BART miRNAs: an unimaginable force in the development of nasopharyngeal carcinoma

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Nasopharyngeal carcinoma (NPC) is a head and neck cancer that represents a major health burden in Southern China and Southeast Asia. Although the close association of NPC with Epstein–Barr virus (EBV) infection has been demonstrated, its exact role in the pathogenesis of this malignancy is still unclear. The expression of EBV-encoded microRNAs, especially BART miRNAs, which are encoded from the BamHI-A region of the viral genome, is detected at a high level in NPC. miRNAs are small noncoding mRNAs that can positively regulate the virus to ensure accurate expression of viral genomes and to modify the gene expression of host cells by negative regulation. Accumulating evidence suggests that \textit{ebv-mir-BARTs} play a critical role in host cell survival, immune escape, cell proliferation, cell apoptosis, and cancer metabolism, promoting the generation of NPC. This review will summarize our current understanding of the nature and function of \textit{ebv-mir-BARTs} in NPC. \textit{European Journal of Cancer Prevention} 26:144–150 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Introduction

Nasopharyngeal carcinoma (NPC) is a prevalent malignancy with a high incidence in southern China. The differences in the geographic and ethnic distributions reflect the multifactorial etiology of NPC, including Epstein–Barr virus (EBV) infection, genetic susceptibility, and environmental factors. According to the new classification of the WHO, NPC is classified into two histological subtypes: keratinizing squamous cell carcinoma and nonkeratinizing carcinoma (either differentiated or undifferentiated) (Tsao \textit{et al.}, 2015); the latter accounts for more than 97% of this cancer and is consistently associated with EBV infection (Chou \textit{et al.}, 2008), suggesting that EBV is a crucial factor in the pathogenesis of NPC.

EBV is an oncogenic virus, latently infecting more than 90% of the global population (Cai \textit{et al.}, 2015b), and is closely linked to several human malignancies including Burkitt’s lymphoma, Hodgkin’s disease, post-transplant lymphoma, extranodal nasal natural killer/T-cell lymphoma (NKTCL), EBV-associated gastric cancers (EBVaGCs), and NPC (Hsu \textit{et al.}, 2014; Tsao \textit{et al.}, 2015). Both lytic and latent EBV genes may be involved in the tumorigenesis of human carcinoma, causing at least 200 000 new cancers per year (Kuzembayeva \textit{et al.}, 2014; Cai \textit{et al.}, 2015c). EBV shuttles continuously between B cells and epithelial cells during its infection cycle, maintained by a check-and-balance of the immune system in the body (Tsang and Tsao, 2015), which may be critical to establishing a persistent infection in humans. Once this intricate balance is broken, an uncontrolled proliferation of EBV-infected cells occurs that can induce malignancies. It is now well known that EBV facilitates the pathogenesis of NPC (Gu \textit{et al.}, 2012); several EBV genome products such as viral proteins, RNAs, and miRNAs may participate in the development of NPC (Raab-Traub, 2002). EBNA1, an EBV-encoded protein, promotes DNA damage in NPC cells by reducing P53 levels and inducing reactive oxygen species (ROS) (Raab-Traub, 2002; Gu \textit{et al.}, 2012; Tulalamba and Janvilisri, 2012). ROS may oxidatively modify miRNA and result in alteration of cellular events (Wang \textit{et al.}, 2015). LMP1 and LMP2B have a close association with cell proliferation, apoptosis, invasion, and motility by regulating several signaling pathways to influence the formation of vascular channels, alter the microenvironment of cancer and so on. However, the
pathogenesis and progression of NPC are not only regulated through EBV proteins but also by EBV-encoded miRNAs. Currently, ebv-miRNA, a short single-stranded RNA molecule that post-transcriptionally regulates gene expression, has generated major concern.

To date, a total of 48 mature miRNAs have been identified. These miRNAs are transcribed as two regions: BamHI fragment A rightward transcript (BART) and BamHI fragment H rightward reading frame 1 (BHRF1) in the EBV genome (Raab-Traub, 2002; Gu et al., 2012; Tsang and Tsao, 2015). Of these, BART miRNAs are highly expressed in epithelial tumors of NPC and EBVaGC, regulating the expression of various genes at the post-transcriptional level (Lo et al., 2012; Marquitz and Raab-Traub, 2012). At least 105 host genes are regulated by ebv-miRNA in NPC development, influencing five significant signaling pathways including the Wnt signaling pathway (Zeng et al., 2014), which is the major pathway, and its regulation by EBV is not dependent on the expression of LMP1 (Webb et al., 2008). Evidence of the underlying carcinogenesis of ebv-mir-BARTs is accumulating rapidly. In this review, we will present a summary of the nature and function of ebv-mir-BARTs in NPC (Table 1).

### Table 1: Function of BART miRNAs in nasopharyngeal carcinoma

| BART miRNAs | Target | Effects of BART miRNAs |
|-------------|--------|------------------------|
| BART cluster | LMP1   | Inhibit cell apoptosis  |
| BART1-3p,5p | PTEN   | Promote cell apoptosis  |
| BART1       | G6PD, SAT1 and so on | Regulate cancer metabolism |
| BART2-5P    | MAP3K5 | Inhibit cell apoptosis  |
| BART2       | BALF5  | Maintain virus latency  |
| BART3*      | DICE1  | Promote cellular growth and proliferation |
| BART3-6,8,16,22 | OAS21, TP53N, DICE1, OCT1, CREBBP, PAK2 | Inhibit cell apoptosis |
| BART1-5p,16,17-5p | LMP1 | Inhibit cell apoptosis |
| BART5       | PTEN   | Inhibit cell apoptosis  |
| BART6-5p    | Dicer  | Maintain virus latency  |
| BART7       | Rta    | Promote cellular growth and proliferation |
|             | c-myc and c-Jun | Promote tumor metastasis |
| BART9       | PTEN   | Promote cell proliferation |
| BART10      | BTRC   | Promote cellular growth and proliferation |
| BART17-5p,19-3p | APC | Promote cellular growth and proliferation |
| BART19-3p   | WIF    | Promote cell proliferation |
| BART22      | MAP3K5 | Inhibit cell apoptosis  |
| BART(1-3p,18-5p,19-3p) | TP53N1 | Immune evasion |
| Circulating BART3 and BART7 |    | Biomarker for recurrent NPC; influence radiation sensitivity |
| BART15-3    | TP53N1 | Promote the growth of EBV-associated tumors |
| Circulating miR-BART17 |    | Promote tumor metastasis |

### BART miRNAs contribute toward virus latency in NPC

During the infection cycle of EBV, EBV establishes persistent infection in humans by maintaining a check-and-balance of the immune system. The ebv-miRNA, a key player in establishing and maintaining latency, functions as a regulator of the viral life cycle.

**ebv-mir-BART2**

Important results have been reported on the impact of ebv-mir-BART2 on the transition from latent to lytic infection. It serves as an inhibitor of viral DNA replication through complete complementary with the 3′ UTR of BALF5 (Barth et al., 2008), degrading mRNA and inhibiting transition from latent to lytic viral replication. BALF5 can be defined as a DNA polymerase that can replicate viral genomic DNA in the late phase of lytic infection, producing long concatemeric DNA. However, mir-BART2 is only expressed at very low levels during latent infection; we suggest that other factors regulate BALF5 mRNA to ensure viral replication.

**ebv-mir-BART6-5p**

In addition to BART2, regulation of BART6 may be essential for EBV latent infection. First, ebv-mir-BART6-5p (Iizasa et al., 2010) silences Dicer, which is also regulated by miR103/107 and let-7, affecting the state of virus latency. Furthermore, BART6, an EBV-encoded miRNA, suppresses EBNA2, which is required for the transition of latency types. EBNA2 may be involved in the transactivation of LMP1 and, by inhibiting EBNA2, the virus can remain in a specific state of latency. Finally, BART6 inhibits essential viral proteins such as Zta and Rta, which are important for viral lytic replication. Another independent study reported that either adenosine-to-inosine (A-to-I) editing or mutations of BART6 influence the maintenance of latent EBV infection.

### BART miRNAs are closely associated with cell growth and proliferation in NPC

BART miRNAs play physiologic and pathophysiologic roles in cell proliferation, providing novel insight into the relationship between malignancies and EBV. Accumulating evidence indicates that deregulation of specific miRNAs is associated with cancer initiation and progression in NPC and that they can function as oncogenes to promote cell proliferation.

**ebv-mir-BART3**

A couple of viral and cellular targets of EBV-miRNAs in NPC cells have been validated completely. Of these, BART3* was found to promote cellular growth and transformation in NPC by matching imperfectly with DICE1 (Lei et al., 2013a). DICE1, a tumor suppressor, has growth-suppressing activity and interferes with anchorage-independent growth of IGFR1-transformed tumor cells. Although the inhibitory effect of mir-BART3* might be mild, the level of DICE1 expression is
high in NPC and it may be crucial in promoting cell proliferation in the initiation of NPC tumorigenesis. Similar to BART6, A-to-I editing (Lei et al., 2013b) may interfere with the target of mir-BART3 and induce changes in its expression and function in EBV-infected epithelial cells such as NPC and EBVaGC.

**ebv-mir-BART9**

*ebv-mir-BART9* exerts a tumorigenesis effect by targeting E-cadherin to promote cell invasion (Hsu et al., 2014) and is involved in cell proliferation by targeting a key tumor suppressor, PTEN. PTEN is a protein tyrosine phosphatase that participates in the process of PI3K activation, an abnormal proliferation signaling pathway that contributes toward tumorigenesis of NPC. Although downregulation of PTEN is found in about half of NPC tumors, mutation of the PTEN gene is extremely rare in HNSCC and its promoter hypermethylation has not been investigated in NPC (Chou et al., 2008; Tulalamba and Janvilisri, 2012). Therefore, other mechanisms are likely responsible for the low PTEN levels, such as *ebv-mir-BART*s. *ebv-mir-BART9* has been found to target PTEN to promote cell proliferation, although more evidence is needed to confirm its function in NPC.

**ebv-mir-BART10**

As is well known, regulation of cell-cycle checkpoints may result in tumorigenesis. Results obtained by Zeng et al. (2014) indicated that *ebv-mir-BART10* can efficiently suppress the expression of BTRC and subsequently decrease degradation of its substrates such as β-catenin and Snail, regulating the development of NPC. β-Catenin is the key mediator of canonical signaling in the Wnt pathway. Aberrant activation of the Wnt pathway results in the cytoplasmic β-catenin translocating into the nucleus, thereby interacting with various transcription factors to promote specific gene expression, causing cellular proliferation. miRNA has emerged as a new factor that indirectly regulates the Wnt signaling pathway by targeting β-catenin. WIF and APC, two key Wnt inhibitory genes also targeted by *ebv-mir-BART19-3p* and *ebv-mir-BART17-5p*, 19-3p, respectively (Jiang et al., 2011; Wong et al., 2012; Xie et al., 2013), regulate the Wnt pathway synergistically.

**ebv-mir-BART7**

A number of studies have evaluated the role of *ebv-mir-BART7*, discovering that *ebv-mir-BART7* also enhances cell growth, colony formation, and cell-cycle progression by activating PI3K/Akt/c-myc and c-Jun, eventually promoting cell proliferation and tumorigenesis (Chan et al., 2012; Cai et al., 2015a). c-Myc and c-Jun transcription factors are critical promoters of cellular proliferation, especially c-Myc; increased expression was found in 90% of NPC, sequestering inhibitory p27 and allowing for cell proliferation and progression through the G1 phase. Moreover, evidence from Chan et al. (2012) showed that BART7 alters multiple cancer-related pathways in undifferentiated NPC cells, suggesting that BART7 plays a crucial role in the development of NPC. Use of a gold–PEI nanocarrier to deliver anti-miR-BART7-3p can inhibit the function of BART7 (Cai et al., 2015c). Although nanoparticles may have toxicity and instability, they represent a new therapeutic method based on miRNA.

**miR-BART8**

As mentioned above, *ebv-mir-BART*s are closely associated with cell growth and proliferation in NPC. However, there are very few investigations on the functions of *BART* miRNAs. Huang and Lin (2014) reported that EBV-encoded miR-BART8 inhibits the IFN-γ-STAT1 pathway with secondary suppression of TP53, which may promote tumor growth in nasal NK-cell lymphoma. However, the role of *miR-BART8* in NPC is not clear; further study is warranted to understand the role of *mir-BART*s in the NPC.

**BART miRNAs may play a crucial role in the cell apoptosis in NPC**

Inhibition of apoptosis is critical for development of malignancies, including NPC. Survivin overexpression and high telomerase activity contribute toward NPC cell immortalization and overexpression of *ebv-mir-BART*s, which play an essential role in preventing apoptosis in NPC. Some well-defined examples are BART1-5p, 16, 17-5, *ebv-mir-BART5*, and BART cluster I.

**BART1-5p, 16, 17-5p**

A number of studies have evaluated the role of *ebv-mir-BART1-5p, 16, 17-5p* in apoptosis resistance by targeting LMP1 in epithelial carcinoma including NPC, which plays a role in tumor initiation (Cai et al., 2015b). LMP1 is believed to play a crucial role in the development of NPC (Dawson et al., 2012), but LMP1 protein expression in NPC is variable. In precancerous lesions, a high level of LMP1 expression triggers its oncogenic functions, whereas a relatively low level occurs in advanced cancer. LMP1 is downregulated by *ebv-mir-BART1-5p, 16, 17-5p* to prevent its cytotoxic effects and makes NPC cells resistant to apoptosis.

**BART cluster I**

LMP1 is a target of *ebv-mir-BART1-5p, 16, 17-5p* as well as BART cluster I. BART cluster I negatively regulates NF-κB activity in NPC by regulating LMP1 at the level of posttranscription (Lo et al., 2007). NF-κB dysregulation is one of the most important components of NPC tumorigenesis, indicated by the fact that it modulates cell proliferation and inflammation in carcinogenesis of numerous neoplasms. Activation of NF-κB, promoting the release of cytokines from inflammatory cells, may contribute toward the malignant transformation of premalignant epithelial cells; upregulation of inflammatory cytokines would continue to cause activation of NF-κB, generating a positive loop (Chou et al., 2008; Tulalamba and Janvilisri, 2012).
Moreover, activation of NF-κB may cause accumulation of p53, which may be advantageous to the development of NPC by preventing JNK-induced apoptosis. Yet, NF-κB also activates a number of proliferative signals, including Bel-2. Another independent study showed that BART cluster I also targets the Bel-2 interacting mediator of cell death (Bim), exerting an effect on the inhibition of apoptosis in response to the chemical compound etoposide in the AGS gastric carcinoma cell line (Marquitza et al., 2011). Similarly, it inhibits cisplatin-induced cytotoxicity by directly modulating NF-κB and indirectly regulating telomerase activity and cell immortalization in NPC; finally, it may result in LMP1-induced immortalization, suggesting that tumor cell apoptosis is significantly governed by ebv-mir-BARTs.

**ebv-mir-BART5**

p53 upregulated modulator of apoptosis (PUMA) is a pro-apoptotic member of the BH3-only subgroup of the Bel-2 family. It is a key mediator of p53-dependent and p53-independent apoptosis, having the strongest proapoptotic effects found in recent years (Hikise and Kilianska, 2012). PUMA protein expression, as well as PUMA mRNA, can be detected in cells with virus infection. Previous findings reported that PUMA is a core factor that considerably improved the sensitivity to chemotherapy drugs and radiation. Radiosensitivity and growth inhibition may be ascribed to the knockdown of PUMA in lung cancer, breast cancer, and other malignancies. For NPC, studies found that PUMA was targeted by ebv-mir-BART5 (Choy et al., 2008). BART5 downregulates the expression of PUMA, protecting host cells from apoptosis.

**ebv-mir-BART20**

The Bel-2-associated death promoter has been reduced at the level of both mRNA and protein by ebv-mir-BART20-5p in EBaGC cells (Kim et al., 2015), enhancing cell growth, suppressing cell apoptosis, and inducing chemoresistance to 5-FU and docetaxel. In addition, BART20-5p targets BCLF1 and BRLF1 (Jung et al., 2014), which may trigger the lytic cycle and tightly regulate EBV latency in the EBV-infected gastric carcinoma cell line. Furthermore, mir-BART20-5p may indirectly inhibit p53 in invasive nasal NK/T-cell lymphoma (Lin et al., 2013). Both EBaGC and NPC belong to EBV latency type II; in particular, the level of BART20 in NPC is higher than that of EBaGC. Therefore, we suggest that BART20 may play a more important role in tumorigenesis initiation of NPC than that of EBaGC, influencing the chemosensitivity of cancer cells, the immune response of host cells, and the latency of EBV.

**BART miRNAs may induce tumor metastasis and recurrence in NPC**

Although IMRT has improved the survival rate of NPC significantly, it still has a propensity for distant metastasis, which is one of the main causes of treatment failure. In addition to EBV latency proteins (LMP1, LMP2A), EBV-encoded miRNAs also play a critical role in the tumor metastasis in NPC.

**ebv-mir-BART1, BART7**

Considerable evidence has shown that downregulation of PTEN is responsible for upregulation of the PI3K/Akt pathway in NPC. In addition, loss of PTEN is associated with metastatic disease, with clinical stage III–IV tumors having lower PTEN than clinical stage I–II tumors (Chou et al., 2008; Tulalamba and Janvilisri, 2012). In vitro and in vivo studies have reported that BART1 (BART1-3p,BART1-5p) can directly target PTEN, activate PTEN-dependent pathways, lead to EMT, and finally contribute toward metastasis (Cai et al., 2015b). EMT, a fundamental biological process that enhances the capacity for cell migration and invasion, is considered the initial step of tumor metastasis. Similarly, ebv-mir-BART7-3p also targets suppressor PTEN (Chen et al., 2012; Cai et al., 2015a), modulating PI3K/AKT/GSK-3β signaling and inducing a transition from the epithelial to the mesenchymal phenotype by promoting EMT; eventually leading to cancer metastasis.

**ebv-mir-BART9**

E-cadherin, a transmembrane glycoprotein that functions as a cell adhesion molecule, is essential for the morphogenesis and homeostasis of epithelial tissues. Low E-cadherin expression is associated significantly with metastasis in head and neck cancer patients, playing a key role in EMT by inducing transcription factors such as Twist. As for NPC, lower E-cadherin mRNA and protein levels are found in metastatic NPC tumors, suggesting that decreased E-cadherin levels correlate with metastatic disease (Wong et al., 2014). To date, three main factors account for the low expression of E-cadherin: loss of β-catenin in the cytoplasm, promoter hypermethylation, and microRNA. It has been reported that ebv-mir-BART9 directly downregulates E-cadherin at the post-transcriptional level (Lo et al., 2012; Hsu et al., 2014), whereas LMP1 regulates E-cadherin at the transcriptional level, suggesting that these two viral products may repress E-cadherin synergistically in NPC. It was discovered that BART9 may regulate the level of LMP1 and affect the growth rate in NKTL (Ramakrishnan et al., 2011). We can surmise that BART9 targets LMP1 in NPC to generate motile cells, inducing cell invasion and migration. Unfortunately, it has been found that the effect of BART9 is independent of LMP1, LMP2A, and EBNA1.

**ebv-mir-BART7**

As is well known, local recurrence is another factor that contributes toward treatment failure in NPC. Surgery may play a more important role in local tumor control and survival compared with radiation for recurrent patients. mir-BART7
is present in high levels in plasma and tumor in patients with NPC, especially in the advanced stage. It may predict and identify patients with histologically clear margins (>5 mm) who may have an increased risk of local recurrence after resection of recurrent NPC (Chan et al., 2015). In addition, mir-BART7 may influence radiation sensitivity, contributing toward altered treatment outcomes.

**Regulation of cancer metabolism by BART miRNAs**

Metabolic pathway alterations, including aerobic glycolysis and the Warburg effect in cancer cells, are also observed in NPC. BART miRNAs can participate in cancer cell metabolism by regulating the expression of metabolism-associated genes whose protein products regulate metabolism either directly or indirectly. Ye et al. (2013) reported, using both assays in cells and NPC tissues, that ebc-mir-BART1 could significantly influence the expression of G6PD, SAT1, and other key genes associated with metabolism. Notably, PAST1 and PHGDH appeared to be upregulated mostly in NPC; they may also be critical for the proliferation and growth of cancer cells, respectively.

**Immune evasion function of BART miRNAs in NPC**

It is well known that the existence of EBV may have less opportunity to induce host immune response, promoting tumor cell survival. ebc-mir-BART21 and ebc-mir-BART22 are highly expressed in NPC cell lines and primary tissues. Importantly, BART22 can downregulate LMP2A at the level of translation and eventually escape the host immune response (Lung et al., 2009), promoting the survival of cancer cells of NPC. Newer data show that LMP2, especially LMP2A, a potent immunogenic viral antigen, has diverse functions including mediation of tumor cell survival and inducing NPC cells to become migratory and invasive (Chou et al., 2008; Dawson et al., 2012). BART2-5P and BART3 can target MICB and IPO7 (Nachmani et al., 2009), respectively, escaping immune recognition and killing in human B cell lines, while their functions in NPC have not been investigated. Details of the dysregulated miRNAs and their corresponding targets in NPC are presented in Fig. 1.

**BART miRNAs serve as a biomarker**

Increasing evidence suggests that circulating microRNAs in malignant diseases are significant, and this is currently a very

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**Fig. 1**

Dysregulated miRNAs and their corresponding targets in nasopharyngeal carcinoma. EBV, Epstein–Barr virus; NPC, nasopharyngeal carcinoma.
active field. Several ebv-miRNAs including miR-BART1, miR-BART4, miR-BART7, miR-BART9, miR-BART12, miR-BART13, and miR-BART16 were found to be secreted selectively through two main carriers, microvesicles and exosomes, and transported to adjacent cells. For example, mir-BART7 and mir-BART13 can be detected in plasma from NPC patients; in particular, plasma levels of miR-BART7 and mir-BART13 decrease after radiotherapy (Kawano et al., 2013; Zhang et al., 2015). In addition, BART7 can be used to differentiate patients with NPC from healthy individuals (Chan et al., 2012). On the basis of the above findings, investigators suggest that circulating EBV BART miRNA (detected in plasma or serum) could serve as a biomarker for diagnosis and prognosis in NPC, especially in cases where detection of circulating EBV DNA is not applicable. Another study supports this point. Circulating mir-BART17 appears abundantly in plasma samples from NPC patients irrespective of patient origins. As a marker of NPC plasma samples, cbc-mir-BART17 has good sensitivity (77%) and high specificity (90%) (Gourzounes et al., 2013). One remarkable characteristic of circulating microRNAs is its stability. Interestingly, Gourzounes et al. (2013) found a marked increase in the concentration of mir-BART17 accompanied by an increase in tumor mass in one patient, suggesting that the concentration of mir-BART17 in plasma may be associated with the progression of tumor. Although it has been speculated that circulating ebv-miRNAs may function as a biomarker, their role in NPC development remains to be understood.

Discussion
EBV infection is a strong predisposing factor in the development of NPC. It is the first human virus that has been found to express miRNAs, most of whose functions remain largely unknown. It can regulate both host cells and virus cells at the transcriptional or the post-transcriptional level by forming imperfect or perfect complementary duplexes with their target mRNAs. Although several studies have reported the upregulation of multiple EBV-encoded miRNAs in NPC, further study is needed to determine the role of mir-BARTs in NPC. For example, BART16, BART11-5p, BART13, and BART15 can target TOM22 (Dolken et al., 2010), EBF1 (Ross et al., 2013), MDS (Borze et al., 2011), and NLRP3 (Haneklaus et al., 2012), respectively, regulating the circumstance of malignancies and modulating the development of cancer; their role in NPC, however, has not been determined. In conclusion, NPC with EBV infection has the propensity to escape immune recognition, induce cell invasion and metastasis, and promote tumorigenesis. mir-BARTs proteins play a restricted role in NPC, whereas BART miRNAs may cooperate with host genes and play a critical role in the development of NPC (Pfeffer and Voinnet, 2006; Riley et al., 2012). To date, at least 25 EBV-miR precursors containing 48 mature miRNAs have been identified; a major challenge is to confirm miRNAs that target more than one gene from EBV or the host cell, ensuring perfect profiling of ebv-miRNAs; in particular, their function in different cancers is difficult to determine and further study is needed.

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Conflicts of interest
There are no conflicts of interest.

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