Critical Reviews in Oncology / Hematology 137 (2019) 108–114

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

The interplay between viruses & host microRNAs in cancer – An emerging role for HIV in oncogenesis

L. Mapekula, B.R. Ramorola, T. Goolam Hoosen, S. Mowla*

Division of Haematology, Department of Pathology, Faculty of Health Sciences, University of Cape Town, Observatory, 7925, Cape Town, South Africa

ARTICLE INFO

Keywords:
Viruses
Cancer
microRNAs
EBV
KSHV
HPV
HIV

ABSTRACT

Human cancers attributed to viral infections represent a growing proportion of the global cancer burden, with these types of cancers being the leading cause of morbidity and mortality in some regions. The concept that viruses play a causal role in human cancers is not new, but the mechanism thereof, while well described for some viruses, still remains elusive and complex for others, especially in the case of HIV-associated B-cell derived cancers. In the last decade, compelling evidence has demonstrated that cellular microRNAs are deregulated in cancers, with an increasing number of studies identifying microRNAs as potential biomarkers for human cancer diagnosis, prognosis and therapeutic targets or tools. Recent research demonstrates that viruses and viral components manipulate host microRNA expressions to their advantage, and the emerging picture suggests that the virus/microRNA pathway interaction is defined by a plethora of complex mechanisms. In this review, we highlight the current knowledge on virus/microRNA pathway interactions in the context of cancer and provide new insights on HIV as an oncogenic virus.

1. Introduction

MicroRNAs (MiRNAs) are a class of endogenous, single stranded and evolutionary conserved noncoding RNAs (ncRNA) that are 18 to 25 nucleotides (nt) in length (Kozloski et al., 2016; Lee et al., 2013). These small RNAs are generated from precursor miRNAs (pre-miRNAs) and provide a crucial post-transcriptional mechanism to negatively regulate gene expression, through sequence-guided interactions with messenger RNA (mRNA) targets (Kozloski et al., 2016; Lee et al., 2013; Long and Chen, 2009; Amir et al., 2016). The biogenesis of miRNA is a two-step process whereby miRNA genes are transcribed in the nucleus to form primary miRNA (pri-miRNA) which is then cleaved into 60 to 80 nt pre-miRNA transcripts in the nucleus (Amir et al., 2016; Hossain et al., 2009; Lee et al., 2003). The resulting pre-miRNA is transported to the cytoplasm, and subsequently cleaved to generate a short double stranded RNA duplex. Dissociation of one of the miRNA strands from the duplex yields a mature miRNA, which thereafter couples with proteins into a protein-RNA complex known as the RNA-Induced Silencing Complex (RISC) (Kozloski et al., 2016; Amir et al., 2016). Only in this form can the mature miRNA be guided to gene targets where it binds to seed sequences in the open reading frames (ORFs) or the 3′ untranslated regions (UTRs) of mRNA to perform its function.

Approximately 30% of human protein coding genes are under miRNA regulation (Sassen et al., 2008). However, since miRNAs do not exhibit a perfect match with mRNA target sequences, they can regulate multiple targets (Zhou et al., 2013a). In the context of normal cellular homeostasis miRNAs are generally considered to be negative gene regulators, acting to fine-tune gene expression both spatially and temporally, in a cell-specific manner. Notably, miRNAs have been shown to play crucial roles during eukaryotic development and the specification of cell identity (Kozloski et al., 2016; Lee et al., 2013).

2. MiRNA deregulation & carcinogenesis

Approximately 12% of all human cancers worldwide are caused by oncoviruses with more than 80% occurring in the developing world (de Martel et al., 2012). Some of these viruses, in particular herpesviruses, adenoviruses, and polyomaviruses encode specific viral miRNAs that exploit the miRNA regulatory mechanism within host cells and establish a cellular environment which facilitates viral replication (Skalsky and Cullen, 2010). In contrast to viral proteins, miRNAs are non-immunogenic, require less coding capacity and can specifically target multiple gene transcripts (Skalsky and Cullen, 2010; Zhou et al., 2013a). Therefore, it is not surprising that the dysregulation of cellular miRNA function is a more appealing approach for viruses to evade immune responses and promote carcinogenesis. These oncogenic

* Corresponding author.
E-mail address: shaheen.mowla@uct.ac.za (S. Mowla).

https://doi.org/10.1016/j.critrevonc.2019.02.007
Received 20 November 2018; Received in revised form 16 February 2019; Accepted 17 February 2019

Table 1
Human Papilloma Virus and modulation of host miRNAs.

Altered cellular miRNA	HPV strain	Gene target(s)*	Study
miR-3156-3p (downregulated)	HPV 16	*SLC6A6*	Xia et al., 2017
miR-15a-5p, miR-17-5p, miR-20a-5p, miR-21-5p, miR-96, miR-106b-5p, and miR-3653 (upregulated) miR-497-5p (downregulated)	HPV 16	*Cyclin E1*	Gao et al., 2016
miR-21 (upregulated)	Unspecified	*PDCD4*	Deftereos et al., 2011
miR-375 (downregulated)	HPV 16 & 18	*SP1*	Wang et al., 2011a
miR-34a (downregulated)	HPV 16 & 18	*p18Ink4c* (CDK4 and CDK6 inhibitor)	Wang et al., 2011b
miR-26a; miR-143; miR-145; miR-99a; miR-203; miR-513; miR-29; miR-199 (downregulated) miR-148a; miR-302b; miR-10a; miR-196a miR-132 (upregulated)	Unspecified	*CDK6, SOX6, TGFB3, STAT3*	Pereira et al., 2010
miR-203 (downregulated)	HPV 16 & 18	*ΔNp63*	Melar-New and Laimins, 2010
miR-34a (downregulated)	HPV 16 & 18	Unspecified	Wang et al., 2009
miR-218 (downregulated)	HPV 16	*LAMB3*	Martinez et al., 2008
miR-126; miR-143; miR-145 (downregulated) miR-15b; miR-16; miR-146a; miR-155 (upregulated)	HPV 16	Unspecified	Wang et al., 2008
let-7b; let-7c; miR-23b; miR-143; miR-196b (downregulated) miR-21 (upregulated)	Unspecified	Unspecified	Lui et al., 2007

* Not all targets investigated are listed.

viruses are able to produce persistent infection and modify specific cellular pathways, favouring tumour development, by deregulating cell proliferation and inhibiting apoptosis (Fiorucci et al., 2015). The discussion below will explore how a selected number of cancer-associated viruses manipulate this mechanism.

2.1. Human papillomavirus

The human papillomavirus (HPV) is one of the most common sexually transmitted infection amongst young high-risk adolescents and young adult women (Clifford et al., 2003; Moscicki et al., 2004). The virus is a causative agent for cervical cancer which is the second most prevalent cancer among women worldwide and the most common female cancer in large areas of the developing world (Clifford et al., 2003; Bruni et al., 2015). The virus infects cells lining the squamous-columnar transition zone of the uterine cervix and its main survival strategy is through downregulation of immune surveillance and evasion of immune detection by using a multifaceted approach involving the action of the viral encoded E5, E6 and E7 oncoproteins. The expression of E6 and E7 leads to the sequestration and degradation of the tumour suppressor, TP53 and phosphorylated retinoblastoma (pRb) respectively, which are key cell cycle regulators (Wang et al., 2014; Ben et al., 2015;). This causes cells to proliferate uncontrollably in the presence of DNA damage and absence of growth signals.

An early study using sequencing of small RNA libraries identified nine putative HPV-encoded miRNAs, four of which were successfully validated in both tumour tissues and cell lines (Qian et al., 2013). Of these four miRNAs, two were encoded by HPV16, one by HPV38 and another by HPV68. The authors focused on the miRNAs encoded by HPV16, the strain which causes about half of all cervical cancers. Using predictions based on the seed sequence of HPV16-miR-H1 and HPV16-miR-H2, cellular targets were identified which align with specific cellular processes including cell cycle progression, cell migration and cancer development. One of these genes is CYP26B1, of the Cytochrome P450 Family 26 Subfamily B Member 1 encoding an enzyme essential in retinoic acid (RA) metabolism (MacLean et al., 2001). Interestingly, RA has been shown to interfere with Fas/FasL mediated apoptosis of CaSki and HeLa cells harbouring HPV (Darmochwal-Kolarz et al., 2009). Later studies focused on the differential expression of cellular miRNAs in HPV-infected compared to uninfected tissue and identified a number of miRNAs which had altered expression in HPV-infected tissue, with differential expression in early stage compared to later stage disease (Gocze et al., 2015). Of those, miR-27a was found to be significantly upregulated in high grade neoplasia and there is abundant evidence to support an oncogenic role for this miRNA including its ability to target tumour suppressors such as PTEN phosphatase and actin-binding protein tropomyosin I (Jong-Lyul et al., 2015).

Approximately 15 HPV types have been identified to have oncogenic properties. These have been termed high risk (HR) – HPVs (Muñoz et al., 2003). The most common HPV type that is in high accord with the global incidence of cervical cancer is HPV16, accounting for around half of the cases, with HPV18 being the second most common, at around 15%–20%) (Ben et al., 2015; de Sanjose et al., 2010). A study by Wang et al. (2014) identified thirteen cellular miRNAs regulated by HPV16 and/or HPV18. The authors then went on to determine the expression of selected miRNAs in cervical cancer and cervical intraepithelial neoplasia (CIN) tissues positive for HR-HPVs and found that hsa-miR-25, hsa-miR-92a and hsa-miR-378 were significantly upregulated in the HPV infected tissue groups compared to normal cervical tissue. Furthermore, hsa-miR-25 and hsa-miR-92a were noted as credible biomarkers of cervical cancer and CIN, as the increased expression of these miRNAs correlated with progression of the cervical lesions (Wang et al., 2014). Furthermore, and more recently, Ben et al. (2015) reported the function of the E6 oncoprotein as a cellular miRNA modulator and provided an important clue to explain the mechanism of HPV induced carcin ogenesis. The authors reported that E6 protein can upregulate the expression of hsa-miR-21 and reduce hsa-miR-27a and hsa-miR-218 expression. Of note hsa-miR-21 is located in an HPV16 integration loci at 17q23.3; moreover, hsa-miR-21 is known to regulate apoptosis, cell proliferation and cell migration in breast and colorectal cancer. As a result, hsa-miR-21 upregulation correlates with the downregulation of phosphatase-tensin homolog (PTEN) tumour suppressor gene expression and upregulation of Akt activity. The hsa-miR-21 mediated modulation of the PTEN/Akt signalling axis therefore encourages cell proliferation (Ben et al., 2015).

Other studies corroborate the findings by Ben et al., (2015) and also provide clinical evidence that a functional loop, comprising of hsa-miR-21 and hsa-miR-let-7a, regulates epithelial transformation through signal transducer and activator of transcription 3 (STAT3) signaling (Shishodia et al., 2015; Bumrungthai et al., 2015). Undoubtedly, these researchers have provided substantial molecular evidence that links cellular miR-21 dysregulation with the progression of HPV16 infection and the etiology of cervical cancer. Several more studies have demonstrated significant changes in cellular miRNA expression in cervical cancer tissues associated with HPV infection, some of which are listed in Table 1.

2.2. Kaposi sarcoma-associated herpesvirus

Kaposi sarcoma-associated herpesvirus (KSHV) also known as Human Herpes Virus 8 is a gammaherpesvirus and the etiological agent of Kaposi's sarcoma (KS), a tumour of endothelial origin (Dahlke et al., 2012; Yao et al., 2015). KS is characterized by abnormal blood vessel proliferation and encompasses four clinical variants with the Acquired Immunodeficiency Syndrome related KS (AIDS-KS), having a more aggressive clinical course (Yao et al., 2015). Infection with KSHV is necessary for the development of KS but not sufficient (Zhou et al., 2013b); nevertheless, co-infection with HIV has been characterized as a crucial contributor to KS development with the incidence of KS shifting from 1 in 100,000 (in the general population) to 1 in 20 in HIV- infected individuals (Zhou et al., 2013b). KSHV is also associated with the development of lymphoproliferative diseases including multicentric Castleman's disease (MCD), and primary effusion lymphoma (PEL) (Yao et al., 2015). These conditions intimately associate with human immunodeficiency virus (HIV) infection and published literature has effectively characterized some of the synergistic interactions between these two viruses (Yao et al., 2015; Xue et al., 2014) which are briefly discussed in this review.

Like other herpesviruses the KSHV life cycle comprises of latent and lytic replication stages. In vivo, KSHV targets B-cells and establishes a default program of chronic latent infection; during which the virus expresses a handful of viral genes that aid in the maintenance of latency and evasion of immune surveillance (Dahlke et al., 2012; Yao et al., 2015). For years, the molecular components that allow KSHV to establish chronic states of latency in target cells and promote cellular transformation had not been well characterized. Wu and colleagues attempted to bridge this gap and identified 170 differentially expressed miRNAs (69 upregulated and 101 downregulated) (Table 2) in KS compared to normal tissues (Wu et al., 2015) using a microarray containing 3100 human miRNA probes. Furthermore, a microarray analysis of 17 KS specimens revealed 185 differentially expressed cellular miRNAs (76 upregulated and 109 downregulated) which were confirmed by quantitative reverse transcriptase polymerase chain reaction (Ene et al., 2014). The predicted gene targets of these miRNAs are involved in a variety of cellular processes including angiogenesis and apoptosis, suggesting a role for these miRNAs in KS pathogenesis.

Out of the plethora of KSHV expressed miRNAs, miR-K12-11 is the candidate of extensive research. KSHV miR-K12-11 shares its seed sequence with cellular miR-155 (Dahlke et al., 2012; Gottwein et al., 2007). Hsa-MiR-155 plays a crucial role in haematopoiesis and the fine-tuning of germinal centre responses (Dahlke et al., 2012; Thai et al., 2007; Rodriguez et al., 2007). A dysregulation of hsa-miR-155 expression has been reported in breast cancer, lymphoma and leukaemia cells (O'Connell et al., 2008; Eis et al., 2005; Volinia et al., 2006), and studies have shown that the heterologous expression of hsa-miR-155 induces proliferative disease in mice (O'Connell et al., 2008; Costinean et al., 2006). Consequently, it is postulated that the development of KSHV-associated tumours depends (though not exclusively) on mimicry of hsa-miR-155 functions by kshv-miR-K12-11 (Dahlke et al., 2012).

Dahlke et al. (2012) examined the impact of constitutive hsa-miR-155 and kshv-miR-K12-11 expression on haematopoietic stem cells (HSC) in mice and found that the overexpression (of either miRNA) resulted in the expansion of B-cell pools in the murine spleens from both miRNA expressing cohorts, with concomitant decrease in the T-cell populations. This observation was further corroborated by several studies that also reported an activation of cell survival signals and proliferation following hsa-miR-155 expression (O'Connell et al., 2008; Liu et al., 2011). Additionally, a study conducted by Boss et al. (2011) further supported the finding that hsa-miR-155 as well as kshv-miR-K12-11 support splenic B-cell expansion and that kshv-miR-K12-11 acts to repress tumour suppressor genes, like Jarid2, in order to allow KSHV to latently infect B-cells. The aforementioned highlight key results that were yielded from independent studies. The concordance in the observed phenotype in mice expressing hsa-miR-155 and kshv-miR-K12-11 shows that seed sharing is sufficient to allow mimicry of hsa-miR-155 functions. In lymphatic endothelial cells, KSHV was shown to specifically downregulate the hsa-miR-221/hsa-miR-222 cluster, while hsa-miR-31 was upregulated, and these changes were linked to enhancement of endothelial cell motility, contributing to KS progression (Wu et al., 2011). Table 2 provides further examples of studies which have reported the alteration of cellular miRNA expression by KSHV.

2.3. Epstein-Barr Virus

The Epstein-Barr Virus (EBV) is a human gammaherpes virus that establishes persistent infection in over 90% of the global population (Chêne et al., 2007). Infection with EBV is a pervasive feature in human populations and was the first characterized oncovirus that targets epithelial cells and B-lymphocytes, being associated with a number of malignancies. These include nasopharyngeal carcinoma (NPC), sporadic and endemic Burkitt lymphoma (BL) (15%–30% and 95% of the cases, respectively) and post-transplant lymphoma disease (PTLD) (Chêne et al., 2007; Ferry, 2006; Brady et al., 2008). In the majority of cases, EBV infection is benign and seldom results in malignancy unless the virus-host equilibrium is disturbed (Chêne et al., 2007).

The EBV life cycle mirrors that of other herpesviruses, consisting of latent infection and lytic infection. Subsequent to primary infection, EBV chronically persists in a latent state within memory B-cells and most children (in Africa) show serological markers of infection by 3 years of age (Chêne et al., 2007). The terminal differentiation of B-cells to plasma cells has been implicated as the trigger for EBV reactivation in vivo (Chêne et al., 2007). Clinically, the virus sporadically reactivates (at low levels) into lytic replication, thereby allowing viral shedding in the saliva and infection of new cells. Interestingly, depending on the cellular context, different latency associated genes are expressed by the EBV genome; thereby giving rise to four different patterns of gene expression known as latency types 0, I, II, III, with different latency types prevailing in different EBV-associated diseases (Delecluse et al., 2007; Yin et al., 2008; Piedade and Azevedo-Pereira, 2016). Similarly, EBV-encoded miRNAs exhibit differential expression profiles with respect to cell context and host immune control (Piedade

Table 2
Kaposi Sarcoma Associated Herpes Virus and modulation of host miRNAs.

Cellular miRNA	Gene target(s)*	Study
miR-34a upregulated	CDCA3, CCNB2, TRP53	Krause et al., 2017
miR-99a, miR-200 family; miR-199b-5p; miR-100; miR-335 (downregulated)	Unspecified	Ene et al., 2014
miR-718 (upregulated)	*PTEN*	Xue et al., 2014
miR-17/92 (upregulated)	Unspecified	Chugh et al., 2013
miR-146a (upregulated)	*CXCR4*	Punj et al., 2010
miR-221; miR-222 (downregulated) miR-31 (upregulated)	*ETS2, ETS1, FAT4*	Wu et al., 2011
miR-21 (upregulated)	Unspecified	Tsai et al., 2009

* Not all targets investigated are listed.

and Azevedo-Pereira, 2016; Murata et al., 2014).

Marquitz et al. (2015) were the first to show that the introns from BamHI A rightward transcripts (BARTs), in EBV infected epithelial cells, form a template for the production of 44 EBV-encoded miRNAs. Published literature has also demonstrated that these EBV miRNAs are distributed by three clusters; BamH I fragment H rightward open reading frame 1 (BHRF1)-cluster, BART-cluster 1 and BART-cluster 2 (Barth et al., 2011; Wang et al., 2018). Interestingly, EBV miRNAs can target both cellular and viral mRNAs, as a means to create a more favorable environment for the virus in infected cells, including immune evasion, downregulating tumour suppressor genes and regulating the EBV switch from latent to lytic infection (Piedade and Azevedo-Pereira, 2016). For example, EBV-miR-BART6-5p has been reported to interfere with and reduce cellular miRNA biogenesis by targeting dicer mRNA (Iizasa et al., 2010; Wang et al., 2018). A recent study by Verhoeven and colleagues has shed some light on a regulatory loop that exists between EBV-encoded Latent membrane protein 1 (LMP1), BART miRNAs and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling. The study shows that LMP1 promotes the expression of BART miRNAs, through NF-κB signaling (Verhoeven et al., 2016). The constitutively active NF-kB signaling in turn promotes LMP1 expression. Furthermore, EBV-miR-BART5-5p and other BART miRNAs target the 3′UTR of LMP1, negatively regulating its expression. This ensures that EBV latency is maintained, ultimately resulting in immune evasion, cell survival and uncontrolled proliferation of these EBV-infected cells (Verhoeven et al., 2016)

Research done in NPC, one of the most prominent EBV related tumours, has shown that a number of cellular miRNAs are dysregulated in NPC tumours. These include hsa-miR-200c, hsa-miR-652 and hsa-miR-320 and research to identify their targets and impact on cellular activity is ongoing. In the laboratory, EBV has been used to transform primary B-cells into infinitely proliferating lymphoblastoid cells lines and several B-cell derived cancers are closely associated with EBV infection, including BL and diffuse large B-cell lymphomas (DLBCL) (Linnstaedt et al., 2010). EBV has been shown to induce the expression of several cellular miRNAs, one of which is hsa-miR-155, found in high levels in many types of B-cell lymphomas (Linnstaedt et al., 2010). Expression of BIC, the precursor RNA of hsa-miR-155, can be directly activated by LMP1, which in turn attenuates the NF-kB pathway, stabilizing viral latency (Lu et al., 2008). In a more recent study, EBNA2 expression in B-cells was linked to high expression of the Programmed Cell death Ligand PD-L1 (Anastasiadou et al., 2018). This was linked to the suppression of hsa-miR-34a, which is known to target PD-L1. The expression of hsa-miR-34a was found to be dependent on the presence of EBNA2 and this was linked to the association of the latter with early B-cell factor 1 (EBF1), a known repressor of this miRNA. Table 3 provides further examples of studies which have reported the alteration of cellular miRNA expression by EBV.

2.4. HIV infection and Cancer

HIV infection is a global public health issue that has claimed more than 39 million lives to date (Joint United Nations Programme on HIV/AIDS (UNAIDS) and Joint United Nations Programme on HIV/AIDS (UNAIDS, 2016). Sub-Saharan Africa carries the bulk of the HIV burden, with 25.8 million people living with HIV as of 2015, accounting for 70% of the global total (Joint United Nations Programme on HIV/AIDS (UNAIDS) and Joint United Nations Programme on HIV/AIDS (UNAIDS, 2016). Although there is currently no known cure for HIV, an effective antiretroviral therapy (ART) programme can significantly increase the longevity of people living with the virus. Viral persistence is primarily due to the latent reservoirs that the virus establishes upon infecting host cells, with latently infected cells exhibiting the potential to escape viral immune responses and persist indefinitely even in patients undergoing ART (Sung and Margolis, 2018).

Table 3
Epstein Barr-Virus and modulation of host miRNAs.

Cellular miRNA	Gene target(s)	Study
miR-204 (downregulated)	*CDC42*	Ma et al., 2014
miR-28 (downregulated)	*MYC*	Schneider et al., 2014
miR-31 (downregulated)	*FIH1* and *MCM2*	Cheung et al., 2014
miR-155 (upregulated) miR-200c (downregulated)	*JMJD1A*	Du et al., 2011
miR-127 (upregulated)	*BLIMP-1* and *XBP-1*	Leucci et al., 2010
miR-155 (upregulated)	*BACH1*	Yin et al., 2008
miR-146a (upregulated)	Unspecified	Godshalk et al., 2008

Among HIV-associated cancers, B-cell lymphomas are the most common and are a major cause of mortality (Dolcetti et al., 2016). HIV-1 infection causes progressive $CD4^+$ T-cell loss making individuals susceptible to infections and the development of a wide range of immunological abnormalities. The virus does not infect B-cells, but studies have shown that secreted HIV proteins, such as HIV-1 transactivator of transcription (Tat), accumulate in lymphoid tissues, driving specific biological events which promote lymphoma development (El-amine et al., 2017). These findings challenge the current view that the involvement of HIV in lymphoma development is indirect and support the possibility that HIV has oncogenic potential. The two most common lymphomas arising in HIV-infected individuals are BL and DLBCL. Interestingly, these show distinct cytological, histological and biological characteristics when arising in HIV-positive patients compared to the general population (Carbone et al., 2014).

Previous studies in KS have demonstrated how HIV-1 proteins can promote KSHV reactivation through the JAK/STAT pathway and exert synergy, with KS factors, in order to modulate proliferative signaling pathways and promote both angiogenesis and tumourigenesis (Zhou et al., 2013b; Xue et al., 2014). Additionally, HIV-1 Tat protein has been shown to promote the expression of KSHV oncogene Orf-K1 (K1) in KS tumours. Consequently, Tat and K1 synergize to induce the expression of cellular miR-891a-5p, which targets and inhibits the negative regulator, IκBα; in order to mediate the activation of NF-κB and promote angiogenesis (Yao et al., 2015). Similarly, HIV-1 negative regulatory factor (Nef) and KSHV K1 protein were shown to synergistically promote angiogenesis by inducing miR-718 expression which in turn regulates the pTEN/AKT/mTOR signaling pathway (Xue et al., 2014). In 2016, the HIV-1 Vpr protein was shown to upregulate the cellular miRNA miR-942-5p which directly targets IκBα, thus demonstrating that internalised HIV-1 Vpr inhibits KSHV lytic replication (Yan et al., 2016).

In recent years there has been growing evidence in support of HIV as an oncogenic virus in B-cell derived cancers. Combined antiretroviral (cART) therapy has significantly improved the outcome of HIV-infected patients who develop cancer, with response rates being comparable to that of the overall population. However there is now enough evidence to show that some cancer subtypes, such as some non-Hodgkin lymphomas still occur at significantly higher rates among HIV infected individuals, even those with low viral counts (Shiels et al., 2018). Intriguingly, the incidence of Burkitt lymphoma has not significantly declined among HIV-infected treated individuals compared to the pre-cART era (Cobucci et al., 2015; Gibson et al., 2014). Despite the fact that B-cells are not the natural host of HIV-1, proteins encoded by the virus have been found to invade these cells. Xu et al. (2009) demonstrated that following macrophage infection, HIV-1 Nef protein is expressed. The expressed Nef protein interferes with several biological processes that encourage macrophages to form cellular conduits that connect to B-cells and selectively transport Nef protein. This allows Nef to simultaneously bypass B-cell immunoglobulin surface receptors, increase differentiation factors within these cells and promote lymphomagenesis (Xu et al., 2009). Moreover, HIV-encoded p17 protein variants which were shown to enhance the oncogenic potential of B-cells, and which work cooperatively with other factors such as EBV proteins

and cell-bound ligands, have been isolated in individuals who have HIV-associated lymphoma (Martorelli et al., 2015). The HIV Tat protein, which has been shown to circulate in blood plasma and to internalise cells, interacts with the chromatin and hence potentially modulating cellular genes and processes (Marban et al., 2011). The Vassetzky research laboratory has demonstrated that Tat is able to induced oxidative stress and DNA damage in lymphocytes, while in normal B cells, they found that it is responsible for the repositioning of the *MYC* locus, bringing it closer to the *IGH* locus, potentially facilitating the *MYC/IGH* translocation event which is a defining feature of Burkitt lymphoma (Germini et al., 2017; El-Amine et al., 2018). More recently, they reported that Tat activates the expression of the B cell specific gene *AICDA*, an important component of antibody diversification (Bintou-Sall et al., 2019). The product of the *AICDA* gene, activation-induced cytidine deaminase (AID), is a DNA mutator able to create double-strand breaks in DNA and facilitating the *MYC-IGH* rearrangement and promoting the cancer.

The existence and role of HIV encoded miRNAs has been controversial; nevertheless, in a recent review the function of several HIV encoded miRNAs are described (Fruci et al., 2017). Among those, the Nef-derived miRNA, miR-N367, is reported to block expression of HIV Nef and long terminal repeat (LTR) transcription, hence negatively impacting the transcription of the virus. TAR-miR (5p and 3p), encoded by HIV-1 transactivation RNA (TAR) has been shown to downregulate host genes, preventing cell death, hence enhancing the survival of the virus. There are very few reports in the literature of changes in host cell miRNA upon infection with HIV but one of the HIV-1 encoded miRNAs, hiv1-mir-H1 has been reported to downregulate the host miR149 which targets the HIV Vpr gene and in this way ensuring virus replication. In addition, eleven miRNAs were found to be upregulated in Jurkat cells infected with HIV (Triboulet et al., 2007). In the same cells, the polycistronic miRNA cluster miR-17/92 was downregulated – miRNAs encoded within this cluster have been reported to be involved in genomic amplification in malignant lymphoma and lung cancer. It is clear that miRNAs play a crucial role in cancer development and progression, including HIV-related lymphomas, and it is also clear that viruses, including HIV, are able to alter cellular gene expression to their advantage. There is therefore a need to specifically define the miRNA signatures of HIV-associated lymphomas and establish whether HIV infection contributes directly to alteration of these miRNAs which contribute to the disease.

3. Conclusion

Carcinogenesis can stem from a myriad of factors. As biological agents, viruses have been shown to be the etiological agents of some aggressive malignancies. It is evident that viruses and their components utilize unique mechanisms to encourage cellular transformation and that knowledge of this will provide insight into disease mechanisms and treatment strategies. Cellular miRNA dysregulation is a crucial denominator by which viruses can influence cellular transformation. For this reason, the search to characterize cellular miRNA dysregulation in disease should be at the forefront of current research. Developing a cancer cure remains the holy grail of medical research; however, the role of how viruses have evolved to manipulate an evolutionary conserved host mechanism, and cause disease is an area of research that requires attention.

References

Amir, S., Simion, C., Umeh-Garcia, M., Krig, S., Moss, T., Carraway 3rd, K.L., Sweeney, C., 2016. Regulation of the T-box transcription factor Tbx3 by the tumour suppressor microRNA-206 in breast cancer. Br. J. Cancer 114 (10), 1125–1134.

Anastasiadou, E., Stroopinsky, D., Alimperti, S., Jiao, A.L., Pyzer, A.R., Cippitelli, C., Pepe, G., Severa, M., Rosenblatt, J., Etna, M.P., Rieger, S., 2018. Epstein – Barr virus-encoded EBNA2 alters immune checkpoint PD-L1 expression by downregulating miR-34a in B-cell lymphomas. Leukemia 1.

Barth, S., Meister, G., Grässer, F.A., 2011. EBV-encoded miRNAs. Biochimica et Biophysica Acta (BBA)-Gene Regulatory Mechanisms 1809 (11), 631–640.

Ben, W., Yang, Y., Yuan, J., Sun, J., Huang, M., Zhang, D., Zheng, J., 2015. Human papillomavirus 16 E6 modulates the expression of host microRNAs in cervical cancer. Taiwan. J. Obstet. Gynecol. 54 (4), 364–370.

Bintou-Sall, F., El-Amine, R., Markozashvili, D., Tsfasman, T., Oksenhendler, E., Lipinski, M., Vassetzky, Y., Germini, D., 2019. HIV-1 Tat protein induces aberrant activation of AICDA in human B-lymphocytes from peripheral blood. J. Cell Physiol. https://doi.org/10.1002/jcp.2821.

Boss, I.W., Nadeau, P.E., Abbott, J.R., Yang, Y., Mergia, A., Renne, R., 2011. A Kaposi's sarcoma-associated herpesvirus-encoded ortholog of microRNA miR-155 induces human splenic B-cell expansion in NOD/LtSz-scid IL2Rγnull mice. J. Virol. 85 (19), 9877–9886.

Brady, G., MacArthur, G.J., Farrell, P.J., 2008. Epstein–Barr virus and Burkitt lymphoma. Postgrad. Med. J. 84 (993), 372–377.

Bruni, L., Barrionuevo-Rosas, L., Albero, G., Aldea, M., Serrano, B., Valencia, S., Brotons, M., Mena, M., Cosano, R., Muñoz, J., Bosch, F.X., 2015. ICO Information Centre on HPV and Cancer (HPV Information Centre)c. Human papillomavirus and related diseases in India. Summary Report. pp. 12–23.

Bumrungthai, S., Ekalaksananan, T., Evans, M.F., Chopjitt, P., Tangsiriwatthana, T., Patarapadungkit, N., Kleebkaow, P., Luanratanakorn, S., Kongyingyoes, B., Worawichawong, S., Pientong, C., 2015. Up-regulation of miR-21 is associated with cervicitis and human papillomavirus infection in cervical tissues. PLoS One 10 (5), e0127109.

Carbone, A., Vaccher, E., Gloghini, A., Pantanowitz, L., Abayomi, A., De Paoli, P., Franceschi, S., 2014. Diagnosis and management of lymphomas and other cancers in HIV-infected patients. Nat. Rev. Clin. Oncol. 11 (4), 223.

Chêne, A., Donati, D., Guerreiro-Cacais, A.O., Levitsky, V., Chen, Q., Falk, K.I., Orem, J., Kironde, F., Wahlgren, M., Bejarano, M.T., 2007. A molecular link between malaria and Epstein–Barr virus reactivation. PLoS Pathog. 3 (6), p.e80.

Cheung, C.C.M., Chung, G.T.Y., Lun, S.W.M., To, K.F., Choy, K.W., Lau, K.M., Siu, S.P.K., Guan, X.Y., Ngan, R.K.C., Yip, T.T.C., Busson, P., 2014. miR-31 is consistently inactivated in EBV-associated nasopharyngeal carcinoma and contributes to its tumorigenesis. Mol. Cancer 13 (1), 184.

Chugh, P.E., Sin, S.H., Ozgur, S., Henry, D.H., Menezes, P., Griffith, J., Eron, J.J., Damania, B., Dittmer, D.P., 2013. Systemically circulating viral and tumor-derived microRNAs in KSHV-associated malignancies. PLoS Pathog. 9 (7), e1003484.

Clifford, G.M., Smith, J.S., Plummer, M., Munoz, N., Franceschi, S., 2003. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. Br. J. Cancer 88 (1), 63–73.

Cobucci, R.N.O., Lima, P.H., de Souza, P.C., Costa, V.V., Cornetta, M., Cornetta, Mda, Gonçalves, A.K., 2015. Assessing the impact of HAART on the incidence of defining and non-defining AIDS cancers among patients with HIV/AIDS: a systematic review. J. Infect. Public Health 8 (1). https://doi.org/10.1016/j.jiph.2014.08.003.

Costinean, S., Zanesi, N., Pekarsky, Y., Tili, E., Volinia, S., Heerema, N., Croce, C.M., 2006. Pre-B cell proliferation and lymphoblastic leukemia/high-grade lymphoma in Eμ-miR155 transgenic mice. Proc. Natl. Acad. Sci. 103 (18), 7024–7029.

Dahlke, C., Maul, K., Christalla, T., Walz, N., Schult, P., Stocking, C., Grundhoff, A., 2012. A microRNA encoded by Kaposi sarcoma-associated herpesvirus promotes B-cell expansion in vivo. PLoS One 7 (11), e49435.

Darmochwal-Kolarz, D., Gasowska-Giszczak, U., Paduch, R., Kolarz, B., Wilciński, P., Oleszczuk, J., Kwasniewska, A., 2009. Apoptosis of HeLa and CaSki cell lines incubated with All-trans retinoid acid. Folia Histochem. Cytobiol. 47 (4), 599–603.

De Martel, C., Ferlay, J., Franceschi, S., Vignat, J., Bray, F., Forman, D., Plummer, M., 2012. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 13 (6), 607–615.

de Sanjose, S., Quint, W.G., Alemany, L., Geraets, D.T., Klaustermeier, J.E., Lloveras, B., Tous, S., Felix, A., Bravo, L.E., Shin, H.R., Vallejos, C.S., 2010. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 11 (11), 1048–1056.

Deftereos, G., Corrie, S.R., Feng, Q., Morihara, J., Stern, J., Hawes, S.E., Kiviat, N.B., 2011. Expression of mir-21 and mir-143 in cervical specimens ranging from histologically normal through to invasive cervical cancer. PLoS One 6 (12), e28423.

Delecluse, H.J., Feederle, R., O'Sullivan, B., Taniere, P., 2007. Epstein–barr virus-associated tumours: an update for the attention of the working pathologist. J. Clin. Pathol. 60 (12), 1358–1364.

Dolcetti, R., Gloghini, A., Caruso, A., Carbone, A., 2016. A lymphomagenic role for HIV beyond immune suppression? Blood 127 (11), 1403–1409.

Du, Z.M., Hu, L.F., Wang, H.Y., Yan, L.X., Zeng, Y.X., Shao, J.Y., Ernberg, I., 2011. Upregulation of MiR-155 in nasopharyngeal carcinoma is partly driven by LMP1 and LMP2A and downregulates a negative prognostic marker JMJD1A. PLoS One 6 (4), e19137.

Eis, P.S., Tam, W., Sun, L., Chadburn, A., Li, Z., Gomez, M.F., Lund, E., Dahlberg, J.E., 2005. Accumulation of miR-155 and BIC RNA in human B cell lymphomas. Proc. Natl. Acad. Sci. 102 (10), 3627–3632.

El-Amine, R., Germini, D., Zakharova, V.V., Tsfasman, T., Sheval, E.V., Louzada, R.A., Dupuy, C., Bilhou-Nabera, C., Hamade, A., Najjar, F., Oksenhendler, E., 2018. HIV-1 Tat protein induces DNA damage in human peripheral blood B-lymphocytes via mitochondrial ROS production. Redox Biol. 15, 97–108.

Ene, A.M.C., Borze, I., Guled, M., Costache, M., Leen, G., Sajin, M., Ionica, E., Chitu, A., Knuutila, S., 2014. MicroRNA expression profiles in Kaposi's sarcoma. Pathol. Oncol. Res. 20 (1), 153–159.

Ferry, J.A., 2006. Burkitt's lymphoma: clinicopathologic features and differential diagnosis. Oncologist 11 (4), 375–383.

Fiorucci, G., Chiantore, M.V., Mangino, G., Romeo, G., 2015. MicroRNAs in virus-induced tumorigenesis and IFN system. Cytokine Growth Factor Rev. 26 (2), 183–194.

Fruci, D., Rota, R., Gallo, A., 2017. The role of HCMV and HIV-1 microRNAs: processing, and mechanisms of action during viral infection. Front. Microbiol. 8, 689.
Gao, D., Zhang, Y., Zhu, M., Liu, S., Wang, X., 2016. miRNA expression profiles of HPV-Infected patients with cervical Cancer in the uyghur population in China. PLoS One 11 (10), e0164701.
Germini, D., Tsfasman, T., Klibi, M., El-Amine, R., Pichugin, A., Iarovaia, O.V., et al., 2017. HIV Tat induces a prolonged MYC relocalization next to IGH in circulating B-cells. Leukemia 31 (11), 2515–2522.
Gibson, T.M., Morton, L.M., Shiels, M.S., Clarke, C.A., Engels, E.A., 2014. Risk of non-Hodgkin lymphoma subtypes in HIV-infected people during the HAART era: a population-based study. AIDS 28 (15), 2313–2318.
Gocze, K., Gombos, K., Kovacs, K., Juhasz, K., Gocze, P., Kiss, I., 2015. MicroRNA expressions in HPV-induced cervical dysplasia and cancer. Anticancer Res. 35 (1), 523–530.
Godshalk, S., Bhaduri-McIntosh, S., Slack, F.J., 2008. Epstein-Barr virus-mediated dysregulation of human microRNA expression. Cell Cycle 7 (22), 3595–3600.
Gottwein, E., Mukherjee, N., Sachse, C., Frenzel, C., Majoros, W.H., Chi, J.T.A., Braich, R., Manoharan, M., Soutschek, J., Ohler, U., Cullen, B.R., 2007. A viral microRNA functions as an orthologue of cellular miR-155. Nature 450 (7172), 1096–1099.
Hossain, M.M., Ghanem, N., Hoelker, M., Rings, F., Phatsara, C., Tholen, E., Schellander, K., Tesfaye, D., 2009. Identification and characterization of miRNAs expressed in the bovine ovary. BMC Genomics 10 (1), 443.
Iizasa, H., Wulff, B.E., Alla, N.R., Maragkakis, M., Megraw, M., Hatzigeorgiou, A., Iwakiri, D., Takada, K., Wiedmer, A., Showe, L., Lieberman, P., 2010. Editing of Epstein-Barr virus-encoded BART6 microRNAs controls their dicer targeting and consequently affects viral latency. J. Biol. Chem. 285 (43), 33358–33370.
Joint United Nations Programme on HIV/AIDS (UNAIDS) and Joint United Nations Programme on HIV/AIDS (UNAIDS), 2016. Global AIDS Update 2016. Geneva, Switzerland. Available at. [http://www.unaids.org/en/resources/documents/2016/Global-AIDS-update-2016].
Jong-Lyul, P., Miranf, K., Kyu-Sang, S., Seon-Young, K., Yong Sung, K., 2015. Cell-free miR-27a, a potential doagnostic and prosgnostic biomarker for gastric Cancer. Genomics Inform. 13 (3), 70–75.
Kozloski, G.A., Jiang, X., Bhatt, S., Ruiz, J., Vega, F., Shaknovich, R., Melnick, A., Lossos, I.S., 2016. miR-181a negatively regulates NF-κB signaling and affects activated B-cell–like diffuse large B-cell lymphoma pathogenesis. Blood 127 (23), 2856–2866.
Krause, C.J., Popp, O., Thirunarayanan, N., Dittmar, G., Lipp, M., Muller, G., 2017. MicroRNA-34a promotes genomic instability by a broad suppression of genome maintenance mechanisms downstream of the oncogene KSHV-vGPCR. Oncotarget 7 (9), 10414–10432 1.
Lee, Y., Ahn, C., Han, J., Choi, H., Kim, J., Yim, J., Lee, J., Provost, P., Rådmark, O., Kim, S., Kim, V.N., 2003. The nuclear RNase III drosha initiates microRNA processing. Nature 425 (6956), 415–419.
Lee, J.M., Yoo, J.K., Yoo, H., Jung, H.Y., Lee, D.R., Jeong, H.C., Oh, S.H., Chung, H.M., Kim, J.K., 2013. The novel miR-7515 decreases the proliferation and migration of human lung cancer cells by targeting c-Met. Mol. Cancer Res. 11 (1), 43–53.
Leucci, E., Onnis, A., Cocco, M., De Falco, G., Imperatore, F., Giuseppina, A., Costanzo, V., Cerino, G., Mannucci, S., Cantisani, R., Nyagol, J., 2010. B-cell differentiation in EBV-positive Burkitt lymphoma is impaired at posttranscriptional level by miRNA-altered expression. Int. J. Cancer 126 (6), 1316–1326.
Linnstaedt, S.D., Gottwein, E., Skalsky, R.L., Luftig, M.A., Cullen, B.R., 2010. Virally induced cellular microRNA miR-155 plays a key role in B-cell immortalization by Epstein-Barr virus. J. Virol. 84 (22), 11670–11678.
Liu, J., van Mil, A., Vrijsen, K., Zhao, J., Gao, L., Metz, C.H., Goumans, M.J., Doevendans, P.A., Sluijter, J.P., 2011. MicroRNA-155 prevents necrotic cell death in human cardiomyocyte progenitor cells via targeting RIP1. J. Cell. Mol. Med. 15 (7), 1474–1482.
Long, J.E., Chen, H.X., 2009. Identification and characteristics of cattle microRNAs by homology searching and small RNA cloning. Biochem. Genet. 47 (5-6), 329–343.
Lu, F., Weidmer, A., Liu, C.G., Volinia, S., Croce, C.M., Lieberman, P.M., 2008. Epstein-Barr virus-induced miR-155 attenuates NF-κB signaling and stabilizes latent virus persistence. J. Virol. 82 (21), 10436–10443.
Lui, W.O., Pourmand, N., Patterson, B.K., Fire, A., 2007. Patterns of known and novel small RNAs in human cervical cancer. Cancer Res. 67 (13), 6031–6043.
Ma, L., Deng, X., Wu, M., Zhang, G., Huang, J., 2014. Down-regulation of miRNA-204 by LMP-1 enhances CDC42 activity and facilitates invasion of EBV-associated nasopharyngeal carcinoma cells. FEBS Lett. 588 (9), 1562–1570.
MacLean, G., Abu-Abed, S., Dollé, P., Tahayato, A., Chambon, P., Petkovich, M., 2001. Cloning of a novel retinoic-acid metabolizing cytochrome P450, Cyp26B1, and comparative expression analysis with Cyp26A1 during early murine development. Mech. Dev. 107 (1), 195–201.
Marban, C., Su, T., Ferrari, R., Li, B., Vatakis, D., Pellegrini, M., et al., 2011. Genome-wide binding map of the HIV-1 Tat protein to the human genome. PLoS One 6 (11).
Marquitz, A.R., Mathur, A., Edwards, R.H., Raab-Traub, N., 2015. Host gene expression is regulated by two types of noncoding RNAs transcribed from the Epstein-Barr virus BamHI a rightward transcript region. J. Virol. 89 (22), 11256–11268.
Martinez, I., Gardiner, A.S., Board, K.F., Monzon, F.A., Edwards, R.P., Khan, S.A., 2008. Human papillomavirus type 16 reduces the expression of microRNA-218 in cervical carcinoma cells. Oncogene 27 (18), 2575–2582.
Martorelli, D., Muraro, E., Mastorci, K., Dal Col, J., Faè, D.A., Furlan, C., Giagulli, C., Caccuri, F., Rusnati, M., Fiorentini, S., Carbone, A., 2015. A natural HIV p17 protein variant up-regulates the LMP-1 EBV oncoprotein and promotes the growth of EBV-infected B-lymphocytes: Implications for EBV-driven lymphomagenesis in the HIV setting. Int. J. Cancer 137 (6), 1374–1385.
Moscicki, A.B., Ellenberg, J.H., Farhat, S., Xu, J., 2004. Persistence of human papillomavirus infection in HIV-infected and-uninfected adolescent girls: risk factors and differences, by phylogenetic type. J. Infect. Dis. 190 (1), 37–45.
Muñoz, N., Bosch, F.X., De Sanjosé, S., Herrero, R., Castellsagué, X., Shah, K.V., Snijders, P.J., Meijer, C.J., 2003. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N. Engl. J. Med. 348 (6), 518–527.
Murata, T., Sato, Y., Kimura, H., 2014. Modes of infection and oncogenesis by the Epstein–Barr virus. Rev. Med. Virol. 24 (4), 242–253.
O'Connell, R.M., Rao, D.S., Chaudhuri, A.A., Boldin, M.P., Taganov, K.D., Nicoll, J., Paquette, R.L., Baltimore, D., 2008. Sustained expression of microRNA-155 in hematopoietic stem cells causes a myeloproliferative disorder. J. Exp. Med. 205 (3), 585–594.
Pereira, P.M., Marques, J.P., Soares, A.R., Carreto, L., Santos, M.A., 2010. MicroRNA expression variability in human cervical tissues. PLoS One 5 (7), e11780.
Piedade, D., Azevedo-Pereira, J.M., 2016. The role of microRNAs in the pathogenesis of herpesvirus infection. Viruses 8 (6), 156.
Punj, V., Matta, H., Schamus, S., Tamewitz, A., Anyang, B., Chaudhary, P.M., 2010. Kaposi's sarcoma-associated herpesvirus-encoded viral FLICE inhibitory protein (vFLIP) K13 suppresses CXCR4 expression by upregulating miR-146a. Oncogene 29 (12), 1835–1844.
Qian, K., Pietilä, T., Rönty, M., Michon, F., Frilander, M.J., Ritari, J., Tarkkanen, J., Paulín, L., Auvinen, P., Auvinen, E., 2013. Identification and validation of human papillomavirus encoded microRNAs. PLoS One 8 (7), e70202.
Rodriguez, A., Vigorito, E., Clare, S., Warren, M.V., Couttet, P., Soond, D.R., van Dongen, S., Grocock, R.J., Das, P.P., Miska, E.A., Vetrie, D., 2007. Requirement of bic/microRNA-155 for normal immune function. Science 316 (5824), 608–611.
Sassen, S., Miska, E.A., Caldas, C., 2008. MicroRNA—implications for cancer. Virchows Arch. 452 (1), 1–10.
Schneider, C., Setty, M., Holmes, A.B., Maute, R.L., Leslie, C.S., Mussolin, L., Rosolen, A., Dalla-Favera, R., Basso, K., 2014. MicroRNA 28 controls cell proliferation and is down-regulated in B-cell lymphomas. Proc. Natl. Acad. Sci. 111 (22), 8185–8190.
Shiels, M.S., Islam, J.Y., Rosenberg, P.S., Hall, H.I., Jacobson, E., Engels, E.A., 2018. Projected cancer incidence rates and burden of incident cancer cases in HIV-infected adults in the United States through 2030. Ann. Intern. Med. 168, 866–873.
Shishodia, G., Shukla, S., Srivastava, Y., Masaldan, S., Mehta, S., Bhambhani, S., Sharma, S., Mehrotra, R., Das, B.C., Bharti, A.C., 2015. Alterations in microRNAs miR-21 and let-7a correlate with aberrant STAT3 signaling and downstream effects during cervical carcinogenesis. Mol. Cancer 14 (1), 116.
Skalsky, R.L., Cullen, B.R., 2010. Viruses, microRNAs, and host interactions. Annu. Rev. Microbiol. 64, 123–141.
Sung, J.M., Margolis, D.M., 2018. HIV persistence on antiretroviral therapy and barriers to a cure. HIV Vaccines and Cure. Springer, Singapore, pp. 165–185.
Thai, T.H., Calado, D.P., Casola, S., Ansel, K.M., Xiao, C., Xue, Y., Murphy, A., Frendewey, D., Valenzuela, D., Kutok, J.L., Schmidt-Supprian, M., 2007. Regulation of the germinal center response by microRNA-155. Science 316 (5824), 604–608.
Triboulet, R., Mari, B., Lin, Y.L., Chable-Bessia, C., Bennasser, Y., Lebrigand, K., Cardinaud, B., Maurin, T., Barbry, P., Baillat, V., Reynes, J., 2007. Suppression of microRNA-silencing pathway by HIV-1 during virus replication. Science 315 (5818), 1579–1582.
Tsai, Y.H., Wu, M.F., Wu, Y.H., Chang, S.J., Lin, S.F., Sharp, T.V., Wang, H.W., 2009. 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. 83 (2), 622–632.
Verhoeven, R.J., Tong, S., Zhang, G., Zong, J., Chen, Y., Jin, D.Y., Chen, M.R., Pan, J., Chen, H., 2016. NF-κB signaling regulates expression of Epstein-Barr virus BART microRNAs and long noncoding RNAs in nasopharyngeal carcinoma. J. Virol. JVI-00613.
Volinia, S., Calin, G.A., Liu, C.G., Ambs, S., Cimmino, A., Petrocca, F., Visone, R., Iorio, M., Roldo, C., Ferracin, M., Prueitt, R.L., 2006. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc. Natl. Acad. Sci. 103 (7), 2257–2261.
Wang, X., Tang, S., Le, S.Y., Lu, R., Rader, J.S., Meyers, C., Zheng, Z.M., 2008. Aberrant expression of oncogenic and tumor-suppressive microRNAs in cervical cancer is required for cancer cell growth. PLoS One 3 (7), e2557.
Wang, X., Wang, H.K., McCoy, J.P., Banerjee, N.S., Rader, J.S., Broker, T.R., Meyers, C., Chow, L.T., Zheng, Z.M., 2009. Oncogenic HPV infection interrupts the expression of tumor-suppressive miR-34a through viral oncoprotein E6. Rna 15 (4), 637–647.
Wang, F., Li, Y., Zhou, J., Xu, J., Peng, C., Ye, F., Shen, Y., Lu, W., Wan, X., Xie, X., 2011a. miR-375 is down-regulated in squamous cervical cancer and inhibits cell migration and invasion via targeting transcription factor SP1. Am. J. Pathol. 179 (5), 2580–2588.
Wang, X., Meyers, C., Guo, M., Zheng, Z.M., 2011b. Upregulation of p18Ink4c expression by oncogenic HPV E6 via p53-miR-34a pathway. Int. J. Cancer 129 (6), 1362–1372.
Wang, X., Wang, H.K., Li, Y., Hafner, M., Banerjee, N.S., Tang, S., Briskin, D., Meyers, C., Chow, L.T., Xie, X., Tuschl, T., 2014. microRNAs are biomarkers of oncogenic human papillomavirus infections. Proc. Natl. Acad. Sci. 111 (11), 4262–4267.
Wang, M., Yu, F., Wu, W., Wang, Y., Ding, H., Qian, L., 2018. Epstein-Barr virus-encoded microRNAs as regulators in host immune responses. Int. J. Biol. Sci. 14 (5), 565.
Wu, Y.H., Hu, T.F., Chen, Y.C., Tsai, Y.N., Tsai, Y.H., Cheng, C.C., Wang, H.W., 2011. The manipulation of miRNA-gene regulatory networks by KSHV induces endothelial cell motility. Blood 118 (10), 2896–2905.
Wu, X.J., Pu, X.M., Zhao, Z.F., Zhao, Y.N., Kang, X.J., Wu, W.D., Zou, Y.M., Wu, C.Y., Qu, Y.Y., Zhang, D.Z., Feng, Y.Y., 2015. The expression profiles of microRNAs in Kaposi's sarcoma. Tumor Biol. 36 (1), 437–446.
Xia, Y.-F., Pei, G.-H., Wang, N., Che, Y.-C., Yu, F.-S., Yin, F.-F., Liu, H.-X., luo, B., Wang, Y.-K., 2017. miR-3156-3p is downregulated in HPV-positive cervical cancer and performs as a tumor-suppressive miRNA. Virol. J. 14 (20). https://doi.org/10.1186/s12985-017-0695-7.
Xu, W., Santini, P.A., Sullivan, J.S., He, B., Shan, M., Ball, S.C., Dyer, W.B., Ketas, T.J.,

Chadburn, A., Cohen-Gould, L., Knowles, D.M., 2009. HIV-1 evades virus-specific IgG2 and IgA responses by targeting systemic and intestinal B cells via long-range intercellular conduits. Nat. Immunol. 10 (9), 1008–1017.

Xue, M., Yao, S., Hu, M., Li, W., Hao, T., Zhou, F., Zhu, X., Lu, H., Qin, D., Yan, Q., Zhu, J., 2014. HIV-1 Nef and KSHV oncogene K1 synergistically promote angiogenesis by inducing cellular miR-718 to regulate the PTEN/AKT/mTOR signaling pathway. Nucleic Acids Res. gku583.

Yan, Q., Shen, C., Qin, J., Li, W., Hu, M., Lu, H., Qin, D., Zhu, J., Gao, S.J., Lu, C., 2016. HIV-1 vpr inhibits Kaposi's sarcoma-associated herpesvirus lytic replication by inducing MiR-942-5p and activating NF-κB signaling. J. Virol. 90 (19), 8739–8753.

Yao, S., Hu, M., Hao, T., Li, W., Xue, X., Xue, M., Zhu, X., Zhou, F., Qin, D., Yan, Q., Zhu, J., 2015. MiRNA-891a-5p mediates HIV-1 Tat and KSHV Orf-K1 synergistic induction of angiogenesis by activating NF-κB signaling. Nucleic Acids Res. 43 (19), 9362–9378.

Yin, Q., McBride, J., Fewell, C., Lacey, M., Wang, X., Lin, Z., Cameron, J., Flemington, E.K., 2008. MicroRNA-155 is an Epstein-Barr virus-induced gene that modulates Epstein-Barr virus-regulated gene expression pathways. J. Virol. 82 (11), 5295–5306.

Zhou, P., Xu, W., Peng, X., Luo, Z., Xing, Q., Chen, X., Hou, C., Liang, W., Zhou, J., Wu, X., Songyang, Z., 2013a. Large-scale screens of miRNA-mRNA interactions unveiled that the 3′ UTR of a gene is targeted by multiple miRNAs. PLoS One 8 (7), e68204.

Zhou, F., Xue, M., Qin, D., Zhu, X., Wang, C., Zhu, J., Hao, T., Cheng, L., Chen, X., Bai, Z., Feng, N., 2013b. HIV-1 Tat promotes Kaposi's sarcoma-associated herpesvirus (KSHV) vIL-6-induced angiogenesis and tumorigenesis by regulating PI3K/PTEN/AKT/GSK-3β signaling pathway. PLoS One 8 (1), e53145.