Chapter 19
Roles of Epstein–Barr Virus Micro RNAs in Epstein–Barr Virus-Associated Malignancies

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Abstract Epstein–Barr virus (EBV) is an oncogenic human γ-herpes virus that causes various cancers such as Burkitt's lymphoma, Hodgkin's lymphoma, diffuse large B-cell lymphoma (DLBCL), gastric cancer, and nasopharyngeal carcinoma, one of the most common cancers in China.

miRNAs are small noncoding RNAs approximately 22 nucleotides long that posttranscriptionally regulate deadenylation, translation, and decay of their target messenger RNAs (mRNAs). The first viral miRNAs were discovered in human B-cells latently infected with EBV. EBV encodes at least 44 miRNAs. Forty of these miRNAs are transcribed from the BamH1 fragment A rightward transcript (*BART*) region. Several groups reported that EBV-encoded miRNAs target proapoptotic genes, preventing cells from entering the lytic phase. In this review, I discuss several recent findings centered on EBV-encoded miRNAs. In addition, I highlight the fact that small RNAs play important roles in inflammation.

Keywords EBV • miRNA • BART cluster • *BHRF1* • Lymphoma • Cancer

19.1 Introduction

Epstein–Barr virus (EBV) was discovered by examination of electron micrographs of cells isolated from Burkitt's lymphoma, a pediatric tumour common in sub-Saharan Africa, where its unusual geographic distribution indicated a viral etiology. EBV, which belongs to the γ-herpes virus family, has widespread distribution among humans and results in persistent asymptomatic infection of B cells.

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EBV usually results in clinically asymptomatic infections but may also cause infectious mononucleosis. In rare cases, EBV infection induces malignant transformation and development of cancers such as Burkitt's lymphoma, gastric carcinoma, and nasopharyngeal carcinoma (NPC), one of the most common cancers in China (Fang et al. 2008). In addition, EBV causes several lymphoid malignancies, including acquired immunodeficiency syndrome (AIDS)-associated lymphoma, Hodgkin's lymphoma, posttransplant lymphoma, age-associated B-cell lymphoma, and peripheral T- and NK-cell lymphomas (Parkin et al. 2005; Parkin 2006).

The primary site of EBV infection is the oropharyngeal cavity (Borza and Hutt-Fletcher 2002). EBV infection induces two distinct patterns of gene expression. During acute (lytic) EBV infection, the virus expresses all its genes sequentially. Linear, double-stranded viral genomes produced during the lytic state are packaged into virions. Shortly after the initial infection, EBV enters into a latent state and expresses only select 'latent' genes, which allows the virus to evade immune surveillance mechanisms of the host and establish a lifelong persistent infection (Ghosh et al. 2007). Serology analyses indicate that approximately 95 % adults worldwide are infected with EBV. After the primary infection, hosts remain lifelong carriers of the virus (Thorley-Lawson 2001).

19.2 EBV Micro-RNAs

19.2.1 Micro-RNAs

Micro-RNAs (miRNAs) are small, noncoding, single-stranded RNAs approximately 21–25 nucleotides in length. They posttranscriptionally regulate mRNA expression and are transcribed from the noncoding regions of genes in all multicellular organisms and in certain viruses (Wang et al. 2008; Chen and Rajewsky 2007). EBV was the first human virus found to encode miRNAs (Pfeffer et al. 2004). EBV encodes 44 miRNAs and a small RNA. EBV miRNAs are encoded by regions located within the *BHRF1* and BamHI-A rightward transcript (*BART*) loci of the EBV genome. The *BHRF1* cluster of miRNAs includes BHRF1-1, BHRF1-2, BHRF1-3, and BHRF1-4 (Chen and Rajewsky 2007; Pfeffer et al. 2004; Grundhoff et al. 2006). The remaining EBV miRNAs, except miR-BART2, are encoded by *BART* clusters 1 and 2. MiR-BART2 is encoded by a region outside the *BART* clusters (Chen and Rajewsky 2007; Pfeffer et al. 2004; Grundhoff et al. 2006; Griffiths-Jones et al. 2006). MiRNAs bind to the 3′ untranslated region (UTR) of mRNAs and interfere with their translation, thus downregulating protein expression. EBV miRNAs have been isolated from various EBV-associated carcinomas and lymphomas such as NPC, gastric carcinoma, diffuse large B-cell lymphoma, nasal T- and NK-cell lymphomas, and Hodgkin's lymphoma (Pfeffer et al. 2004; do Kim et al. 2007). Viral miRNAs play vital roles in immunogenesis, survival and proliferation of host cells, differentiation, lymphomagenesis, and regulation of viral infection and latency (Table 19.1) (Pfeffer et al. 2004; Rana 2007; Xia et al. 2008; Barth et al. 2011; Lu et al. 2012).

Table 19.1 Summary of EBV coding miRNAs

	Function	Target viral	Host target	Cluster
BLHF1-1	Transformation	BFLF2	LILRB-5,E2F1,p53, CBFA2T2	BHRF1
BLHF1-2	Transformation	BFLF2	PIK3R1	BHRF1
BLHF1-3	Transformation	BFLF2	CXCL11,PRF1,TGIF, NSEP1	BHRF1
BART1-5p	Cancer development	LMP1	CXCL12	BART Cluster1
BART2-5p	Viral replication	BALF5, LMP1	MIC B, Bim	
BART3		LMP1	IPO7, Bim	BART Cluster1
BART4		LMP1	Bim	BART Cluster1
BART5	Host cell survival	LMP1	PUMA, Bim	BART Cluster1
BART6	Maintain viral latency	EBNA2,LMP1, Rta,Zta	Dicer, Bim	BART Cluster1
BART7	EMT induction	LMP1	PTEN, Bim	BART Cluster2
BART8				BART Cluster2
BART9				BART Cluster2
BART10				BART Cluster2
BART11				BART Cluster2
BART12				BART Cluster2
BART13				BART Cluster2
BART14				BART Cluster2
BART15				BART Cluster1
BART16	Cancer development	LMP1	TOMM22	BART Cluster1
BART17	Cancer development	LMP1		BART Cluster1
BART18				BART Cluster2
BART19				BART Cluster2
BART20				BART Cluster2

(continued)

Table 19.1 (continued)

	Function	Target viral	Host target	Cluster
BART21				BART Cluster2
BART22		LMP2		BART Cluster2

19.2.2 Functions of EBV miRNAs

EBV miR-BART2 expression is low during latency. It prevents aberrant expression of *BALF5* mRNA, which is essential for viral DNA replication during lytic infection (Barth et al. 2008), The sequence of miR-BART2 is perfectly complementary to the 3′ UTR of *BALF5* mRNA. Thus, miR-BART2 inhibits viral DNA replication by degrading *BALF5* mRNA. MiRNA-guided cleavage of mRNAs requires association with AGO2 (Meister et al. 2004), a member of the Argonaute family of proteins and a component of RNA-induced silencing complex (RISC). MiR-BART2 associates with AGO2 and guides the sequence-specific cleavage of *BALF5* mRNA. MiR-BART2-guided cleavage of *BALF5* mRNA substantially decreases after induction of the lytic cycle in EBV-infected cells (Barth et al. 2008). The amount of miR-BART2 is reduced during lytic infection, which in turn derepresses BALF5 expression (Barth et al. 2008). However, it is unclear whether miR-BART2-mediated regulation of viral replication is completely controlled by BALF5.

MiR-BART6, which is regulated by RNA editing, is another regulator of the shift from latent EBV infection to lytic infection (Iizasa et al. 2010). Editing of wild-type primary (pre)-miR-BART6 dramatically decreases loading of miR-BART6-5p onto RISC without affecting the processing of precursor or mature miRNAs (Iizasa et al. 2010). Editing of pre-miRNA might affect selection and loading of the guide strand onto RISC (Khvorova et al. 2003). MiR-BART6-5p silences *DICER* by binding to multiple target sites in the 3′ UTR of *Dicer* mRNA. In contrast, miR-BART6-3p is unable to perform this function (Iizasa et al. 2010).

MiR-BART5 promotes host cell survival by regulating p53-upregulated modulator of apoptosis (PUMA) (Choy et al. 2008). PUMA is an apoptotic protein belonging to the BH3-only group of the Bcl-2 family of proteins and is encoded by *BBC3* (Han et al. 2001; Nakano and Vousden 2001; Yu et al. 2001). The 3′ UTR of *BBC3* is perfectly complementary to miR-BART5, and binding of miR-BART5 to this region suppresses PUMA expression.

Abundant expression of miR-BART5 significantly downregulates PUMA expression in 60 % of NPC tissues (Choy et al. 2008). BART5 uses this mechanism to promote survival of NPC cells, EBV-infected gastric carcinoma cells, and

EBV-infected epithelial cells (Choy et al. 2008). Therefore, miR-BART5 may be a good target for anticancer therapy in EBV-infected cancer cells.

LMP1 is a viral protein expressed during type III latent EBV infections (Hislop et al. 2007; Pagano et al. 2004). LMP1 promotes cell growth and B-cell transformation, resists serum deprivation-induced apoptosis, and induces phenotypic changes in epithelial cells. *BART1* cluster miRNAs negatively regulate LMP1 expression and limit its inappropriately high levels, thereby preventing apoptosis induced by LMP1-mediated changes in UPR. *BART1* cluster miRNAs, namely miR-BART16, miR-BART17-5p, and miR-BART1-5p, are recognized by target sites in the 3′ UTR of the mRNA expressing *LMP1* (Lo et al. 2007). These miRNAs regulate LMP1 expression at the posttranscriptional level.

BHRF1 is a latent protein expressed in growth-transformed cells that contributes to virus-associated lymphomagenesis (Kelly et al. 2009). MiR-BHRF1 downregulates BHRF1 expression, modulates cell transformation (Seto et al. 2010), and promotes B-cell proliferation following EBV infection. EBV-infected B cells lacking miR-BHRF1 progress into the cell cycle less efficiently and eventually die through apoptosis (Seto et al. 2010). MiR-BHRF1 is constitutively expressed in LCLs (Seto et al. 2010). The proportion of G1/G0 cells increases whereas that of S-phase cells decreases in the absence of miR-BHRF1 (Seto et al. 2010), indicating its key role in controlling proliferation of latently-infected cells. EBV-mediated differentiation of resting B cells into active B cells requires time. MiR-BHRF1 acts at the stage of the EBV life cycle during which multiple EBV oncogenes are activated.

EBV miR-BART7-3p enhances cell migration and invasion in vitro and cancer metastasis in vivo. EMT is characterized by the loss of epithelial markers and gain of mesenchymal features in NPC cells. Mechanistic studies indicate that EBV miR-BART7-3p targets PTEN, a major human tumour suppressor, and modulates PI3K/Akt/GSK-3β signalling, thus upregulating the expression and nuclear accumulation of Snail and β-catenin, which favor EMT (Lu et al. 2012; Cai et al. 2015).

19.3 EBV-Encoded Secretory miRNAs

19.3.1 Secretory miRNAs

Cellular and viral miRNAs control gene expression by repressing the translation of mRNAs into proteins, a process that is tightly regulated in healthy cells but that is deregulated in cancerous and virus-infected cells. Interestingly, miRNAs are not strictly intracellular; they are found in peripheral blood and are secreted into the culture media in small vesicles called exosomes (Kosaka et al. 2010). It has been suggested that exosome-associated miRNAs play important roles in intercellular communication (Kosaka et al. 2010); however, experimental evidence supporting

this is not enough. Moreover, the dynamics and mechanism of miRNA secretion by exosomes are poorly understood. It is unclear whether miRNAs are secreted in physiologically relevant amounts and whether exogenous exosome-associated miRNAs can access the molecular machinery to undergo processing.

19.3.2 EBV-Encoded Secretory miRNAs

Pegtel et al. were the first to show that exosomes deliver viral miRNAs to noninfected cells (Pegtel et al. 2010). They used EBV B95.8-immortalised LCLs and showed that exosomes containing *BHRF1* cluster miRNAs targeted *CXCL11* mRNA in nearby uninfected cells. Furthermore, they showed that non-B cells obtained from EBV-infected patients with elevated viral loads contained EBV miRNAs, suggesting that exosomes transferred miRNAs to uninfected cells in vivo. These findings were confirmed by two studies reporting the release of exosomes from NPC cells. Gourzones et al. detected EBV miR-BART-containing exosomes in serum samples from patients with NPC and from mice xenografted with human NPC cells (Lu et al. 2012; Gourzones et al. 2010).

19.4 EBV miRNAs Regulate Inflammation and Immune Evasion

19.4.1 Inflammation and Oncogenesis

The potential of chronic inflammation to lead to oncogenesis has been established in malignancies. Chronic hepatitis caused by HCV can develop into hepatocarcinoma, autoimmune-mediated chronic colitis, colon cancer, *Helicobacter pilori*-induced chronic gastritis, and gastric cancer. These transitions require molecular and cellular interactions involving immune and nonimmune cells, cytokines, pathogens, and other factors (Grivennikov 2013; Shlomai et al. 2014).

Deficiency of proinflammatory cytokines such as TNF-alpha limits inflammation and suppresses oncogenesis in several models. Conversely, genetic deletion of immunosuppressive cytokines such as IL-10, and TGF-beta exacerbate inflammation and facilitate oncogenesis (Rickinson 2014). The mechanisms underlying inflammation-mediated regulation of oncogenesis have not been fully elucidated, but several studies are currently addressing this issue. Proinflammatory cytokines cause oxidative stress and production of reactive oxygen species (ROS) that induce DNA damage such as double strand breaks (DSB), and genomic instability (Lemercier 2015; Anuranjani 2014). Genomic instability can also be induced by active mutagenesis caused by activation-induced cytidine deaminase (AID). The

minimal promoter of the gene encoding AID is controlled by NF-kB and gene expression is induced by several proinflammatory cytokines such as TNF-alpha (Okazaki et al. 2007). AID was originally discovered in the year 2000 as an essential component of the DNA modification step of class switch recombination (CSR) and somatic hypermutation (SHM) events that occur in B-cell immunoglobulin genes. AID expression is tightly regulated only in transient pre-B cells, in germinal center B cells (GC-B cells), and in activated mature B cells (Okazaki et al. 2007; Shimizu et al. 2012; Honjo et al. 2012). Interestingly, AID dysregulation induces SHM in genes other than immunogloblins. In B-cell lymphoma, MYC, BCL6, PIM1, and numerous other genes were found to be massively mutated (Kotani et al. 2005). Moreover, aberrant AID expression outside B cells has been reported to be involved in oncogenesis associated with cancers where inflammation has been linked to oncogenesis, such as gastric cancer, hepatocarcinoma, and others (Okazaki et al. 2007).

19.4.2 EBV-Related Cancer and Inflammation

EBV-related cancers are usually accompanied by severe inflammation. EBV-positive DLBCL of the elderly and EBV-positive Hodgkin's lymphoma show massive infiltration of tumours with lymphocytes, eosinophils, stromal cells, and fibroblasts. NKT lymphomas have poor prognoses and are characterised by severe inflammation. These observations strongly suggest that inflammation is involved in EBV oncogenesis (Lu et al. 2012). This hypothesis is supported by a study showing that in EBV-associated lymphoma, only tumour cells without bystander cells fail to be engrafted into immunodeficient mice. This observation suggests that bystander cells support tumour cell survival. EBV infection has been shown to activate NFkB, which as previously mentioned induces AID expression in mature B cells (Okazaki et al. 2007). However, whether aberrant AID expression during EBV infections is involved in EBV oncogenesis remains to be elucidated. Intriguingly, certain EBV-related cancers present with coinfection with malaria or HIV. For example, endemic Burkitt's lymphoma is common in sub-Saharan Africa, which also happens to be the endemic area for malaria. Several lines of evidence, including epidemiological studies, strongly indicate that malaria induces Burkitt's lymphoma through a mechanism that involves T-cell dysfunction, or other direct cofactors. Similarly, HIV infection has been reported to play certain roles in EBV-induced lymphomagenesis. The fact that T-cell maintenance in the HAART era is not associated with decreased incidence of EBV-related lymphomas such as Hodgkin's lymphoma, suggests that HIV infection and not the degree of immunocompromise, plays a role in these diseases (Rickinson 2014).

19.4.3 EBV miRNAs Regulate Inflammation and Immune Evasion

Several EBV miRNAs have been reported to be involved in inflammation and immune evasion. Major histocompatibility complex class I polypeptide-related sequence B (MICB) is a ligand of the NKG2D type II receptor, a stress-induced immune molecule (Bahram et al. 1994; Groh et al. 1996). Both B cells and endothelial cells, which are the targets of EBV, express MICB. Binding of MICB activates NK, $CD8^{+}\alpha\beta$, and $CD8^{+}\gamma\delta$ T cells (Suarez-Alvarez et al. 2009). MICB expression on the cell surface is upregulated in response to various insults such as viral infection, tumour formation, heat shock, and DNA damage. Therefore, EBV downregulates MICB expression to decrease immune detection by NK cells. Previous studies have shown that downregulated MICB expression decreases the lysis of infected cells by NK cells (Stern-Ginossar et al. 2007). The 3′ UTR of *MICB* mRNA has potential binding sites for EBV miR-BART2-5p (Nachmani et al. 2009). EBV downregulates MICB expression by employing miR-BART2-5p, thus decreasing NK-cell–mediated lysis to prevent detection by immune cells.

MiR-BART1-1 is expressed from the 5′ UTR and miR-BART1-2 and miR-BART1-3 are expressed from the 3′ UTR of *BHRF1* in EBV-infected cells (Xia et al. 2008). MiR-BART1-3 expression is markedly elevated in EBV-infected type III latent cells (Xia et al. 2008). In addition, miR-BART1-3 has been detected in cells isolated from EBV-positive primary effusion lymphoma and AIDS-associated diffuse large B-cell lymphoma (Xia et al. 2008). *BHRF1* cluster miRNAs are characteristically detected in EBV-infected type III latent cells (Xing and Kieff 2007). EBV miR-BHRF1-3 regulates host immunity by downregulating interferon (IFN)-inducible T-cell–attracting chemokine (I-TAC, also known as CXCL11). CXCL11 belongs to the CXC family of chemokines, and its expression is strongly induced by both IFN-β and IFN-γ (Rani et al. 1996). CXCL11 promotes cell-mediated immunity by attracting activated T cells. The 3′ UTR of *CXCL11* mRNA shows 100 % complementarity to miR-BART1-3 and therefore is a target of miR-BART1-3. MiR-BART1-3 inversely regulates CXCL11 expression whereas the antisense sequence of miR-BART1-3 has an opposite effect (Pfeffer et al. 2004). MiR-BART1-3 significantly reduces CXCL11 expression at both the mRNA and protein levels (Xia et al. 2008). Thus, because cellular chemokines are the targets of viral miRNAs, EBV may regulate antigen processing and presentation and downregulate CTL cytokine networks through this mechanism.

19.5 Concluding Remarks

EBV-associated cancers are generally difficult to cure. Despite extensive studies on well-known concepts and methods, the molecular mechanisms through which EBV induces tumourigenesis and eludes immune surveillance remain unclear. Recent studies using mouse models of EBV-mediated lymphoproliferative diseases have shown that EBV infection of B cells is necessary but not sufficient to induce tumourigenesis because all peripheral mononuclear cells are needed to generate tumours in these mice (Kuppers 2009). Immune cells are also indispensable for EBV-induced tumourigenesis. However, the detailed roles of inflammation in EBV-induced lymphomagenesis and the relationship between these cells and EBV-infected cells with respect to tumourigenesis remain unclear. Moreover, the mechanisms underlying drug resistance, which results in poor prognoses of EBV-related tumours, have not yet been elucidated. Therefore, it is important to study the biology of EBV-associated tumours from a new perspective such as that provided by investigations focused on EBV miRNAs.

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