -27a, and -34a are expressed at higher levels, whereas miR-28 is expressed at lower levels in EBV-infected type III latency cells compared to EBV-infected type I latency cells [64]. Some of these miRNAs may similarly contribute to the tumorigenic phenotype of EBV-infected cells.

Leucci and colleagues found that miR-127 expression remains high in EBV-positive Burkitt's lymphoma cells, but not in EBV-negative BL cells [96]. The induction of miR-127 may inhibit B-cell differentiation and promote lymphomagenesis by targeting *BLIMP1* and *XBPI* transcripts, the protein products of which are considered to be the master regulators of plasma cell differentiation [96]. The induction of miR-21 by EBV latency III infection has significant implications for both the EBV life-cycle and EBV-mediated tumorigenesis. As an oncomir, elevated expression of miR-21 has been demonstrated in a number of malignancies including metastatic breast cancers, colorectal cancers, hepatocellular cancers, cervical cancers, pancreatic cancers, and glioblastoma [89;97;98;99;100;101]. In vitro, over-expression of miR-21 promotes cell proliferation, migration and invasion, and inhibition of miR-21 suppresses cell growth, migration, and invasion, and increases apoptosis [97;98;99;102]. Several studies have demonstrated that miR-21 down-regulates expression of the tumor suppressor genes, programmed cell death 4 (*PDCD4*) and tropomyosin 1 (*TPM1*) [97;99;103]. It is possible that in the setting of EBV-infected B lymphocytes, miR-21 may similarly inhibit *PDCD4* and/or *TPM1* expression.

Recently, Shinozaki and colleagues have reported that EBV infection results in the down-regulation of miR-200 family members [104]. We and others have shown that the miR-200 family of miRNAs can trigger the EBV lytic switch, causing the transition from latency to the lytic cycle [105;106]. The suppression of miR-200 family members by EBV may facilitate the maintenance of EBV latency thereby supporting establishment and/or maintenance of the tumor phenotype.

4. KSHV

Kaposi's sarcoma-associated herpesvirus (KSHV) is the causative agent of Kaposi's sarcoma (KS) and is associated with the pathogenesis of primary effusion lymphoma (PEL) and multicentric Castleman's disease [107;108;109]. Like EBV, KSHV encodes its own miRNAs. To date, at least 24 mature miRNAs have been identified in KSHV [110;111;112;113]. All of these miRNAs are located in a single cluster within the viral latency-associated region of the KSHV genome. KSHV miRNAs can be readily detected in latently infected B-cell lines (e.g. primary effusion lymphoma cell lines BC-1, BC-3, and BCBL1) [110;111;112;113] and have been detected in biopsy samples from patients with KS and multicentric Castleman's disease [114].

Accumulating studies have shown that KSHV miRNAs regulate a number of cellular genes whose inhibition may contribute to tumorigenesis. Through microarray studies, Samols et al. [115] found that ectopic expression of a portion of the KSHV miRNA cluster results in the down-regulation of 65 cellular genes. Among them, thrombospondin 1 (*THBS1*) shows a significant decrease at both the mRNA and protein levels. A 3'-UTR reporter assay demonstrated that *THBS1* is directly targeted by multiple KSHV miRNAs including miR-K12-1, miR-K12-3-3p, miR-K12-6-3p, and miR-K12-11. This observation fits nicely into

previous studies showing that THBS1 is a strong tumor suppressor, an anti-angiogenic factor, and an immune-modulator that is commonly decreased in KS lesions [116].

Recently, Qin and colleagues [117] have shown that miR-K12-3 and miR-K12-7 selectively activate the transcription and secretion of IL6 and IL10 by macrophages and myelomonocytic cells. They further showed that the induction of *IL6* and *IL10* expression was achieved, at least partially, through down-regulating a dominant-negative isoform of the transcription factor, C/EBPB (referred to as LIP). IL6 and IL10 are known to play an active role in the pathogenesis of KSHV-associated malignancies by promoting tumor cell growth, angiogenesis, and by suppressing T-cell activation.

As discussed above, KSHV miR-K12-11 shares the same seed sequence as the cellular oncomir, miR-155 [23;24]. Further, the enforced expression of miR-K12-11 or miR-155 causes the down-regulation of a common group of targets indicating that miR-K12-11 is, in fact, a functional ortholog of miR-155 [23;24]. It is likely that miR-K12-11 provides many of the same needs for the KSHV life cycle as miR-155 does for EBV. Nevertheless, there may be unique aspects of the respective viral life cycles that partly explain the different mechanisms used by these two viruses to achieve a miR-155/miR-K12-11-like function. Although miR-155 has been found to be dysregulated in a variety of tumor types, its normal expression appears to be preferentially targeted to immune cells. KSHV may benefit from having its own version of miR-155 to more easily enforce a miR-155-like function in settings, such as in endothelial cells, in which the expression of cellular miR-155 may be more difficult to accomplish through normal signal transduction pathways.

Other KSHV encoded miRNAs have also been shown to target cellular pathways that may promote oncogenesis. The cyclin-dependent kinase inhibitor *CDKN1A* (p21) was recently shown to be a direct target of miR-K12-1 [118] indicating that the KSHV miRNAs can inhibit core components of the cell cycle regulatory machinery. Stable inhibition of miR-K12-1 in virally infected B-cells was found to cause de-repression of *CDKN1A* and increased cell cycle arrest after p53 (encoded by *TP53*) activation [118].

KSHV miRNAs appear to also play a direct role in preventing apoptosis through the targeting of apoptosis regulators. Ziegelbauer et al. showed that multiple KSHV encoded miRNAs (miR-K12-5, -9, -10a, and -10b) inhibit the expression of *BCLAF1*, a gene encoding a Bcl2-associated factor that promotes apoptosis [119]. The targeting of *BCLAF1* by multiple miRNAs may be a strategy to enforce a more robust inhibition to better ensure host survival and/or reduce host susceptibility to apoptosis [119]. KSHV miR-K12-7 has been shown to inhibit expression of the stress-induced immune regulatory gene, *MICB*, thereby preventing NK cell mediated cell killing during KSHV infection [55].

Like EBV, the ability to establish a primarily latent infection is critical for KSHV tumor pathologies. Recently, Bellare and colleagues have reported that KSHV miR-K12-9* directly targets the lytic immediate early transcription factor, RTA (ORF50), and prevents viral reactivation [120]. In another study, Lu et al. [121] found that a mutant KSHV with deleted viral miRNAs displayed higher lytic activity and that RTA is targeted by miR-K12-5 (either directly or indirectly). Another viral miRNA, miR-K12-4-5p, was shown to enhance DNA methyltransferase activity and overall CpG methylation by inhibiting expression of the cellular repressor protein, RB12 [121]. The maintenance of DNA methylation within certain regions of the viral genome, such as the RTA promoter, is believed to help stabilize viral latency [121]. Through yet another mechanism, KSHV miR-K12-1 was found to promote viral latency by activating the NF- κ B pathway, in part, through targeting the mRNA of the NF- κ B inhibitor *NFKBIA* (IkBa) [122]. Together, these studies illustrate that like EBV,

KSHV-encoded miRNAs support the maintenance of latency through a variety of mechanisms.

KSHV has now been shown to regulate a number of cellular miRNAs that may specifically play roles in its life cycle. Punj et al. showed that the KSHV viral protein K13 induces miR-146a which suppresses expression of the chemokine receptor gene, *CXCR4* [123]. *CXCR4* is normally expressed at high levels on immature endothelial cells in bone marrow where it plays a key role in holding these progenitor cells for their further maturation. Thus, the downregulation of *CXCR4* by miR-146a may facilitate the premature release of these KSHV-infected endothelial progenitors into the circulation, possibly contributing to the subsequent development of Kaposi's sarcoma from these immature cells.

The KSHV latent protein K15M has been reported to up-regulate miR-21 and miR-31 expression. In turn, miR-21 and miR-31 are believed to regulate key factors involved in cell migration and contribute to K15M induced cell motility and invasion [124].

5. HPV

High-risk human papillomaviruses (such as HPV-16 and HPV-18) are the causative agents of human cervical, penile, and anal cancers. Although no HPV-encoded miRNA has been identified to date, HPV has been found to regulate cellular miRNAs that appear to modulate cellular signal transduction pathways in a way that facilitates a more optimal environment for viral replication. First, the HPV E7 oncoprotein suppresses the cellular miRNA, miR-203, which is normally expressed in differentiating epithelial cells [125]. MiR-203 targets the *TP53* family member, *TP63* [126;127], which unlike *TP53*, appears to promote cellular proliferation. The HPV mediated down-regulation of miR-203 and the resulting up-regulation of *TP63* protein is believed to facilitate more robust viral genome replication by forcing differentiating cells into S phase where nucleotide pools and DNA replication associated factors are elevated [125].

Wang and colleagues [128] have reported that the tumor suppressor miRNA, miR-34a, is down-regulated in both clinical cervical cancer samples and cervical cancer derived cell lines. The down-regulation of miR-34a here is likely the result of HPV infection since the high-risk HPV E6 oncoprotein was shown to inhibit miR-34a expression [128]. The inhibition of miR-34a by E6 occurs indirectly through destabilizing the cellular *TP53* protein which otherwise binds and activates the miR-34a promoter [128]. Evidence that inhibition of miR-34a is important for HPV-associated cancers has been inferred from experiments showing that overexpression of miR-34a in HPV-infected cells induces cell growth arrest and apoptosis [128].

Lastly, Martinez et al. [129] have shown that E6 (from HPV-16) can also inhibit the cellular miRNA, miR-218. In these studies, miR-218 was found to inhibit expression of the cellular gene, *LAMB3*, which was previously shown to enhance cell migration, tumorigenesis, and viral infection. An HPV mediated downregulation of miR-218 and the subsequent up-regulation of *LAMB3* is therefore expected to promote viral infection as well as HPV's tumor promoting functions [129].

6. HCV

Hepatitis C virus (HCV) is a hepatotropic positive-stranded RNA virus that belongs to the Flaviviridae family. Patients with HCV infection usually end up with chronic active viral infection which, in turn, leads to cirrhosis and hepatocellular carcinoma. Cellular miRNAs have been shown to mediate critical interactions between HCV and host cells. Among these miRNAs, miR-122 is probably one of the most highly studied. MiR-122 is expressed at high

levels in liver tissues and is considered to be principally a liver-specific miRNA. Interestingly, miR-122 is thought to play a critical role in HCV's life-cycle as a positive regulator of HCV replication. Although the underlying mechanism is unclear, miR-122 has been shown to bind to the 5'-UTR of the HCV RNA genome and increase HCV RNA abundance as well as the production of infectious viral particles [130;131;132;133]. Clinically, the strong influence of miR-122 on HCV replication makes miR-122 an attractive potential pharmaceutical target for HCV treatment and it has recently been reported that therapeutic silencing of miR-122 (using an anti-miR-122 locked nucleic acid inhibitor) indeed showed promising results in the treatment of HCV infection in animals [134].

7. HBV

Hepatitis B virus (HBV) is a DNA virus that is closely associated with the development of hepatocellular carcinoma. Although virally encoded miRNAs have not been identified for HBV, a number of cellular miRNAs have been reported to be involved in HBV-associated malignancies. The expression of miR-602 was found to be elevated in HBV-infected liver and in hepatocellular carcinoma, and miR-602 may contribute to the HBV-mediated tumorigenesis through targeting of the tumor suppressor gene, *RASSF1A* [135]. Recently, Zhang et al. showed that miR-143 was dramatically increased in HBV related hepatocellular carcinoma samples. Although miR-143 is generally considered to be a tumor suppressor, these investigators suggested that the up-regulation of miR-143 may contribute to tumor metastasis by inhibiting the expression of the fibronectin type 3 domain containing 3B (*FNDC3B*) gene, whose protein product is a regulator of cell motility [136].

8. Concluding remarks

Despite their extremely small size, miRNAs have profound influences on cell signaling pathways. It is no wonder that viruses, the kings of efficiency in the biological world, would evolve to include miRNAs in their arsenal of regulators to achieve the various and sundry tasks necessary to facilitate their respective life cycles. As a field, we now have a pretty good cataloging of miRNA repertoires encoded by most of the more commonly studied viruses, although there will certainly be further additions in the years to come. We also have at least some appreciation for some of the functions of these virus-encoded miRNAs. Nevertheless, given that only a handful of viral miRNAs have been studied functionally, and considering that miRNAs often regulate hundreds of genes, we haven't yet scratched the surface in our understanding of the biological functions of these miRNAs. Progress in this area will be ramped up substantially in the near future, however, with the advent of new technologies to globally assess miRNA targeting, such as cross linking-argonaute/RNA immuno-precipitation methods [137], and miRNA induced transcriptome [74] and proteome changes [138]. These data sets will lay the foundation to get at the biological roles of these miRNAs so that we can better understand the functions they play in virus and tumor biology. Along the way, we can anticipate unique clinical opportunities for the diagnosis, prognosis and treatment of virus associated cancers.

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References

1. Lee RC, Feinbaum RL, Ambros V. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell*. 1993; 75:843–854. [PubMed: 8252621]

2. Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T. Identification of novel genes coding for small expressed RNAs. *Science*. 2001; 294:853–858. [PubMed: 11679670]
3. Lau NC, Lim LP, Weinstein EG, Bartel DP. An abundant class of tiny RNAs with probable regulatory roles in *Caenorhabditis elegans*. *Science*. 2001; 294:858–862. [PubMed: 11679671]
4. Lee RC, Ambros V. An extensive class of small RNAs in *Caenorhabditis elegans*. *Science*. 2001; 294:862–864. [PubMed: 11679672]
5. Molnar A, Schwach F, Studholme DJ, Thuenemann EC, Baulcombe DC. miRNAs control gene expression in the single-cell alga *Chlamydomonas reinhardtii*. *Nature*. 2007; 447:1126–1129. [PubMed: 17538623]
6. Pfeffer S, Zavolan M, Grasser FA, Chien M, Russo JJ, Ju J, John B, Enright AJ, Marks D, Sander C, Tuschl T. Identification of virus-encoded microRNAs. *Science*. 2004; 304:734–736. [PubMed: 15118162]
7. Filipowicz W, Bhattacharyya SN, Sonenberg N. Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight? *Nat Rev Genet*. 2008; 9:102–114. [PubMed: 18197166]
8. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell*. 2004; 116:281–297. [PubMed: 14744438]
9. Nakahara K, Carthew RW. Expanding roles for miRNAs and siRNAs in cell regulation. *Curr Opin Cell Biol*. 2004; 16:127–133. [PubMed: 15196554]
10. Esquela-Kerscher A, Slack FJ. Oncomirs - microRNAs with a role in cancer. *Nat Rev Cancer*. 2006; 6:259–269. [PubMed: 16557279]
11. Iorio MV, Ferracin M, Liu CG, Veronese A, Spizzo R, Sabbioni S, Magri E, Pedriali M, Fabbri M, Campiglio M, Menard S, Palazzo JP, Rosenberg A, Musiani P, Volinia S, Nenci I, Calin GA, Querzoli P, Negrini M, Croce CM. MicroRNA gene expression deregulation in human breast cancer. *Cancer Res*. 2005; 65:7065–7070. [PubMed: 16103053]
12. Iorio MV, Visone R, Di Leva G, Donati V, Petrocca F, Casalini P, Taccioli C, Volinia S, Liu CG, Alder H, Calin GA, Menard S, Croce CM. MicroRNA signatures in human ovarian cancer. *Cancer Res*. 2007; 67:8699–8707. [PubMed: 17875710]
13. Lee JW, Choi CH, Choi JJ, Park YA, Kim SJ, Hwang SY, Kim WY, Kim TJ, Lee JH, Kim BG, Bae DS. Altered MicroRNA expression in cervical carcinomas. *Clin Cancer Res*. 2008; 14:2535–2542. [PubMed: 18451214]
14. Tong AW, Fulgham P, Jay C, Chen P, Khalil I, Liu S, Senzer N, Eklund AC, Han J, Nemunaitis J. MicroRNA profile analysis of human prostate cancers. *Cancer Gene Ther*. 2009; 16:206–216. [PubMed: 18949015]
15. Motoyama K, Inoue H, Takatsuno Y, Tanaka F, Mimori K, Uetake H, Sugihara K, Mori M. Over- and under-expressed microRNAs in human colorectal cancer. *Int J Oncol*. 2009; 34:1069–1075. [PubMed: 19287964]
16. Katada T, Ishiguro H, Kuwabara Y, Kimura M, Mitui A, Mori Y, Ogawa R, Harata K, Fujii Y. microRNA expression profile in undifferentiated gastric cancer. *Int J Oncol*. 2009; 34:537–542. [PubMed: 19148490]
17. Chen HC, Chen GH, Chen YH, Liao WL, Liu CY, Chang KP, Chang YS, Chen SJ. MicroRNA deregulation and pathway alterations in nasopharyngeal carcinoma. *Br J Cancer*. 2009; 100:1002–1011. [PubMed: 19293812]
18. Ortholan C, Puissegur MP, Ilie M, Barbry P, Mari B, Hofman P. MicroRNAs and lung cancer: new oncogenes and tumor suppressors, new prognostic factors and potential therapeutic targets. *Curr Med Chem*. 2009; 16:1047–1061. [PubMed: 19275611]
19. Petillo D, Kort EJ, Anema J, Furge KA, Yang XJ, Teh BT. MicroRNA profiling of human kidney cancer subtypes. *Int J Oncol*. 2009; 35:109–114. [PubMed: 19513557]
20. Zhao H, Wang D, Du W, Gu D, Yang R. MicroRNA and leukemia: Tiny molecule, great function. *Crit Rev Oncol Hematol*. 2009
21. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, Shimizu M, Rattan S, Bullrich F, Negrini M, Croce CM. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. *Proc Natl Acad Sci U S A*. 2004; 101:2999–3004. [PubMed: 14973191]

22. Calin GA, Liu CG, Ferracin M, Hyslop T, Spizzo R, Sevignani C, Fabbri M, Cimmino A, Lee EJ, Wojcik SE, Shimizu M, Tili E, Rossi S, Taccioli C, Pichiorri F, Liu X, Zupo S, Herlea V, Gramantieri L, Lanza G, Alder H, Rassenti L, Volinia S, Schmittgen TD, Kipps TJ, Negrini M, Croce CM. Ultraconserved regions encoding ncRNAs are altered in human leukemias and carcinomas. *Cancer Cell*. 2007; 12:215–229. [PubMed: 17785203]
23. Skalsky RL, Samols MA, Plaisance KB, Boss IW, Riva A, Lopez MC, Baker HV, Renne R. Kaposi's sarcoma-associated herpesvirus encodes an ortholog of miR-155. *J Virol*. 2007; 81:12836–12845. [PubMed: 17881434]
24. Gottwein E, Mukherjee N, Sachse C, Frenzel C, Majoros WH, Chi JT, Braich R, Manoharan M, Soutschek J, Ohler U, Cullen BR. A viral microRNA functions as an orthologue of cellular miR-155. *Nature*. 2007; 450:1096–1099. [PubMed: 18075594]
25. Zhao Y, Yao Y, Xu H, Lambeth L, Smith LP, Kgosana L, Wang X, Nair V. A functional MicroRNA-155 ortholog encoded by the oncogenic Marek's disease virus. *J Virol*. 2009; 83:489–492. [PubMed: 18945769]
26. Young LS, Rickinson AB. Epstein-Barr virus: 40 years on. *Nat Rev Cancer*. 2004; 4:757–768. [PubMed: 15510157]
27. Rickinson, AB.; Kieff, E. Epstein-Barr virus. In: Knipe, DM.; Howley, PM., editors. *Fields Virology*. 5th. Lippincott Williams & Wilkins; Philadelphia, PA: 2007. p. 2655-2700.
28. Tierney RJ, Steven N, Young LS, Rickinson AB. Epstein-Barr virus latency in blood mononuclear cells: analysis of viral gene transcription during primary infection and in the carrier state. *J Virol*. 1994; 68:7374–7385. [PubMed: 7933121]
29. Cullen BR. Viruses and microRNAs. *Nat Genet*. 2006; 38(Suppl):S25–30. [PubMed: 16736021]
30. Hitt MM, Allday MJ, Hara T, Karran L, Jones MD, Busson P, Tursz T, Ernberg I, Griffin BE. EBV gene expression in an NPC-related tumour. *EMBO J*. 1989; 8:2639–2651. [PubMed: 2479554]
31. Sugiura M, Imai S, Tokunaga M, Koizumi S, Uchizawa M, Okamoto K, Osato T. Transcriptional analysis of Epstein-Barr virus gene expression in EBV-positive gastric carcinoma: unique viral latency in the tumour cells. *Br J Cancer*. 1996; 74:625–631. [PubMed: 8761381]
32. Webster-Cyriaque J, Raab-Traub N. Transcription of Epstein-Barr virus latent cycle genes in oral hairy leukoplakia. *Virology*. 1998; 248:53–65. [PubMed: 9705255]
33. Tao Q, Robertson KD, Manns A, Hildesheim A, Ambinder RF. Epstein-Barr virus (EBV) in endemic Burkitt's lymphoma: molecular analysis of primary tumor tissue. *Blood*. 1998; 91:1373–1381. [PubMed: 9454768]
34. Deacon EM, Pallesen G, Niedobitek G, Crocker J, Brooks L, Rickinson AB, Young LS. Epstein-Barr virus and Hodgkin's disease: transcriptional analysis of virus latency in the malignant cells. *J Exp Med*. 1993; 177:339–349. [PubMed: 8381153]
35. Chiang AK, Tao Q, Srivastava G, Ho FC. Nasal NK- and T-cell lymphomas share the same type of Epstein-Barr virus latency as nasopharyngeal carcinoma and Hodgkin's disease. *Int J Cancer*. 1996; 68:285–290. [PubMed: 8903467]
36. Raab-Traub N, Dambaugh T, Kieff E. DNA of Epstein-Barr virus VIII: B95-8, the previous prototype, is an unusual deletion derivative. *Cell*. 1980; 22:257–267. [PubMed: 6253079]
37. Smith PR, de Jesus O, Turner D, Hollyoake M, Karstegl CE, Griffin BE, Karran L, Wang Y, Hayward SD, Farrell PJ. Structure and coding content of CST (BART) family RNAs of Epstein-Barr virus. *J Virol*. 2000; 74:3082–3092. [PubMed: 10708423]
38. Zhang J, Chen H, Weinmaster G, Hayward SD. Epstein-Barr virus BamHi-a rightward transcript-encoded RPMS protein interacts with the CBF1-associated corepressor CIR to negatively regulate the activity of EBNA2 and NotchIC. *J Virol*. 2001; 75:2946–2956. [PubMed: 11222720]
39. Al-Mozaini M, Bodelon G, Karstegl CE, Jin B, Al-Ahdal M, Farrell PJ. Epstein-Barr virus BART gene expression. *J Gen Virol*. 2009; 90:307–316. [PubMed: 19141439]
40. Edwards RH, Marquitz AR, Raab-Traub N. Epstein-Barr virus BART microRNAs are produced from a large intron prior to splicing. *J Virol*. 2008; 82:9094–9106. [PubMed: 18614630]
41. Cai X, Schafer A, Lu S, Bilello JP, Desrosiers RC, Edwards R, Raab-Traub N, Cullen BR. Epstein-Barr virus microRNAs are evolutionarily conserved and differentially expressed. *PLoS Pathog*. 2006; 2:e23. [PubMed: 16557291]

42. Walz N, Christalla T, Tessmer U, Grundhoff A. A global analysis of evolutionary conservation among known and predicted gammaherpesvirus microRNAs. *J Virol.* 2010; 84:716–728. [PubMed: 19889779]
43. Riley KJ, Rabinowitz GS, Steitz JA. Comprehensive analysis of Rhesus lymphocryptovirus microRNA expression. *J Virol.* 2010; 84:5148–5157. [PubMed: 20219930]
44. Grundhoff A, Sullivan CS, Ganem D. A combined computational and microarray-based approach identifies novel microRNAs encoded by human gamma-herpesviruses. *RNA.* 2006; 12:733–750. [PubMed: 16540699]
45. Zhu JY, Pfuhl T, Motsch N, Barth S, Nicholls J, Grasser F, Meister G. Identification of novel Epstein-Barr virus microRNA genes from nasopharyngeal carcinomas. *J Virol.* 2009; 83:3333–3341. [PubMed: 19144710]
46. Cosmopoulos K, Pegtel M, Hawkins J, Moffett H, Novina C, Middeldorp J, Thorley-Lawson DA. Comprehensive profiling of Epstein-Barr virus microRNAs in nasopharyngeal carcinoma. *J Virol.* 2009; 83:2357–2367. [PubMed: 19091858]
47. Kim do N, Chae HS, Oh ST, Kang JH, Park CH, Park WS, Takada K, Lee JM, Lee WK, Lee SK. Expression of viral microRNAs in Epstein-Barr virus-associated gastric carcinoma. *J Virol.* 2007; 81:1033–1036. [PubMed: 17079300]
48. Xia T, O'Hara A, Araujo I, Barreto J, Carvalho E, Sapucaia JB, Ramos JC, Luz E, Pedroso C, Manrique M, Toomey NL, Brites C, Dittmer DP, Harrington WJ Jr. EBV microRNAs in primary lymphomas and targeting of CXCL-11 by ebv-mir-BHRF1-3. *Cancer Res.* 2008; 68:1436–1442. [PubMed: 18316607]
49. Pratt ZL, Kuzembayeva M, Sengupta S, Sugden B. The microRNAs of Epstein-Barr Virus are expressed at dramatically differing levels among cell lines. *Virology.* 2009; 386:387–397. [PubMed: 19217135]
50. Gottwein E, Cai X, Cullen BR. A novel assay for viral microRNA function identifies a single nucleotide polymorphism that affects Drosha processing. *J Virol.* 2006; 80:5321–5326. [PubMed: 16699012]
51. Choy EY, Siu KL, Kok KH, Lung RW, Tsang CM, To KF, Kwong DL, Tsao SW, Jin DY. An Epstein-Barr virus-encoded microRNA targets PUMA to promote host cell survival. *J Exp Med.* 2008; 205:2551–2560. [PubMed: 18838543]
52. Murakami Y, Yasuda T, Saigo K, Urashima T, Toyoda H, Okanoue T, Shimotohno K. Comprehensive analysis of microRNA expression patterns in hepatocellular carcinoma and non-tumorous tissues. *Oncogene.* 2006; 25:2537–2545. [PubMed: 16331254]
53. Murphy E, Vanicek J, Robins H, Shenk T, Levine AJ. Suppression of immediate-early viral gene expression by herpesvirus-coded microRNAs: implications for latency. *Proc Natl Acad Sci U S A.* 2008; 105:5453–5458. [PubMed: 18378902]
54. Barth S, Pfuhl T, Mamiani A, Ehses C, Roemer K, Kremmer E, Jaker C, Hock J, Meister G, Grasser FA. Epstein-Barr virus-encoded microRNA miR-BART2 down-regulates the viral DNA polymerase BALF5. *Nucleic Acids Res.* 2008; 36:666–675. [PubMed: 18073197]
55. Nachmani D, Stern-Ginossar N, Sarid R, Mandelboim O. Diverse herpesvirus microRNAs target the stress-induced immune ligand MICB to escape recognition by natural killer cells. *Cell Host Microbe.* 2009; 5:376–385. [PubMed: 19380116]
56. Lo AK, To KF, Lo KW, Lung RW, Hui JW, Liao G, Hayward SD. Modulation of LMP1 protein expression by EBV-encoded microRNAs. *Proc Natl Acad Sci U S A.* 2007; 104:16164–16169. [PubMed: 17911266]
57. Lung RW, Tong JH, Sung YM, Leung PS, Ng DC, Chau SL, Chan AW, Ng EK, Lo KW, To KF. Modulation of LMP2A expression by a newly identified Epstein-Barr virus-encoded microRNA miR-BART22. *Neoplasia.* 2009; 11:1174–1184. [PubMed: 19881953]
58. Hensbergen PJ, Wijnands PG, Schreurs MW, Scheper RJ, Willemze R, Tensen CP. The CXCR3 targeting chemokine CXCL11 has potent antitumor activity in vivo involving attraction of CD8+ T lymphocytes but not inhibition of angiogenesis. *J Immunother.* 2005; 28:343–351. [PubMed: 16000952]

59. Yang X, Chu Y, Wang Y, Guo Q, Xiong S. Vaccination with IFN-inducible T cell alpha chemoattractant (ITAC) gene-modified tumor cell attenuates disseminated metastases of circulating tumor cells. *Vaccine*. 2006; 24:2966–2974. [PubMed: 16503368]
60. Jiang J, Lee EJ, Schmittgen TD. Increased expression of microRNA-155 in Epstein-Barr virus transformed lymphoblastoid cell lines. *Genes Chromosomes Cancer*. 2006; 45:103–106. [PubMed: 16175574]
61. Kluiver J, Haralambieva E, de Jong D, Blokzijl T, Jacobs S, Kroesen BJ, Poppema S, van den Berg A. Lack of BIC and microRNA miR-155 expression in primary cases of Burkitt lymphoma. *Genes Chromosomes Cancer*. 2006; 45:147–153. [PubMed: 16235244]
62. Yin Q, McBride J, Fewell C, Lacey M, Wang X, Lin Z, Cameron J, Flemington EK. MicroRNA-155 is an Epstein-Barr virus-induced gene that modulates Epstein-Barr virus-regulated gene expression pathways. *J Virol*. 2008; 82:5295–5306. [PubMed: 18367535]
63. Cameron JE, Yin Q, Fewell C, Lacey M, McBride J, Wang X, Lin Z, Schaefer BC, Flemington EK. Epstein-Barr virus latent membrane protein 1 induces cellular MicroRNA miR-146a, a modulator of lymphocyte signaling pathways. *J Virol*. 2008; 82:1946–1958. [PubMed: 18057241]
64. Cameron JE, Fewell C, Yin Q, McBride J, Wang X, Lin Z, Flemington EK. Epstein-Barr virus growth/latency III program alters cellular microRNA expression. *Virology*. 2008; 382:257–266. [PubMed: 18950829]
65. Mrazek J, Kreutmayer SB, Grasser FA, Polacek N, Huttenhofer A. Subtractive hybridization identifies novel differentially expressed ncRNA species in EBV-infected human B cells. *Nucleic Acids Res*. 2007; 35:e73. [PubMed: 17478510]
66. Clurman BE, Hayward WS. Multiple proto-oncogene activations in avian leukosis virus-induced lymphomas: evidence for stage-specific events. *Mol Cell Biol*. 1989; 9:2657–2664. [PubMed: 2548084]
67. Tam W, Ben-Yehuda D, Hayward WS. bic, a novel gene activated by proviral insertions in avian leukosis virus-induced lymphomas, is likely to function through its noncoding RNA. *Mol Cell Biol*. 1997; 17:1490–1502. [PubMed: 9032277]
68. Tam W. Identification and characterization of human BIC, a gene on chromosome 21 that encodes a noncoding RNA. *Gene*. 2001; 274:157–167. [PubMed: 11675008]
69. Eis PS, Tam W, Sun L, Chadburn A, Li Z, Gomez MF, Lund E, Dahlberg JE. Accumulation of miR-155 and BIC RNA in human B cell lymphomas. *Proc Natl Acad Sci U S A*. 2005; 102:3627–3632. [PubMed: 15738415]
70. Yin Q, Wang X, McBride J, Fewell C, Flemington E. B-cell receptor activation induces BIC/miR-155 expression through a conserved AP-1 element. *J Biol Chem*. 2008; 283:2654–2662. [PubMed: 18048365]
71. Gatto G, Rossi A, Rossi D, Kroening S, Bonatti S, Mallardo M. Epstein-Barr virus latent membrane protein 1 trans-activates miR-155 transcription through the NF-kappaB pathway. *Nucleic Acids Res*. 2008; 36:6608–6619. [PubMed: 18940871]
72. Lu F, Weidmer A, Liu CG, Volinia S, Croce CM, Lieberman PM. Epstein-Barr virus-induced miR-155 attenuates NF-kappaB signaling and stabilizes latent virus persistence. *J Virol*. 2008; 82:10436–10443. [PubMed: 18753206]
73. Yin Q, Wang X, Fewell C, Cameron J, Zhu H, Baddoo M, Lin Z, Flemington EK. MiR-155 inhibits Bone Morphogenetic Protein (BMP) signaling and BMP mediated Epstein Barr virus reactivation. *J Virol*. 2010
74. Xu G, Fewell C, Taylor C, Deng N, Hedges D, Wang X, Zhang K, Lacey M, Zhang H, Yin Q, Cameron J, Lin Z, Zhu D, Flemington EK. Transcriptome and targetome analysis in MIR155 expressing cells using RNA-seq. *RNA*. 2010
75. Kanezaki R, Toki T, Yokoyama M, Yomogida K, Sugiyama K, Yamamoto M, Igarashi K, Ito E. Transcription factor BACH1 is recruited to the nucleus by its novel alternative spliced isoform. *J Biol Chem*. 2001; 276:7278–7284. [PubMed: 11069897]
76. Wertz IE, O'Rourke KM, Zhang Z, Dornan D, Arnott D, Deshaies RJ, Dixit VM. Human De-etioloated-1 regulates c-Jun by assembling a CUL4A ubiquitin ligase. *Science*. 2004; 303:1371–1374. [PubMed: 14739464]

77. Kumar R, Manning J, Spendlove HE, Kremmidiotis G, McKirdy R, Lee J, Millband DN, Cheney KM, Stampfer MR, Dwivedi PP, Morris HA, Callen DF. ZNF652, a novel zinc finger protein, interacts with the putative breast tumor suppressor CBFA2T3 to repress transcription. *Mol Cancer Res.* 2006; 4:655–665. [PubMed: 16966434]
78. Itkes A, Allegra CJ, Zajac-Kaye M. Multiprotein complexes present at the MIF motifs flanking the promoter of the human c-myc gene. *FEBS Lett.* 2000; 474:23–28. [PubMed: 10828444]
79. Fujii H, Gabrielson E, Takagaki T, Ohtsuji M, Ohtsuji N, Hino O. Frequent down-regulation of HIVEP2 in human breast cancer. *Breast Cancer Res Treat.* 2005; 91:103–112. [PubMed: 15868437]
80. Yao Y, Zhao Y, Xu H, Smith LP, Lawrie CH, Sewer A, Zavolan M, Nair V. Marek's disease virus type 2 (MDV-2)-encoded microRNAs show no sequence conservation with those encoded by MDV-1. *J Virol.* 2007; 81:7164–7170. [PubMed: 17459919]
81. Bolisetty MT, Dy G, Tam W, Beemon KL. Reticuloendotheliosis virus strain T induces miR-155 which targets JARID2 and promotes cell survival. *J Virol.* 2009
82. Tam W, Hughes SH, Hayward WS, Besmer P. Avian bic, a gene isolated from a common retroviral site in avian leukosis virus-induced lymphomas that encodes a noncoding RNA, cooperates with c-myc in lymphomagenesis and erythroleukemogenesis. *J Virol.* 2002; 76:4275–4286. [PubMed: 11932393]
83. Kong W, Yang H, He L, Zhao JJ, Coppola D, Dalton WS, Cheng JQ. MicroRNA-155 is regulated by the transforming growth factor beta/Smad pathway and contributes to epithelial cell plasticity by targeting RhoA. *Mol Cell Biol.* 2008; 28:6773–6784. [PubMed: 18794355]
84. Taganov KD, Boldin MP, Chang KJ, Baltimore D. NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. *Proc Natl Acad Sci U S A.* 2006; 103:12481–12486. [PubMed: 16885212]
85. Motsch N, Pfuhl T, Mrazek J, Barth S, Grasser FA. Epstein-Barr virus-encoded latent membrane protein 1 (LMP1) induces the expression of the cellular microRNA miR-146a. *RNA Biol.* 2007; 4:131–137. [PubMed: 18347435]
86. Jazdzewski K, Murray EL, Franssila K, Jarzab B, Schoenberg DR, de la Chapelle A. Common SNP in pre-miR-146a decreases mature miR expression and predisposes to papillary thyroid carcinoma. *Proc Natl Acad Sci U S A.* 2008; 105:7269–7274. [PubMed: 18474871]
87. He H, Jazdzewski K, Li W, Liyanarachchi S, Nagy R, Volinia S, Calin GA, Liu CG, Franssila K, Suster S, Kloos RT, Croce CM, de la Chapelle A. The role of microRNA genes in papillary thyroid carcinoma. *Proc Natl Acad Sci U S A.* 2005; 102:19075–19080. [PubMed: 16365291]
88. Wang X, Tang S, Le SY, Lu R, Rader JS, Meyers C, Zheng ZM. Aberrant expression of oncogenic and tumor-suppressive microRNAs in cervical cancer is required for cancer cell growth. *PLoS One.* 2008; 3:e2557. [PubMed: 18596939]
89. Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, Visone R, Iorio M, Roldo C, Ferracin M, Prueitt RL, Yanaihara N, Lanza G, Scarpa A, Vecchione A, Negrini M, Harris CC, Croce CM. A microRNA expression signature of human solid tumors defines cancer gene targets. *Proc Natl Acad Sci U S A.* 2006; 103:2257–2261. [PubMed: 16461460]
90. Lin SL, Chiang A, Chang D, Ying SY. Loss of mir-146a function in hormone-refractory prostate cancer. *RNA.* 2008; 14:417–424. [PubMed: 18174313]
91. Liu X, Nelson A, Wang X, Kanaji N, Kim M, Sato T, Nakanishi M, Li Y, Sun J, Michalski J, Patil A, Basma H, Rennard SI. MicroRNA-146a modulates human bronchial epithelial cell survival in response to the cytokine-induced apoptosis. *Biochem Biophys Res Commun.* 2009; 380:177–182. [PubMed: 19167348]
92. Bhaumik D, Scott GK, Schokrpur S, Patil CK, Campisi J, Benz CC. Expression of microRNA-146 suppresses NF-kappaB activity with reduction of metastatic potential in breast cancer cells. *Oncogene.* 2008
93. Hurst DR, Edmonds MD, Scott GK, Benz CC, Vaidya KS, Welch DR. Breast cancer metastasis suppressor 1 up-regulates miR-146, which suppresses breast cancer metastasis. *Cancer Res.* 2009; 69:1279–1283. [PubMed: 19190326]
94. Jazdzewski K, de la Chapelle A. Genomic sequence matters: a SNP in microRNA-146a can turn anti-apoptotic. *Cell Cycle.* 2009; 8:1642–1643. [PubMed: 19411858]

95. De Falco G, Antonicelli G, Onnis A, Lazzi S, Bellan C, Leoncini L. Role of EBV in microRNA dysregulation in Burkitt lymphoma. *Semin Cancer Biol.* 2009
96. Leucci E, Onnis A, Cocco M, De Falco G, Imperatore F, Antonicelli G, Costanzo V, Cerino G, Mannucci S, Cantisani R, Nyagol J, Mwanda W, Iriso R, Owang M, Schurfeld K, Bellan C, Lazzi S, Leoncini L. B cell differentiation in EBV-positive Burkitt Lymphoma is impaired at post-transcriptional level by miRNA altered expression. *Int J Cancer.* 2009
97. Asangani IA, Rasheed SA, Nikolova DA, Leupold JH, Colburn NH, Post S, Allgayer H. MicroRNA-21 (miR-21) post-transcriptionally downregulates tumor suppressor Pdc4 and stimulates invasion, intravasation and metastasis in colorectal cancer. *Oncogene.* 2008; 27:2128–2136. [PubMed: 17968323]
98. Chan JA, Krichevsky AM, Kosik KS. MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. *Cancer Res.* 2005; 65:6029–6033. [PubMed: 16024602]
99. Frankel LB, Christoffersen NR, Jacobsen A, Lindow M, Krogh A, Lund AH. Programmed cell death 4 (PDCD4) is an important functional target of the microRNA miR-21 in breast cancer cells. *J Biol Chem.* 2008; 283:1026–1033. [PubMed: 17991735]
100. Lui WO, Pourmand N, Patterson BK, Fire A. Patterns of known and novel small RNAs in human cervical cancer. *Cancer Res.* 2007; 67:6031–6043. [PubMed: 17616659]
101. Meng F, Henson R, Wehbe-Janek H, Ghoshal K, Jacob ST, Patel T. MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer. *Gastroenterology.* 2007; 133:647–658. [PubMed: 17681183]
102. Si ML, Zhu S, Wu H, Lu Z, Wu F, Mo YY. miR-21-mediated tumor growth. *Oncogene.* 2007; 26:2799–2803. [PubMed: 17072344]
103. Zhu S, Si ML, Wu H, Mo YY. MicroRNA-21 targets the tumor suppressor gene tropomyosin 1 (TPM1). *J Biol Chem.* 2007; 282:14328–14336. [PubMed: 17363372]
104. Shinozaki A, Sakatani T, Ushiku T, Hino R, Isogai M, Ishikawa S, Uozaki H, Takada K, Fukayama M. Downregulation of microRNA-200 in EBV-associated gastric carcinoma. *Cancer Res.* 2010; 70:4719–4727. [PubMed: 20484038]
105. Lin Z, Wang X, Fewell C, Cameron J, Yin Q, Flemington EK. Differential expression of the miR-200 family microRNAs in epithelial and B-cells and regulation of Epstein-Barr virus reactivation by the miR-200 family member, miR-429. *J Virol.* 2010
106. Ellis-Connell AL, Iempridee T, Xu I, Mertz JE. Cellular MicroRNAs 200b and 429 Regulate the Epstein-Barr Virus Switch Between Latency and Lytic Replication. *J Virol.* 2010
107. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, Moore PS. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science.* 1994; 266:1865–1869. [PubMed: 7997879]
108. Cesarman E, Nador RG, Aozasa K, Delsol G, Said JW, Knowles DM. Kaposi's sarcoma-associated herpesvirus in non-AIDS related lymphomas occurring in body cavities. *Am J Pathol.* 1996; 149:53–57. [PubMed: 8686762]
109. Soulier J, Grollet L, Oksenhendler E, Cacoub P, Cazals-Hatem D, Babinet P, d'Agay MF, Clauvel JP, Raphael M, Degos L, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castelman's disease. *Blood.* 1995; 86:1276–1280. [PubMed: 7632932]
110. Umbach JL, Cullen BR. In-depth analysis of Kaposi's sarcoma-associated herpesvirus microRNA expression provides insights into the mammalian microRNA-processing machinery. *J Virol.* 2010; 84:695–703. [PubMed: 19889781]
111. Cai X, Lu S, Zhang Z, Gonzalez CM, Damania B, Cullen BR. Kaposi's sarcoma-associated herpesvirus expresses an array of viral microRNAs in latently infected cells. *Proc Natl Acad Sci U S A.* 2005; 102:5570–5575. [PubMed: 15800047]
112. Pfeffer S, Sewer A, Lagos-Quintana M, Sheridan R, Sander C, Grasser FA, van Dyk LF, Ho CK, Shuman S, Chien M, Russo JJ, Ju J, Randall G, Lindenbach BD, Rice CM, Simon V, Ho DD, Zavolan M, Tuschl T. Identification of microRNAs of the herpesvirus family. *Nat Methods.* 2005; 2:269–276. [PubMed: 15782219]
113. Samols MA, Hu J, Skalsky RL, Renne R. Cloning and identification of a microRNA cluster within the latency-associated region of Kaposi's sarcoma-associated herpesvirus. *J Virol.* 2005; 79:9301–9305. [PubMed: 15994824]

114. Marshall V, Parks T, Bagni R, Wang CD, Samols MA, Hu J, Wyvil KM, Aleman K, Little RF, Yarchoan R, Renne R, Whitby D. Conservation of virally encoded microRNAs in Kaposi sarcoma--associated herpesvirus in primary effusion lymphoma cell lines and in patients with Kaposi sarcoma or multicentric Castlemann disease. *J Infect Dis.* 2007; 195:645–659. [PubMed: 17262705]
115. Samols MA, Skalsky RL, Maldonado AM, Riva A, Lopez MC, Baker HV, Renne R. Identification of cellular genes targeted by KSHV-encoded microRNAs. *PLoS Pathog.* 2007; 3:e65. [PubMed: 17500590]
116. Taraboletti G, Benelli R, Borsotti P, Rusnati M, Presta M, Giavazzi R, Ruco L, Albini A. Thrombospondin-1 inhibits Kaposi's sarcoma (KS) cell and HIV-1 Tat-induced angiogenesis and is poorly expressed in KS lesions. *J Pathol.* 1999; 188:76–81. [PubMed: 10398144]
117. Qin Z, Kearney P, Plaisance K, Parsons CH. Pivotal advance: Kaposi's sarcoma-associated herpesvirus (KSHV)-encoded microRNA specifically induce IL-6 and IL-10 secretion by macrophages and monocytes. *J Leukoc Biol.* 2010; 87:25–34. [PubMed: 20052801]
118. Gottwein E, Cullen BR. A human herpesvirus microRNA inhibits p21 expression and attenuates p21-mediated cell cycle arrest. *J Virol.* 2010; 84:5229–5237. [PubMed: 20219912]
119. Ziegelbauer JM, Sullivan CS, Ganem D. Tandem array-based expression screens identify host mRNA targets of virus-encoded microRNAs. *Nat Genet.* 2009; 41:130–134. [PubMed: 19098914]
120. Bellare P, Ganem D. Regulation of KSHV lytic switch protein expression by a virus-encoded microRNA: an evolutionary adaptation that fine-tunes lytic reactivation. *Cell Host Microbe.* 2009; 6:570–575. [PubMed: 20006845]
121. Lu F, Stedman W, Yousef M, Renne R, Lieberman PM. Epigenetic regulation of Kaposi's sarcoma-associated herpesvirus latency by virus-encoded microRNAs that target Rta and the cellular Rbl2-DNMT pathway. *J Virol.* 2010; 84:2697–2706. [PubMed: 20071580]
122. Lei X, Bai Z, Ye F, Xie J, Kim CG, Huang Y, Gao SJ. Regulation of NF-kappaB inhibitor IkappaBalpha and viral replication by a KSHV microRNA. *Nat Cell Biol.* 2010; 12:193–199. [PubMed: 20081837]
123. Punj V, Matta H, Schamus S, Tamewitz A, Anyang B, Chaudhary PM. Kaposi's sarcoma-associated herpesvirus-encoded viral FLICE inhibitory protein (vFLIP) K13 suppresses CXCR4 expression by upregulating miR-146a. *Oncogene.* 2010; 29:1835–1844. [PubMed: 20023696]
124. Tsai YH, Wu MF, Wu YH, Chang SJ, Lin SF, Sharp TV, Wang HW. The M type K15 protein of Kaposi's sarcoma-associated herpesvirus regulates microRNA expression via its SH2-binding motif to induce cell migration and invasion. *J Virol.* 2009; 83:622–632. [PubMed: 18971265]
125. Melar-New M, Laimins LA. Human papillomaviruses modulate expression of microRNA 203 upon epithelial differentiation to control levels of p63 proteins. *J Virol.* 2010; 84:5212–5221. [PubMed: 20219920]
126. Lena AM, Shalom-Feuerstein R, Rivetti di Val Cervo P, Aberdam D, Knight RA, Melino G, Candi E. miR-203 represses 'stemness' by repressing DeltaNp63. *Cell Death Differ.* 2008; 15:1187–1195. [PubMed: 18483491]
127. Yi R, Poy MN, Stoffel M, Fuchs E. A skin microRNA promotes differentiation by repressing 'stemness'. *Nature.* 2008; 452:225–229. [PubMed: 18311128]
128. Wang X, Wang HK, McCoy JP, Banerjee NS, Rader JS, Broker TR, Meyers C, Chow LT, Zheng ZM. Oncogenic HPV infection interrupts the expression of tumor-suppressive miR-34a through viral oncoprotein E6. *RNA.* 2009; 15:637–647. [PubMed: 19258450]
129. Martinez I, Gardiner AS, Board KF, Monzon FA, Edwards RP, Khan SA. Human papillomavirus type 16 reduces the expression of microRNA-218 in cervical carcinoma cells. *Oncogene.* 2008; 27:2575–2582. [PubMed: 17998940]
130. Jangra RK, Yi M, Lemon SM. miR-122 Regulation of Hepatitis C Virus Translation and Infectious Virus Production. *J Virol.* 2010
131. Henke JI, Goergen D, Zheng J, Song Y, Schuttler CG, Fehr C, Junemann C, Niepmann M. microRNA-122 stimulates translation of hepatitis C virus RNA. *EMBO J.* 2008; 27:3300–3310. [PubMed: 19020517]

132. Jopling CL, Yi M, Lancaster AM, Lemon SM, Sarnow P. Modulation of hepatitis C virus RNA abundance by a liver-specific MicroRNA. *Science*. 2005; 309:1577–1581. [PubMed: 16141076]
133. Randall G, Panis M, Cooper JD, Tellinghuisen TL, Sukhodolets KE, Pfeffer S, Landthaler M, Landgraf P, Kan S, Lindenbach BD, Chien M, Weir DB, Russo JJ, Ju J, Brownstein MJ, Sheridan R, Sander C, Zavolan M, Tuschl T, Rice CM. Cellular cofactors affecting hepatitis C virus infection and replication. *Proc Natl Acad Sci U S A*. 2007; 104:12884–12889. [PubMed: 17616579]
134. Lanford RE, Hildebrandt-Eriksen ES, Petri A, Persson R, Lindow M, Munk ME, Kauppinen S, Orum H. Therapeutic silencing of microRNA-122 in primates with chronic hepatitis C virus infection. *Science*. 2010; 327:198–201. [PubMed: 19965718]
135. Yang L, Ma Z, Wang D, Zhao W, Chen L, Wang G. MicroRNA-602 regulating tumor suppressive gene RASSF1A is overexpressed in hepatitis B virus-infected liver and hepatocellular carcinoma. *Cancer Biol Ther*. 2010; 9
136. Zhang X, Liu S, Hu T, He Y, Sun S. Up-regulated microRNA-143 transcribed by nuclear factor kappa B enhances hepatocarcinoma metastasis by repressing fibronectin expression. *Hepatology*. 2009; 50:490–499. [PubMed: 19472311]
137. Chi SW, Zang JB, Mele A, Darnell RB. Argonaute HITS-CLIP decodes microRNA-mRNA interaction maps. *Nature*. 2009; 460:479–486. [PubMed: 19536157]
138. Yang Y, Chaerkady R, Kandasamy K, Huang TC, Selvan LD, Dwivedi SB, Kent OA, Mendell JT, Pandey A. Identifying targets of miR-143 using a SILAC-based proteomic approach. *Mol Biosyst*. 2010
139. Andersson MG, Haasnoot PC, Xu N, Berenjian S, Berkhout B, Akusjarvi G. Suppression of RNA interference by adenovirus virus-associated RNA. *J Virol*. 2005; 79:9556–9565. [PubMed: 16014917]
140. Aparicio O, Carnero E, Abad X, Razquin N, Guruceaga E, Segura V, Fortes P. Adenovirus VA RNA-derived miRNAs target cellular genes involved in cell growth, gene expression and DNA repair. *Nucleic Acids Res*. 2010; 38:750–763. [PubMed: 19933264]
141. Seo GJ, Fink LH, O'Hara B, Atwood WJ, Sullivan CS. Evolutionarily conserved function of a viral microRNA. *J Virol*. 2008; 82:9823–9828. [PubMed: 18684810]
142. Glazov EA, Horwood PF, Assavalapsakul W, Kongsuwan K, Mitchell RW, Mitter N, Mahony TJ. Characterization of microRNAs encoded by the bovine herpesvirus 1 genome. *J Gen Virol*. 2010; 91:32–41. [PubMed: 19793906]
143. Grey F, Antoniewicz A, Allen E, Saugstad J, McShea A, Carrington JC, Nelson J. Identification and characterization of human cytomegalovirus-encoded microRNAs. *J Virol*. 2005; 79:12095–12099. [PubMed: 16140786]
144. Dunn W, Trang P, Zhong Q, Yang E, van Belle C, Liu F. Human cytomegalovirus expresses novel microRNAs during productive viral infection. *Cell Microbiol*. 2005; 7:1684–1695. [PubMed: 16207254]
145. Umbach JL, Kramer MF, Jurak I, Karnowski HW, Coen DM, Cullen BR. MicroRNAs expressed by herpes simplex virus 1 during latent infection regulate viral mRNAs. *Nature*. 2008; 454:780–783. [PubMed: 18596690]
146. Cui C, Griffiths A, Li G, Silva LM, Kramer MF, Gaasterland T, Wang XJ, Coen DM. Prediction and identification of herpes simplex virus 1-encoded microRNAs. *J Virol*. 2006; 80:5499–5508. [PubMed: 16699030]
147. Umbach JL, Nagel MA, Cohrs RJ, Gilden DH, Cullen BR. Analysis of human {alpha}-herpesvirus microRNA expression in latently infected human trigeminal ganglia. *J Virol*. 2009
148. Jurak I, Kramer MF, Mellor JC, van Lint AL, Roth FP, Knipe DM, Coen DM. Numerous conserved and divergent microRNAs expressed by herpes simplex viruses 1 and 2. *J Virol*. 2010; 84:4659–4672. [PubMed: 20181707]
149. Tang S, Patel A, Krause PR. Novel less-abundant viral microRNAs encoded by herpes simplex virus 2 latency-associated transcript and their roles in regulating ICP34.5 and ICP0 mRNAs. *J Virol*. 2009; 83:1433–1442. [PubMed: 19019961]

150. Umbach JL, Wang K, Tang S, Krause PR, Mont EK, Cohen JI, Cullen BR. Identification of viral microRNAs expressed in human sacral ganglia latently infected with herpes simplex virus 2. *J Virol.* 2010; 84:1189–1192. [PubMed: 19889786]
151. Hussain M, Taft RJ, Asgari S. An insect virus-encoded microRNA regulates viral replication. *J Virol.* 2008; 82:9164–9170. [PubMed: 18614632]
152. Besecker MI, Harden ME, Li G, Wang XJ, Griffiths A. Discovery of herpes B virus-encoded microRNAs. *J Virol.* 2009; 83:3413–3416. [PubMed: 19144716]
153. Waidner LA, Morgan RW, Anderson AS, Bernberg EL, Kamboj S, Garcia M, Riblet SM, Ouyang M, Isaacs GK, Markis M, Meyers BC, Green PJ, Burnside J. MicroRNAs of Gallid and Meleagrid herpesviruses show generally conserved genomic locations and are virus-specific. *Virology.* 2009; 388:128–136. [PubMed: 19328516]
154. Yao Y, Zhao Y, Smith LP, Watson M, Nair V. Novel microRNAs (miRNAs) encoded by herpesvirus of turkeys: evidence of miRNA evolution by duplication. *J Virol.* 2009; 83:6969–6973. [PubMed: 19403687]
155. Ouellet DL, Plante I, Landry P, Barat C, Janelle ME, Flamand L, Tremblay MJ, Provost P. Identification of functional microRNAs released through asymmetrical processing of HIV-1 TAR element. *Nucleic Acids Res.* 2008; 36:2353–2365. [PubMed: 18299284]
156. Klase Z, Winograd R, Davis J, Carpio L, Hildreth R, Heydarian M, Fu S, McCaffrey T, Meiri E, Ayash-Rashkovsky M, Gilad S, Bentwich Z, Kashanchi F. HIV-1 TAR miRNA protects against apoptosis by altering cellular gene expression. *Retrovirology.* 2009; 6:18. [PubMed: 19220914]
157. Kaul D, Ahlawat A, Gupta SD. HIV-1 genome-encoded hiv1-mir-H1 impairs cellular responses to infection. *Mol Cell Biochem.* 2009; 323:143–148. [PubMed: 19082544]
158. Omoto S, Fujii YR. Regulation of human immunodeficiency virus 1 transcription by nef microRNA. *J Gen Virol.* 2005; 86:751–755. [PubMed: 15722536]
159. Omoto S, Ito M, Tsutsumi Y, Ichikawa Y, Okuyama H, Brisibe EA, Saksena NK, Fujii YR. HIV-1 nef suppression by virally encoded microRNA. *Retrovirology.* 2004; 1:44. [PubMed: 15601474]
160. Rachamadugu R, Lee JY, Wooming A, Kong BW. Identification and expression analysis of infectious laryngotracheitis virus encoding microRNAs. *Virus Genes.* 2009; 39:301–308. [PubMed: 19728068]
161. Cai X, Cullen BR. Transcriptional origin of Kaposi's sarcoma-associated herpesvirus microRNAs. *J Virol.* 2006; 80:2234–2242. [PubMed: 16474131]
162. Burnside J, Bernberg E, Anderson A, Lu C, Meyers BC, Green PJ, Jain N, Isaacs G, Morgan RW. Marek's disease virus encodes MicroRNAs that map to meq and the latency-associated transcript. *J Virol.* 2006; 80:8778–8786. [PubMed: 16912324]
163. Morgan R, Anderson A, Bernberg E, Kamboj S, Huang E, Lagasse G, Isaacs G, Parcells M, Meyers BC, Green PJ, Burnside J. Sequence conservation and differential expression of Marek's disease virus microRNAs. *J Virol.* 2008; 82:12213–12220. [PubMed: 18842708]
164. Yao Y, Zhao Y, Xu H, Smith LP, Lawrie CH, Watson M, Nair V. MicroRNA profile of Marek's disease virus-transformed T-cell line MSB-1: predominance of virus-encoded microRNAs. *J Virol.* 2008; 82:4007–4015. [PubMed: 18256158]
165. Seo GJ, Chen CJ, Sullivan CS. Merkel cell polyomavirus encodes a microRNA with the ability to autoregulate viral gene expression. *Virology.* 2009; 383:183–187. [PubMed: 19046593]
166. Dolken L, Perot J, Cognat V, Alioua A, John M, Soutschek J, Ruzsics Z, Koszinowski U, Voinnet O, Pfeffer S. Mouse cytomegalovirus microRNAs dominate the cellular small RNA profile during lytic infection and show features of posttranscriptional regulation. *J Virol.* 2007; 81:13771–13782. [PubMed: 17942535]
167. Sullivan CS, Sung CK, Pack CD, Grundhoff A, Lukacher AE, Benjamin TL, Ganem D. Murine Polyomavirus encodes a microRNA that cleaves early RNA transcripts but is not essential for experimental infection. *Virology.* 2009; 387:157–167. [PubMed: 19272626]
168. Schafer A, Cai X, Bilello JP, Desrosiers RC, Cullen BR. Cloning and analysis of microRNAs encoded by the primate gamma-herpesvirus rhesus monkey rhadinovirus. *Virology.* 2007; 364:21–27. [PubMed: 17451774]

169. Cantalupo P, Doering A, Sullivan CS, Pal A, Peden KW, Lewis AM, Pipas JM. Complete nucleotide sequence of polyomavirus SA12. *J Virol.* 2005; 79:13094–13104. [PubMed: 16189011]
170. Sullivan CS, Grundhoff AT, Tevethia S, Pipas JM, Ganem D. SV40-encoded microRNAs regulate viral gene expression and reduce susceptibility to cytotoxic T cells. *Nature.* 2005; 435:682–686. [PubMed: 15931223]

Table 1
List of currently identified virus encoded microRNAs

Viruses	Virus-encoded microRNAs	References
Adenovirus	svaRNAs (VA RNA derived microRNAs)	[139;140]
BK virus	bkv-mir-B1	[141]
Bovine herpesvirus 1	bhv1-mir-B1 to bhv1-mir-B10	[142]
CMV	hcmv-mir-UL22A, hcmv-mir-UL36, hcmv-mir-UL112, hcmv-mir-UL148D, hcmv-mir-US5-1, hcmv-mir-US25-1, hcmv-mir-US5-2, hcmv-mir-US25-2, hcmv-mir-US33, hcmv-mir-US4, hcmv-mir-UL70	[112;143;144]
EBV	miR-BART1 to 22, miR-BHRF1-1 to 1-3	[6;41;44;45;46]
HSV-1	hsv1-miR-H1 to H8, hsv1-miR-H11 to H18	[145;146;147;148]
HSV-2	hsv2-mir-H2 to H7, hsv2-mir-H9 to H13, hsv2-mir-H19 to H25	[148;149;150]
Heliothis virescens ascovirus	HvAV-miR-1	[151]
Herpes B virus	hbv-mir-B2RC, hbv-mir-B4, hbv-mir-B20	[152]
Herpesvirus of Turkeys	hvt-mir-H1 to hvt-mir-H5, hvt-mir-H7 to hvt-mir-H18	[153;154]
HIV	hiv1-mir-N367, hiv1-mir-TAR, hiv1-mir-H1	[155;156;157;158;159]
Infectious laryngotracheitis virus	iltv-mir-11 to iltv-mir-17	[153;160]
JC virus	jcv-mir-J1	[141]
KSHV	kshv-miR-K12-1 to kshv-miR-K12-12	[44;111;112;115;161]
MDV	mdv1-mir-M1 to mdv1-mir-M13, mdv1-mir-M31	[162;163;164]
Merkel cell polyomavirus	mcpv-mir-M1	[165]
Mouse CMV	mcmv-mir-m01-1, mcmv-mir-m01-2, mcmv-mir-m01-3, mcmv-mir-m01-4, mcmv-mir-m21-1, mcmv-mir-m22-1, mcmv-mir-M23-1, mcmv-mir-M23-2, mcmv-mir-M44-1, mcmv-mir-M55-1, mcmv-mir-m59-1, mcmv-mir-m59-2, mcmv-mir-M87-1, mcmv-mir-m88-1, mcmv-mir-M95-1, mcmv-mir-m107-1, mcmv-mir-m108-1, mcmv-mir-m108-2	[166]
MHV68	miR-M1-1 to miR-M1-9 (derived from tRNA precursors)	[112]
Murine polyomavirus	MR1	[167]
rLCV	rlcv-mir-rL1-1 to rlcvmir-rL1-35	[41;42;43]
rhesus monkey rhadinovirus	rrv-miR-rR1-1 to rrv-miR-rR1-7	[168]
Polyomavirus SA 12	Not yet named	[169]
SV40	sv40-mir-S1	[170]

Table 2
Summary of herpesvirus microRNAs and their biological effects

Viruses	microRNAs	Biological Effects
EBV	miR-BART2	Down-regulation of EBV BALF5. Inhibits expression of the stress-induced immune molecule, MICB.
	miR-BART5	Down-regulation of the cellular factor PUMA (p53 up-regulated modulator of apoptosis).
	BARTs Cluster1 microRNAs (namely, miR-BART1, miR-BART16, and miR-BART-17)	Down-regulation of EBV LMP1.
	miR-BART15	Predicted to down-regulate expression of the EBV immediate-early transactivators, Zta and Rta.
	miR-BART22	Down-regulation of EBV LMP2A.
	miR-BHRF1-2	Down-regulates BHRF1 (EBV-encoded homolog to cellular anti-apoptotic factor Bcl-2).
	miR-BHRF1-3	Down-regulates interferon-inducible T-cell attracting chemokine CXCL11/I-TAC. Predicted to target EBV immediate-early transactivators, Zta and Rta.
KSHV	KSHV-microRNA cluster (namely, miR-K12-1, miR-K12-3-3p, miR-K12-6-3p, and miR-K12-11)	Down-regulates expression of the cellular factor, thrombospondin 1 (THBS1).
	miR-K12-1	Down-regulates expression of the cellular cyclin-dependent kinase inhibitor <i>CDKN1A</i> (p21) and the NF- κ B inhibitor <i>NFKBIA</i> (I κ Ba).
	miR-K12-3	Down-regulates expression of the cellular factor, LIP; activates transcription and secretion of IL-6 and IL-10.
	miR-K12-4-5p	Down-regulates expression of the cellular repressor protein, RB12.
	miR-K12-5	Directly or indirectly down-regulates expression of the KSHV Immediate-early transactivator RTA (ORF50).
	miR-K12-7	Down-regulates expression of the cellular factor, LIP; activates transcription and secretion of IL-6 and IL-10. Down-regulates expression of the stress-induced immune molecule, MICB.
	miR-K12-9*	Down-regulates expression of the KSHV immediate-early transactivator RTA.
	miR-K12-5, -9, -10a, and -10b	Down-regulates expression of the cellular factor, BCLAF1.
	miR-K12-11	Down-regulates expression of the cellular factor, BACH1 and other miR-155 targets.
rLCV	miR-rL1-1, miR-rL1-2, miR-rL1-5-5p, miR-rL1-5-3p, miR-rL1-6-5p, miR-rL1-6-3p, miR-rL1-8, miR-rL1-9, miR-rL1-13, miR-rL1-14-5p, miR-rL1-14-3p, miR-rL1-15, miR-rL1-16-5p, miR-rL1-16-3p, miR-rL1-19, miR-rL1-20-5p, miR-rL1-20-3p, miR-rL1-23-5p, miR-rL1-23-3p, miR-rL1-24-5p, miR-rL1-24-3p, miR-rL1-25, miR-rL1-27, miR-rL1-29, miR-rL1-32-5p, miR-rL1-32-3p, miR-rL1-33	EBV homologues

Viruses	microRNAs	Biological Effects
MDV	mdv1-miR-M4	Share seed sequence with miR-155.