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Chapter 3

Viral and Cellular MicroRNAs in Regulation of EBV Latency and Oncogenesis

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Abstract

Epstein-Barr virus (EBV), an oncogenic virus that ubiquitously establishes life-long persistence in humans, encodes viral miRNAs in two clusters, BHRF1 and BART. EBV also regulates expression of a large pool of cellular miRNAs, including miR-155, miR-146a, miR-21, miR-29, and miR-34a. These miRNAs targets both viral and cellular genes involved in the entire viral lifetime from lytic infection to oncogenesis, including viral replication, immune responses, cell cycle regulation, apoptosis, and cell proliferation, and are indispensable for persistent infection, latency establishment and maintenance, and cancer development. Among them, circulating miRNAs and unique miRNA profiles are promising diagnosis and prognosis biomarkers alone or with other traditional biomarkers. Elucidation of the precise mechanisms of action of these miRNAs in EBV latent infection will improve our knowlege of EBV persistence and oncogenesis, and may foster new strategies to target these miRNAs for treatments of EBV-associated cancers.

Introduction

microRNAs (miRNAs) have been the focus in the last decade because they represent a new category of regulators in "fine-tuning" gene expression at post-transcriptional level in a broad spectrum of biological processes including cell activation, proliferation and differentiation,

immune responses, tumorigenesis, and maintenance of homeostasis during viral infection or stress [1-8]. The human genome encodes approximately 2,000 miRNAs (according to miRBase). Many viruses have been discovered to encode viral miRNAs, with more than 500 identified by far [9-12]. Rhesus lymphocryptovirus (rLCV), the rhesus monkey gammaherpesvirus closely related to human Epstein-Barr virus (EBV), encodes the most viral miRNAs among all examined viruses, with at least 68 mature miRNAs [10,13]. The herpesvirus family of DNA viruses encode at least half of all known viral miRNAs [10,14], a large portion of which are encoded by the two oncogenic herpesviruses EBV and KSHV [7,15,16]. It is of note that viral miRNAs from the herpersvirus family has share little sequence conservation except a few. They also have a large range of distinct targets in different host cells for similar functional outcomes [17].

In host-virus interaction, a pool of viral and cellular miRNAs are invoked, and their aberrant expression is hallmark of diseases caused by viral infection [6,8-10,18,19]. Among cellular miRNAs, miR-155, miR-146a, miR-21, miR-29a, miR-125b, miR-17/92, and miR-181 are commonly deregulated by oncogenic viruses. These viral and cellular miRNAs have profound impacts on persistent infection and virus-mediated oncogenesis [10,16,20]. They not only regulate viral replication and shape the immune response to infection, but also contribute to the establishment of persistent or latent infection, and to virus-mediated oncogenesis [7,12,17,20,21].

EBV-Encoded Viral miRNAs

EBV encodes the first and the largest number of viral miRNAs in all human oncogenic viruses, with a total of 25 precursor and 49 mature miRNAs discovered by now (Table 1) [22-24], in two genomic clusters, BHRF1 and BART, except miR-BART2-5p and -3p that are transcribed from antisense orientation to the 3'-UTR of the gene encoding BALF5 DNA polymerase (Figure 1) [14]. Both BART and BHRF1 miRNAs targets multiple pathways that control cellular functions to favor EBV infection, persistence, and oncogenesis (Figure 2) [23,25].

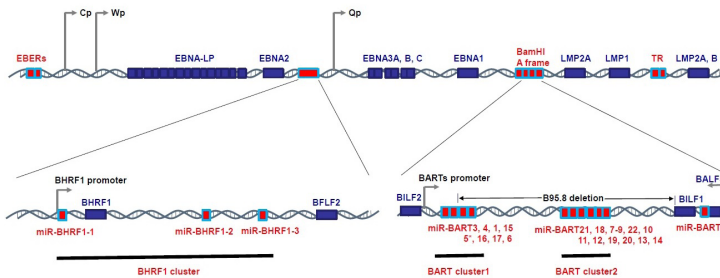

Figure 1: EBV Genomic Organization for Viral miRNAs. Genomic structure for BART and BHRF1 miRNAs and latency proteins are shown [14]. BHRF1 miRNAs are derived from the BHRF1 transcript. BART miRNAs are produced from different introns derived fro6m a large transcript spanning 138081 to 160531 of EBV genome. Region for the two miRNA clusters, BHRF1 and BART, are shown in details at bottom.

Table 1: EBV-encoded viral miRNAs and their targets.

Viral miRNA	**Cellular Functional Orthologue**	**Verified Cellular Targets**	**Verified Viral Targets**	**References**
BART cluster 2		NDRG1		[116]
BART1		BIM, pTEN, G6PD, SAT1, IL12B, IFI30, LGMN, CTSB	LMP1	[27, 39, 44, 117]
BART1-3p	miR-29a/b/c	CASP3, IPO7, TP53INP1, IL1RAP, NFAT5		[51, 110]
BART1-5p		TNFSF4	LMP1	[117-118]
BART2, -5p		MICB, MASPIN, IL12B, IFI30, LGMN, CTSB, VHL, p15, TNFSF4, NFAT5	BALF5	[26-27, 49, 118]
BART3		Dicer, FEM1B, IPO7, CASZ1a	LMP1, EBNA2	[51, 117, 119-120]
BART4, -5p		Bid, TP53INP1, SOCS3, IL1RAP		[118, 121]
BART5		PUMA, ATM	LMP1	[117-118, 122]
BART5-5p	miR-18a/b miR-17-5p		LMP1	[35, 117, 123]
BART6-5p, -3p		Dicer, OCT1, IL6R LOC553103(ln-cRNA)	EBNA2, Zta, Rta	[44, 47, 120, 124-125]
BART7		WIF1, pTEN, c-Myc, c-Jun, E-Cadherin, APC		[44, 118, 121, 126]
BART8		ARID2		[120]
BART9		E-Cadherin, pTEN, Bim, HIPK2, CXCL12	LMP1	[127-129]
BART10, BART10-3p	miR-17-5p miR-142-3p	BTRC, Bcl2L11, NLK, NFAT5, CXCL12, APC	BHRF1	[35, 118, 123]
BART11, -5p		EBF1, Bim, FOXP1, HIPK2, NFAT5	EBNA2	[35, 118, 128, 130]
BART12		Bim		[128]
BART13, -3p	miR-17-5p	CAPRIN2, WIF1		[35]
BART14		Bcl2L11, RBL2, NLK, PTPRC		[118]
BART15		BRUCE, TAX1BP1, NLRP3, NFAT5		[131-133]
BART16		TOMM22, CASP3, IPO7, CREBBP, SH2B3, CBP, NFAT5	LMP1	[48, 51, 117, 120, 134]
BART16-5p	miR-17-5p	CAPRIN2		[35]
BART17, -5p		WIF1, BCLAF1, APC, TAP2, TNFSF4	LMP1	[28, 35, 117]
BART-18-5p		MAP3K2, pTEN, TP53INP1, BclAF1, p57, HIPK2, NLK, SOCS3		[118, 135]
BART19-3p		WIF1, APC, TP53INP1, BclAF1, p21, HIPK2, NLK, SOCS3, IL1RAP, CXCL12, NFAT5		[118]
BART19-5p	miR-17-5p		LMP1	[35, 117]
BART20		BAD	LMP1, EBNA2, Zta, Rta	[35, 50, 123, 136-137]
BART22		MAP3K5, PPP3R1, PAK2, TP53INP1	LMP2A	[120, 138-139]
BART22-3p				[140]
BHRF1, -2, -2*, -3		CXCL11, RNF4, IL12B, TAP2, IFI30, GILT, LGMN, CTSB, PRDM1/Blimp1, pTEN, p27, p53, UBR1, CREBBP, USP3, SCRN1, GUF1, HIPK2, NFAT5	EBNA2, LMP1, BHRF1	[25, 27-28, 33-35, 37, 117-118, 141-142]

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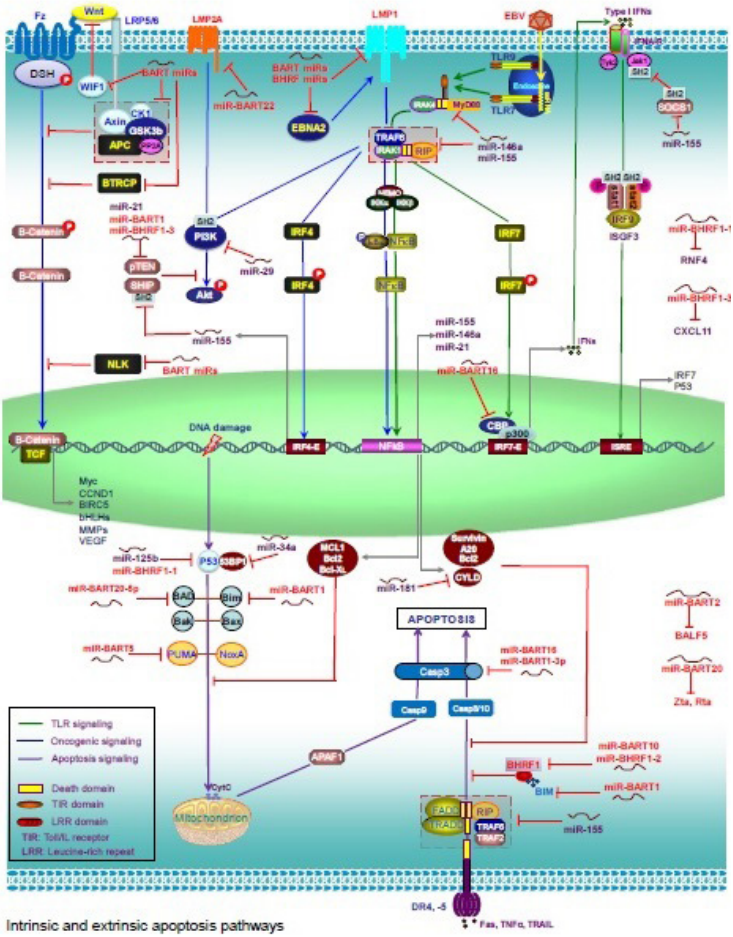
Herpesviridae

Oncogenic and immune pathways



Intrinsic and extrinsic apoptosis pathways

Figure 2: Viral and Cellular miRNAs in EBV Latency and Oncogenesis.

EBV encodes BHRF1 and BART miRNAs. BART miRNAs are enriched in Type II latency that is associated with epithelial carcinomas. BART miRNAs positively regulate Wnt signaling by targeting WIF1, BTRCP, NLK, GSK3β and APC. They also inhibit apoptosis by targeting the mRNAs encoding Caspase-3, and the Bcl-2 family members Bim, BAD, and PUMA. BART miRNAs also target viral transcripts including LMP1, EBNA2, BHRF1, Zta, Rta, and BALF5, and therefore play important roles in limiting EBV lytic replication, maintaining EBV latency, and promoting oncogenesis. BHRF miRNAs are exclusively enriched in Type III latency, and implicated in AIDS-related lymphomas, by taregting a pool of increasingly identified cellular and viral transcripts.

EBV latent infection also regulates expression of a large panel of cellular miRNAs. Specifically, EBV LMP1 signaling pathway induces miR-155, miR-146a, miR-21, amongst other miRNAs, which play important roles in EBV immune evasion, latency maintenance, and oncogenesis, by targeting multiple components in LMP1, TLR, Jak-STAT, and apoptosis pathways.

Cellular miRNAs are indicated in purple fonts, and EBV miRNAs and EBV products are indicated in red fonts.

Of note, both BART and BHRF1 miRNAs target the key EBV oncogene, LMP1, and its inducer EBNA2. Importantly, both BART and BHRF1 miRNAs play important roles in EBV escape of NK cell innate recognization by targeting MICB [26], and in EBV evasion of T cell-mediated adaptive immune responses by interfering with multiple processes, including inhibition of production and release of proinflammatory cytokines such as IL12b and inhibition of antigen presentation by targeting TAP2,

IPO7, GILT and LGMN, amongst others [27-28]. The EBV antigen EBNA1, that has the ability to prevent processing and presentation of its epitopes on MHC class I molecules, is reduced at protein level by EBV miRNAs [28]. EBV miRNAs also control adaptive immune responses by targeting LMP1, which regulates multiple chemokines and cytokines involved in adaptive immunity [17].

BHRF1 miRNAs

BHRF1 miRNAs, including BHRF1-1, -2, -2* and -3, are produced from a transcript that encodes the BHRF1 lytic protein (Figure 1). They are highly and exclusively expressed in B lymphoma cells with EBV Type III latency, and likely stimulate cell cycle progress, repress apoptosis, and promote survival of B cells [29-31]. Specifically, the cluster BHRF1-3 miRNA has potent ability to promote EBV-mediated B cell transformation [31-32], at least by targeting pTEN, p27 and a Bcl-2 homolog [33]. BHRF1 miRNAs have also been implicated in preventing apoptosis during infection of cultured primary B cells [30], and high throughput screens have identified a pool of BHRF1 miRNA targets including GUF1, NAT12, and SCRN1[34]. Both BHRF and BART miRNAs target viral transcripts, including BHRF1, LMP1 and EBNA2, which should be of notable implications in AIDS-related lymphomas [35]. However, a study with mouse models has suggested that BHRF miRNAs did not contribute to EBV oncogenesis [36].

Since the sequences encoding BHRF1 miRNAs are located in the 3'-UTR of the gene encoding the lytic protein BHRF1, BHRF1 miRNAs are expressed in lytic cycle and implicated in EBV reactivation and immune evasion. In fact, miR-BHRF1-3 may contribute to EBV evasion of IFN-mediated immune response by targeting the IFN-inducible chemokine CXCL11[38]. A recent report shows that miR-BHRF1-1 targets RNF4 during lytic infection and promotes virus production [37].

BART miRNAs

In contrast to BHRF miRNAs, BART miRNAs are more abundantly expressed in epithelial cells with Type II latency, although their expression is detectable in all EBV-associated tumors [29,39-41]. Therefore, BART miRNAs are closely associated with the pathogenesis of nasopharyngeal carcinoma (NPC) and gastric carcinoma [39,42-44]. Their expression is at least induced by LMP1/NFκB signaling pathway, and also likely by AP1 and EBV BZLF1/NFκB pathway [41,45]. BART miRNAs may have evolved from the human miR-17/92 cluster, and they co-target hundreds of cellular mRNA 3'-UTRs [35].

Since BART miRNAs are induced by EBV immediate-early transcription factor BZLF1, they are involved in immune evasion during lytic infection and in EBV reactivation [46]. BART miRNAs are also involved in immune evasion in latency. miR-BART6-3p, along with the cellular miR-197, has been shown recently to suppress host im-

mune response by targeting IL6R [47]. miR-BART16 inhibits type I IFN production in EBV-transformed B cells by targeting CREB-Binding Protein (CBP) [48], a crucial transcriptional coactivator of the type I IFN genes. In contrast to most herpesvirus viral miRNAs that mainly regulate lytic transcripts to reinforce latent infection, EBV miRNAs rarely target its own lytic transcripts. Exceptions include miR-BART2 that inhibits lytic replication by targeting the lytic transcript of BALF5 for degradation [49], and miR-BART6 and miR-BART20 that target RTA and Zta, two crucial factors for lytic replication (Table 1) [44,50].

BART miRNAs promote WNT signaling pathway by extensively targeting key Wnt inhibitors such as Wnt-inhibiting factor 1 (WIF1), GSK3B, Adenomatous Polyposis Coli (APC, known as PPP1R46), Beta-Transducin Repeat Containing Protein (BTRCP) that encodes an E3 ubiquitin ligase targeting β-catenin for degradation, and NEMO-Like Kinase (NLK) that interferes with β-catenin/TCF/LEF binding [39,43] (Figure 2). They inhibit apoptosis by targeting Caspase-3 and the Bcl-2 family, and thus may contribute to the maintenance of Burkitt's lymphoma [51].

Although BART miRNAs are also implicated in EBV-mediated B-cell lymphoma, they are dispensable for B-cell transformation as most of them (BART5, -16, -17, and -6 in BART cluster 1 and the entire BART cluster 2) do not exist in the common EBV strain B95-8 (Figure 1), which, however, is still able to immortalize primary B cells in cul-

ture, suggesting that their functions are complemented by cellular miRNA orthologues [9,35,52]. A recent report indicates that BART miRNAs can promote tumor growth in mice, although they are not required for the growth of EBV-infected cells in cell culture [53].

EBV-Regulated Cellular miRNAs

EBV infection has a global impact on cellular miRNA expression in B lymphocytes and epithelial cells [34,54-56]. Specifically, EBV LMP1 induces expression of miR-155 [57-59], miR-146a [60-61], miR-29b [62], miR-21[63-65], miR-10b [66] and miR-34a [67], through NFκB and/or AP1 signaling axes, but downregulates miR-183-96-182 cluster through Akt activity [68]. These cellular miRNAs play crucial roles in oncogenesis, and some oncogenic viruses encode their viral orthologs. For example, KSHV [69-70] and Marek's disease virus [71], encode functional orthologs of miR-155. EBV, instead, has evolved to develop sophisticated strategies to regulate their expression so as to minimize the total numbers of its products. For some other cellular crucial miRNAs in oncogenesis, including miR-29 and the miR-17/92 cluster, EBV BART miRNAs are their functional orthologs.

miR-155

miR-155 is encoded by a single gene called B-cell integration cluster (BIC). miR-155 plays important roles in innate immunity [5,72], and is the first identified oncogenic miRNA (oncomiR) that is implicated in various types of

cancers. miR-155 preferentially targets SHIP1 in immune responses [73], and likely in different cancers, as shown by us and others [74-76]. Targeted expression of miR-155 alone in B cells results in the development of B cell malignancies in transgenic mice [77], in addition to an elevated level of serum TNFα and increased susceptibility to septic shock [78]; whereas targeted expression in mouse bone marrow cells causes myeloid neoplasia [79]. The importance of miR-155 in cancer is also highlighted by the fact that at least two oncogenic herpesviruses, KSHV [69-70] and Marek's disease virus (MDV) [71], encode functional orthologs of miR-155.

EBV does not encode miR-155 ortholog; instead, miR-155 is induced by LMP1 through NFκB and AP1 and also through IRF4 as shown by us [74]. In addition, miR-155 is also induced by LMP2A [80]. miR-155 induction in EBV latency not only stabilizes latency status [81], but also likely contributes to EBV oncogenesis by targeting SHIP [74].

miR-146a

Like miR-155, miR-146a is also encoded by a single gene, and its expression can also be induced by NFκB downstream of TNFα, IL1β, and TLR signaling pathways in immune responses [8]. In turn, miR-146a targets IRAK1, IRAK2, and TRAF6, components critical for these signaling pathways, and therefore controls these pathways through a negative feedback regulatory loop [82].

miR-146a overexpression has been found in papillary thyroid carcinoma and cervical cancer, but acts as a tumor suppressor in hormone-refractory prostate carcinoma by targeting ROCK1 that is a kinase critical for hormone-refractory prostate carcinoma cell transformation [83], and also is a potential tumor suppressor in pancreatic cancer [84]. miR-146a-deficient mice develop many of the same abnormal hematopoietic phenotypes described in a subset of myelodysplastic syndrome (MDS) patients who have the deletion of a region containing the miR-146a gene. Knockdown of miR-146a in mouse hematopoietic stem/progenitor cells can recapitulate many of these abnormalities [85]. Although it has been reported that miR-146a is also induced by LMP1 [60-61,86], and downregulated by EBNA2 independently of LMP1[86] , its precise role in EBV oncogenesis is unclear. It may be involved in innate immune evasion by targeting IRAK1 and TRAF6, two crucial mediators of innate immune signaling pathways.

miR-21

Like miR-155 and miR-146a, miR-21 plays important roles in innate and adaptive immune responses. It is induced by NFκB and STAT3 downstream of TLR signaling [87], IL6 [88], and TGFβ [89], as well as upregulated in autoimmune diseases such as multiple sclerosis [90]. miR-21 is also induced by type I IFNs [91], and in turn, inhibits IFN production by targeting IRAK1 and MyD88 during HCV infection [92]. PDCD4, an important player in inflammatory responses, is a direct target for miR-21 in macrophages [87].

miR-21 is the only oncogenic miRNA overexpressed in most tumor types tested so far, and is deemed a cancer biomarker [93]. Interestingly, like miR-155 and miR-146a, miR-21 is upregulated by NFκB in EBV- and HTLV1-transformed cells [64,94]. Mature miR-21 is also induced by EBNA2, probably through post-transcritpional processing, and thus may contribute to EBNA2-mediated B cell transformation [86]. Targeted expression of miR-21 in mouse hematopoietic compartment induces pre-B cell lymphoma. In contrast, loss of miR-21 results in massive apoptosis, complete tumor regression and a 100% survival rate [95]. pTEN is a key target for miR-21 in cancer [95-98]. Targeting pTEN by miR-21 results in elevated Akt and NFκB activation [99]. In addition, miR-21 plays its oncogenic role by targeting TPM1 (tumor suppressor protein tropomyosin 1) [100] and Wnt1[101] , amongst others [99].

miR-29

The miR-29 family includes miR-29a, -b, and c. They can function as either oncomiRs or tumor suppressors, depending on the contexts [102]. miR-29 also suppresses HIV replication by targeting Nef [103]. As a tumor suppressor, miR-29 can induce p53-mediated apoptosis by targeting p85α, which is a subunit of PI3K for Akt activation. Activated Akt targets MDM2 for degradation and then p53 is activated [104] . miR-29 is overexpressed in chronic lymphocytic leukemias (CLLs), resembling to bovine leukemia virus (BLV)-associated tumors in phe-

notype in that BLV encodes a miR-29 ortholog miR-B4 [105]. When overexpressed in mouse B cells, miR-29 causes CLL-like B lymphoma [106].

In the setting of EBV latency, LMP1 induces expression of miR-29b that targets the oncogene TCL1, and therefore likely functions as a tumor suppressor [62]. In addition to induce miR-29b expression, EBV miR-BART1-3p, together with rLCV miR-rL1-6-3p and MDV2 miR-M21, are encoded with miR-29 seeds [10].

miRNAs as Biomarkers and Therapeutic Targets of EBV-Associated Cancers

miRNAs are promising cancer biomarkers because of their significantly aberrant expression, the lack of complex modifications compared to mRNAs and proteins, and their presence as circulating miRNAs in body fluid [107]. It is notable that, however, some viral and cellular miRNAs have different expression levels between EBV-associated tumors and cell culture, and between precursors and mature miRNAs through transcriptional or post-transcriptional mechanisms [53,108-110]. A single miRNA can serve as a cancer biomarker itself or in combination with other miRNAs and traditional biomarkers. In this light, a unique miRNA expression pattern may be used as biomarker for a given disease.

As to EBV, circulating EBV miR-BART7 and miR-BART13 are overexpressed in NPC patients and down-

regulated after radiotherapy, and therefore they may be useful for diagnosis of NPC and prediction of treatment efficacy [111]. Circulating miR-BART17-5p, combined with BamHI-W DNA, may serve as post-treatment biomarkers for NPC [112]. Overexpression of miR-BART20-5p is associated with poor prognosis of EBV+ gastric cancer [113]. Except these viral miRNAs, the cellular miRNA, miR-10a-5p, has been identified as a predictive biomarker for EBV-associated endemic Burkitt's lymphoma [114].

In terms of miRNA therapeutic applications, understanding their exact roles in, and their biological relevance to, a given disease setting is the base for developing therapeutic strategies. The cellular miR-122 is the only one so far that is being clinically used to hinder HCV replication [115]. The lack of conservation of herpesvirus miRNA sequences and their distinct tagets in different cells raise difficulties for researchers to study their functional relavance. Nevertheless, promising progresses have also been made on some miRNAs in regard to their applications to treat NPC in combination with traditional strategies, including miR-1, miR-29c, miR-34a, amongst others [55].

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