

Review Article

The regulatory network of nasopharyngeal carcinoma metastasis with a focus on EBV, lncRNAs and miRNAs

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Abstract: Metastasis of nasopharyngeal carcinoma (NPC) remains a main cause of death for NPC patients even though great advances have been made in therapeutic approaches. An in-depth study into the molecular mechanisms of NPC metastasis will help us combat NPC. Epstein-Barr virus (EBV) infection is an evident feature of non-keratinizing NPC and is strongly associated with tumor metastasis. Recently, long noncoding RNAs (lncRNAs) and microRNAs (miRNAs) have become a hot topic of research due to their epigenetic regulatory roles in NPC metastasis. The EBV products, lncRNAs and miRNAs can target each other and share several common signaling pathways, which form an interconnected, complex molecular regulatory network. In this review, we discuss the features of this regulatory network and summarize the molecular mechanisms of NPC metastasis, focusing on EBV, lncRNAs and miRNAs with updated knowledge.

Keywords: Nasopharyngeal carcinoma, metastasis, EBV, lncRNA, miRNA, regulation

Background

Nasopharyngeal carcinoma (NPC) is endemic in Southeast Asia, Southern China and North Africa, and males are at a 2 to 3 times higher risk than females [1]. The age-standardized rates can be as high as 20 to 30 per 100,000 population in men and 8 to 15 in women in endemic areas such as Hong Kong [2]. According to the World Health Organization (WHO), type-III NPC, which is nonkeratinizing and undifferentiated, is the most common subtype, as it accounts for 63-95% of all NPC cases worldwide [3]. Once NPC cells migrate, patients have a poor prognosis even if they are treated with advanced therapies [4]. The main causes of metastatic NPC can be categorized into environment, heredity, epigenetic deregulation and viral infection [5-7]. These causes can lead to angiogenesis, disruption of cell junctions, reorganization of the cytoskeleton, overexpression of protein kinase, increased mobility, escape from apoptosis, epithelial-mesenchymal transi-

tion (EMT), invasion, and clonogenicity. With the use of radiotherapy and chemotherapy, the survival rate of NPC patients has increased, but a complete cure of metastatic NPC remains elusive. Thus, a full understanding of the molecular mechanism of NPC metastasis is essential, and cancer-associated molecules can be useful for the prognosis, evaluation of the curative effects of radiotherapy or chemotherapy, and provide new biomarkers for targeted therapy. The scope of this article will focus on the discussion of the molecular mechanism of the regulation of NPC metastasis and will specifically focus on the complex regulatory network of Epstein-Barr virus (EBV), long noncoding RNAs (lncRNAs) and microRNAs (miRNAs).

A complex regulatory network among EBV, lncRNAs, miRNAs and its features

EBV infection is an evident characteristic of nonkeratinizing NPC. In NPC tissues, the latent EBV exists exclusively in tumor cells and facili-

Regulatory network of NPC metastasis

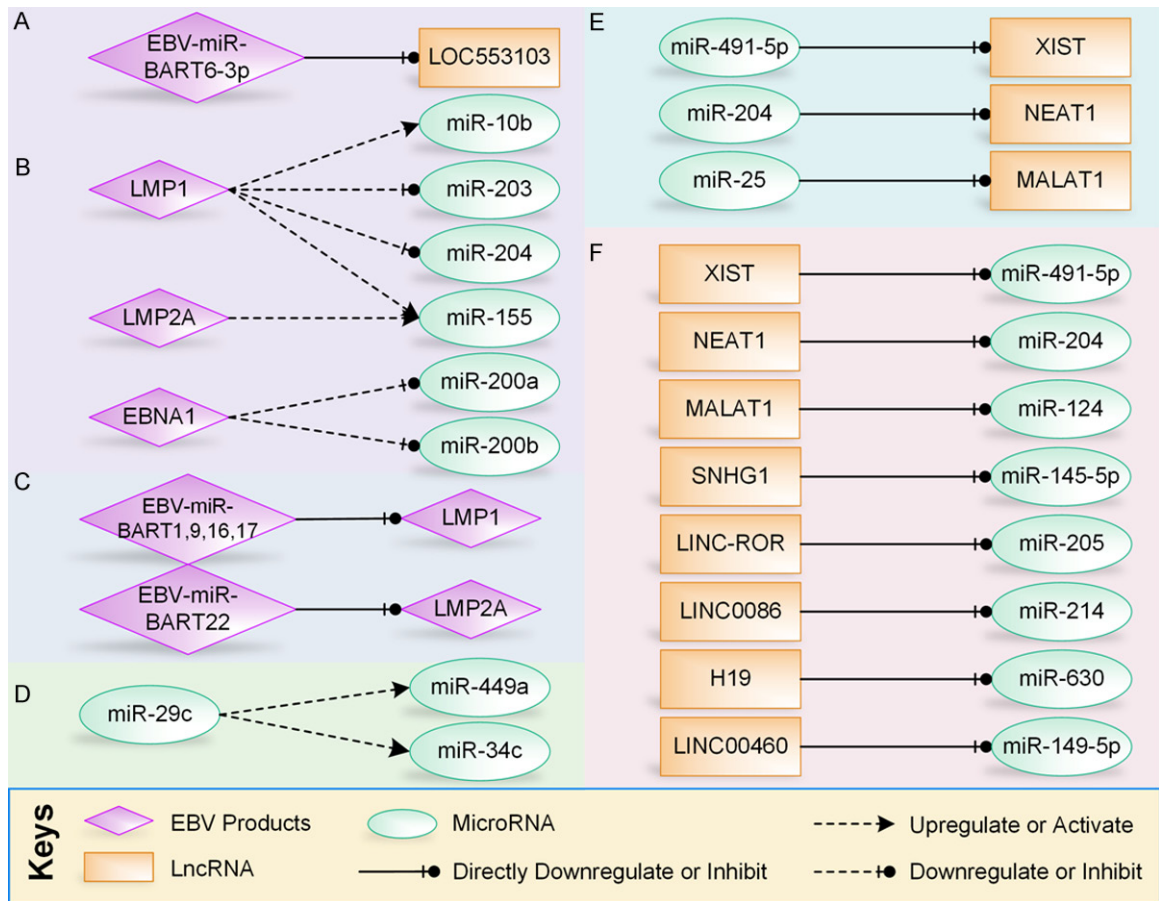


Figure 1. This picture aims to illustrate the mutual regulation of EBV, lncRNAs and miRNAs. A. EBV products target lncRNAs; B. EBV products target miRNAs; C. EBV products target EBV products; D. miRNAs target miRNAs; E. miRNAs target lncRNAs; F. lncRNAs target miRNAs.

tates tumor metastasis via creating a distinct tumor microenvironment (TME) and intracellularly altering cell signaling and products [8, 9]. Studies on NPC treatment against EBV are always a hot topic. Moreover, aberrantly expressed lncRNAs and miRNAs have been discovered in NPC tissues. They have been determined to function as either tumor promoters or suppressors via epigenetically regulating their targets and causing the enhanced proliferation and invasion ability of NPC cells. Researchers have gradually focused their research on the mechanisms of lncRNAs and miRNAs in NPC metastasis due to their significant regulatory functions. Actually, studies on lncRNAs and miRNAs are currently very popular.

The EBV products and deregulation of some lncRNAs and miRNAs can promote NPC metastasis by regulating downstream targets and then activating or inhibiting some tumor-associ-

ated signaling pathways. Interestingly, their downstream targets can also be EBV products, lncRNAs or miRNAs, which means the regulation can be interlaced and mutual. For example, lncRNA-LINC00460 can inhibit miR-149-5p to upregulate interleukin 6 (IL-6), which functions as a tumor promoter [10]. LMP1, a product of EBV, can downregulate oncogenic miR-155 [11]. miR-29c can modulate the level of miR-34c and miR-449a via repression of DNA methyltransferase 3a and 3b, which promote NPC invasion and metastasis [12]. Their specific regulatory relationship is shown in **Figure 1**.

Moreover, EBV, lncRNAs, miRNAs can regulate the common downstream oncogenic or anti-oncogenic molecules such as phosphatase and tensin homologue (PTEN), E-cadherins or signaling pathways like the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway and the transforming growth factor β (TGF- β)/SMAD sig-

Regulatory network of NPC metastasis

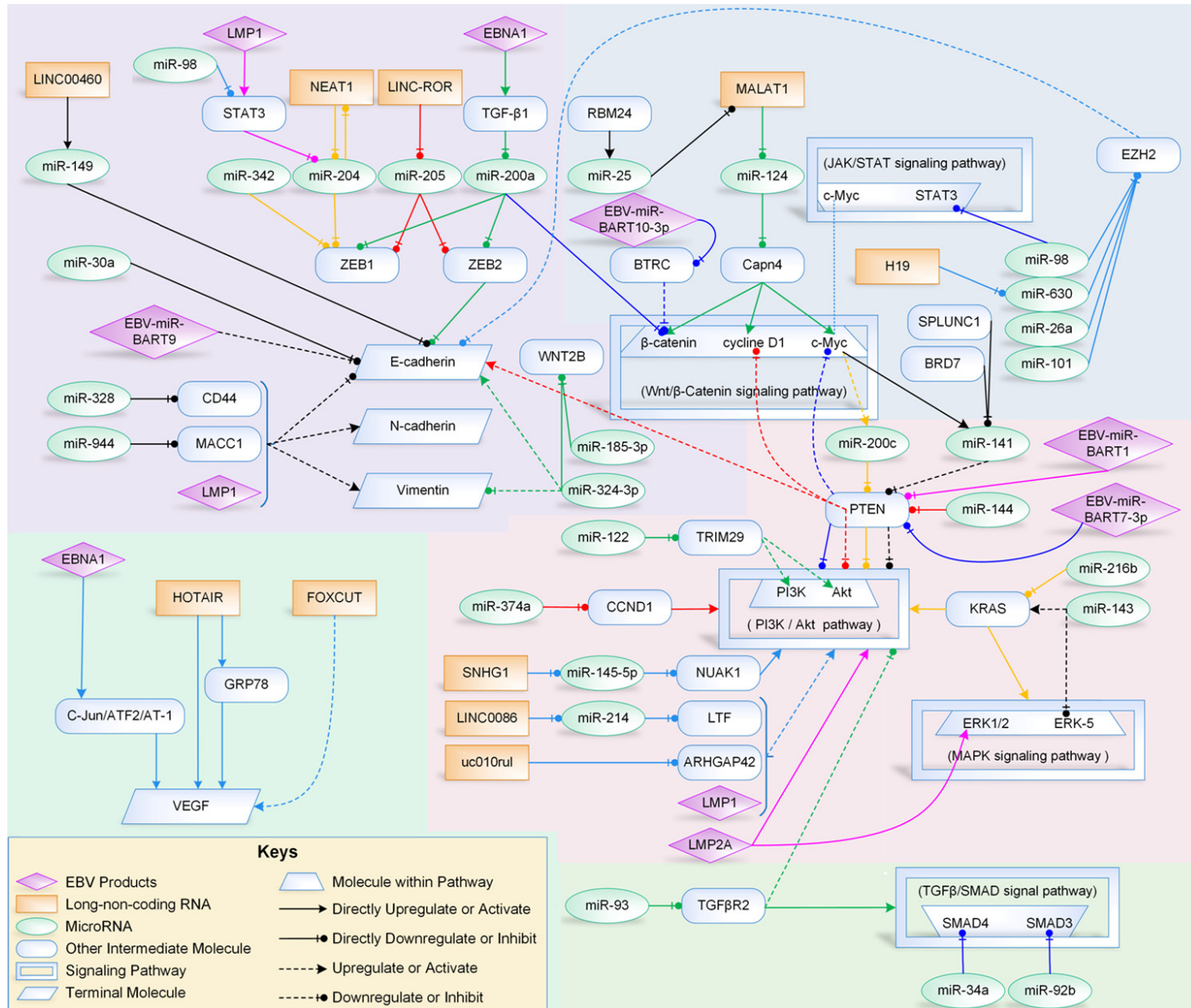


Figure 2. An interlinked network of EBV products, lncRNAs and miRNAs that regulate NPC metastasis. This illustration is intended to briefly show that these molecules can regulate some common signaling pathways and terminal molecules.

nalizing pathway. The mutual regulation and common downstream signaling pathways indicate that the regulation of EBV, lncRNAs and miRNAs form an interlinked, complex regulatory network, which is shown in **Figure 2**.

The detailed regulatory mechanisms of EBV, lncRNAs and miRNAs will be discussed in the following passages.

Roles of EBV in the regulation of NPC metastasis

EBV was discovered as the first human tumor virus by Michael Anthony Epstein and Yvonne Barr in 1964 [13]. It is a ubiquitous virus, and approximately 95% of the world's population experiences asymptomatic lifelong infections [13-15]. The initiation and progression of several cancers are associated with EBV infection, including NPC, gastric carcinoma, non-Hodgkin's lymphoma and Hodgkin's lymphoma [16]. EBV-encoded viral products promote tumor development and progression through alterations in host cell signaling and via the establishment of a tumor microenvironment [8]. In the following passages, we review several EBV-encoded products that have important roles in NPC metastasis, including LMP1, LMP2A, EBNA1 and EBV-miR-BARTs.

LMP1

EB-virus Latent Membrane Protein 1 (LMP1) is an EBV primary oncogene that can induce transformation, inhibit differentiation and promote the migration of epithelial cells [13, 17]. LMP1 activates the nuclear factor- κ B (NF- κ B), PI3K/Akt and p38 pathways through LMP1 functional domains. For example, the LMP1 C-terminal domain, which contains the two transformation effector sites TES1 and TES2, mediates tumor necrosis factor receptor signaling [17]. The detailed biological functions and molecular mechanisms of LMP1 in NPC metastasis are summarized below (also see **Table 1**).

LMP1 upregulates integrin- α 5 and N-cadherin but decreases E-cadherin protein levels, and it also induces focal adhesions and epithelial cell migration [18]. LMP1 promotes the expression of phosphorylated ezrin via the protein kinase C (PKC) pathway and then facilitates cell motility [19]. LMP1 is associated with the expression of Snail, which was verified to play a vital role in

EMT [20]. In addition, LMP1 can inhibit the expression of the junctional protein plakoglobin and can activate PI3K/Akt and NF- κ B signaling, both of which are associated with NPC migration [21]. Moreover, LMP1 directly binds to FYVE, RhoGEF and PH domain containing 4 (FGD4) and enhances FGD4 activity toward cell division control protein 42 homolog (Cdc42), which leads to the rearrangement of the actin cytoskeleton and an increase in NPC cell motility [22]. LMP1 upregulates the expression of matrix metalloproteinase 9 (MMP9) through the NF- κ B and Activin-1 signaling pathways and then contributes to invasiveness and metastasis of NPC [23-25]. In addition, LMP1 promotes the expression of MMP3 in fibroblasts [26]. LMP1 enhances Hypoxia-inducible factor-1 α (HIF1 α), which can promote proliferation, invasiveness and angiogenesis [27-29]. LMP1 also upregulates interleukin 8 (IL-8) through activation of NF- κ B [30] and can induce the receptor for advanced glycation end products (RAGE) through NF- κ B, which promotes NPC angiogenesis and lymph node metastasis [31]. LMP1 upregulates the expression of Decoy receptor 3 (DcR3) via PI3K/Akt and NF- κ B signaling [32]. Moreover, LMP1 can induce tumor necrosis factor α -induced protein 2 (TNFAIP2) via NF- κ B [33, 34]. LMP1 activates the MUC1 promoter and induces Mucin 1 (MUC1) by binding to signal transducer and activator of transcription 1 (STAT1) and STAT3 [35]. LMP1 enhances interferon regulatory factor 7 (IRF7) to promote cervical lymph-node metastasis [36]. In addition, LMP1 inhibits miR-203, a metastatic suppressor of NPC [37, 38]. Our group predicted the presence of miR-203 binding sites within the 3'-untranslated region (3'-UTR) of Cluster of Differentiation 109 (CD109) whose overexpression is positively related to the stemness of NPC cells [39]. We also found that LMP1 upregulates the expression of CD109, and thus regulation of the LMP1/miR-203/CD109 axis may participate in NPC metastasis (these studies have yet to be published). LMP1 represses tissue inhibitor of metalloproteinase-3 (TIMP-3) via the promotion of NPC metastasis by p38 kinase [40]. LMP1 drives EMT and metastasis of NPC through the activation of cadherin 6 (CDH6) and the CDH6 activator, Runt-related transcription factor 2 (RUNX2) [41]. Both CDH6 and Runx2 have been reported in various cancers to be downstream effectors of the TGF- β signaling pathway [42, 43]. LMP1 also upregu-

Regulatory network of NPC metastasis

Table 1. Functions and molecular mechanisms of LMP1 in NPC metastasis

Effectors/Targets	Molecular mechanism	Functional regulation	Reference
Integrin- α 5 and N-cadherin	\uparrow integrin- α 5, \uparrow N-cadherin	EMT, migration	[18]
E-cadherin	\downarrow E-cadherin	EMT, cell motility, migration	[18]
Ezrin	\uparrow PKC, \uparrow phosphorylation of ezrin	Cell motility, invasion	[19]
Snail	\uparrow Snail	EMT, invasion	[20]
Plakoglobin	\downarrow Plakoglobin	EMT, reorganization of cytoskeleton	[21]
Cdc42	\uparrow FGD4, \uparrow Cdc42	Reorganization of cytoskeleton, cell motility	[22]
MMP9	\uparrow NF- κ B, \uparrow activin-1, \uparrow MMP9	EMT, metastasis, invasion	[23-25]
MMP3	\uparrow MMP3	EMT, invasion	[26]
HIF1 α	\uparrow HIF1 α , \downarrow E-cadherins, \uparrow N-cadherins	Angiogenesis, invasion, EMT	[27-29]
IL-8	\uparrow NF- κ B, partly through \uparrow AP-1, \uparrow IL-8	Angiogenesis	[30]
RAGE	\uparrow NF- κ B, \uparrow transactivation the RAGE promoter, \uparrow RAGE	Angiogenesis, lymph node metastasis	[31]
DcR3	\uparrow PI3K/Akt, \uparrow NF- κ B, \uparrow DcR3	Migration, invasion	[32]
TNFAIP2	\uparrow NF- κ B, \uparrow TNFAIP2	Cell motility	[33, 34]
MUC1	Binds STAT1 and STAT3, activates MUC1 promoter, \uparrow MUC1	Invasion, metastasis	[35]
IRF7	\uparrow IRF7	Metastasis	[36]
miR-203	\uparrow JNK, \uparrow NF- κ B, \downarrow miR-203	Metastasis	[38]
TIMP-3	\uparrow p38 kinase, \downarrow TIMP-3	Invasion, migration	[40]
CDH6	\uparrow NF- κ B, \downarrow miR-203, \uparrow CDH6	EMT, metastasis	[41-43]
CXCR4	\uparrow TPST-1, \uparrow Tyrosine sulfation of CXCR4	Metastasis	[44]
miR-10b	\uparrow Twist, \uparrow miR-10b	Metastasis	[45-48]
miR-204	\uparrow STAT3, \downarrow miR-204	Invasion, metastasis	[49]

lates the sulfation of tyrosine on the functional chemokine receptor CXCR4 through the upregulation of tyrosyl protein sulfotransferase-1 (TPST-1) [44]. Several studies have demonstrated that LMP1 promotes metastasis of NPC via the Twist/miR-10b pathway [45, 46] and that LMP1 induces the expression of Twist [47], which can promote EMT of NPC through the upregulation of miR-10b [48]. LMP1 suppresses miR-204 expression through STAT3 activation. miR-204, an inhibitor of NPC invasiveness, inhibits cdc42 [49].

LMP2A

Latent membrane protein 2A (LMP2A), which is the only EBV protein that contains an immunoreceptor tyrosine-based activation motif (ITAM), is overexpressed in most NPC tumor samples [50, 51]. LMP2A expression mimics constitutively active and antigen-independent B-cell receptor (BCR) signaling [52]. LMP2A ITAM and PPPPY(PY) motifs block Ag-dependent BCR and subsequently activate the PI3K/Akt signaling pathway [53]. Localized at the tumor invasive front, LMP2A increases the capacity for NPC metastasis, alters EMT-markers and strongly upregulates the expression of stem cell markers [54-56]. The biological functions and molecular mechanisms of LMP2A in NPC

metastasis are summarized below (also see **Table 2**).

LMP2A upregulates the expression of fibronectin and downregulates E-cadherin, which can promote lymph node metastasis and the malignant progression of NPC [57]. LMP2A induces the phosphorylation of the Akt target, glycogen synthase kinase 3 β (GSK3 β), which can regulate the activity of focal adhesion kinase (FAK) and subsequently promote NPC migration. LMP2A can also induce the expression of membrane-localized α V-integrin [58]. LMP2A interacts with spleen tyrosine kinase (Syk) [59] and enhances integrin- α -6 (ITG α 6) protein, which contribute to the invasiveness and metastasis of NPC [60]. LMP2A also upregulates the expression of MMP9 through the extracellular signal-regulated kinase (ERK)1/2-Fra-1-MMP9 axis [61]. LMP2A induces the expression of metastatic tumor antigen 1 (MTA1) via the activation of the mTOR/4EBP1-eIF4E axis. MTA1 is also a downstream serine/threonine kinase in the PI3K/Akt pathway [62, 63], which can facilitate EMT via the Wnt1 pathway and β -catenin activation [64-66]. LMP2A may promote cell mobility and metastasis through the induction of the kinase activities of ERK and c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) [67]. Furthermore, LMP2A

Regulatory network of NPC metastasis

Table 2. Functions and molecular mechanisms of LMP2A in NPC metastasis

Effectors/Targets	Molecular mechanism	Functional regulation	Reference
Fibronectin	Partly ↑PI3/Akt, ↑fibronectin	EMT, reorganization of cytoskeleton	[57]
E-cadherin	Partly ↑PI3/Akt, ↓E-cadherin	EMT, cell motility, migration	[57]
FAK	↑phosphorylation of the Akt, ↑GSK3β, ↑FAK	EMT, migration	[58]
αV-integrin	ITAM-mediated ↑Syk and ↑Akt, ↑FAK, ↑αV-integrin	EMT, migration	[58]
ITGα6	↑ITGalpha6 RNA, ↑ITGα6 protein	Migration, metastasis	[60]
MMP9	↑ERK1/2, ↑Fra-1, ↑MMP9	EMT, metastasis, invasion	[61]
MTA1	↑mTOR/4EBP1-eIF4E axis, ↑MTA1, ↑Wnt1 pathway, ↑β-catenin	EMT, metastasis	[62-66]
c-Jun	↑ERK, ↑JNK/SAPK, ↑MAPK, ↑phosphorylation of c-Jun protein	Cell mobility, metastasis	[67]
S100A4	↑demethylation of S100A4 promoter, ↑S100A4	EMT, metastasis	[68]

Table 3. Functions and molecular mechanisms of EBNA1 in NPC metastasis

Effectors/Targets	Molecular mechanism	Functional regulation	Reference
Stathmin1, maspin and Nm23-H1	↑stathmin1, ↑maspin, ↑Nm23-H1	EMT, metastasis	[77]
ZEB1/ZEB2	↑TGF-β1, ↓miR-200a/miR-200b, ↑ZEB1/ZEB2	Invasion, metastasis	[76]
AP-1	↑c-Jun, ↑ATF2, ↑AP-1	Angiogenesis, invasion	[78]
VEGF, IL-8, HIF1α	↑AP-1, ↑VEGF, ↑IL-8 ↑HIF1α	Angiogenesis, invasion	[78]
Akt	↑SPHK1, ↑S1P, ↑Akt	Invasion, metastasis	[79]

can induce the hypomethylation of the S100 calcium binding protein A4 (S100A4) promoter, which facilitates EMT occurrence and NPC metastasis [68].

EBNA-1

Epstein-Barr virus nuclear antigen 1 (EBNA1), which is the only EBV protein expressed in all EBV-associated tumors, is essential for the replication and stable persistence of EBV [69]. EBNA-1 is a DNA-binding phosphoprotein and multifunctional dimeric viral protein [70, 71]. EBNA-1 binds to viral DNA elements and cellular promoters for EBNA-1-dependent transcriptional activation and genome persistence [72, 73]. EBNA1 is also responsible for the maintenance of the EBV episome by binding to the oriP, the plasmid origin of viral replication [74, 75]. The biological functions and molecular mechanisms of EBNA1 in NPC metastasis are summarized below (also see **Table 3**).

EBNA1 is associated with NPC lymph node metastasis-characterizing alterations in NPC cell morphology and the expression of extracellular EMT markers [76]. EBNA1 upregulates proteins such as stathmin 1, maspin and Nm23-H1 and increases metastatic potential [77]. Furthermore, the overexpression of EBNA1 inhibits miR-200a and miR-200b, which is mediated by transforming growth factor-β1 (TGF-β1); EBNA1 then upregulates the EMT

mediators zinc finger E-box binding homeobox 1 (ZEB1) and ZEB2 [76]. EBNA1 induces the activity of the AP-1 transcription factor, which targets vascular endothelial growth factor (VEGF), IL-8 and hypoxia-inducible factor-1α (HIF1α). This process is achieved by the binding of EBNA1 to the promoters of c-Jun and the activation of transcription factor 2 (ATF2) [78]. A recent study reported that the ectopic expression of EBNA1, LMP1 and LMP2 can upregulate sphingosine kinase 1 (SPHK1), which is an enzyme that is vital in the production of sphingosine-1-phosphate (S1P). S1P activates Akt and then promotes the migration of NPC cells [79].

EBV-miR-BARTs

microRNAs (miRNAs) are a class of noncoding RNAs that are 17-23 nucleotides in length that participate in tumorigenesis and metastasis through the formation of imperfect complementary duplexes with their target mRNAs in the 3'-UTR [80]. miRNAs in the EBV genome are transcribed from two regions: BamHI fragment A rightward transcript (BART) and BamHI fragment H rightward reading frame 1 (BHRF1) [69, 81]. BHRF1 expresses 4 mature miRNAs from 3 precursor-miRNAs, while BART expresses 40 mature mi-RNAs from 22 precursor-miRNAs [82]. The EBV-miR-BART is expressed at a high level in NPC cells and plays an important role in immune escape, NPC cell proliferation and

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Table 4. Functions and molecular mechanisms of EBV-miR-BARTs in NPC metastasis

EBV-miR-BART	Effectors/Targets	Molecular mechanism	Functional regulation	Reference
EBV-miR-BART1	PTEN	↓PTEN, ↑PI3K/Akt, ↑FAK-p130 (Cas) and ↑Shc-MAPK/ERK1/2	EMT, migration, invasion	[89-91]
EBV-miR-BART6-3p	LOC553103	↓LOC553103	Migration, invasion	[92]
EBV-miR-BART7-3p	c-Myc and c-Jun	↓PTEN, ↑PI3K/Akt, ↑c-Myc and ↑c-Jun	EMT, metastasis	[95]
EBV-miR-BART9	E-cadherin	↓E-cadherin	EMT, cell mobility, invasion	[96-98]
EBV-miR-BART10-3p	β-catenin and Snail	↓BTRC, ↑β-catenin and ↑Snail	EMT, invasion	[99]

tumor metastasis [83, 84]. Moreover, BART can modulate LMP1 and LMP2A. Not only is LMP2A a target of miR-BART22 [85], but EBV-miR-BARTs including miR-BART1, miR-BART9, miR-BART16 and miR-BART17 can negatively regulate the expression of LMP1 [86]. The biological functions and molecular mechanisms by which these EBV-miR-BARTs regulate NPC metastasis are summarized in **Table 4**.

EBV-miR-BART1-5p is highly expressed in NPC and is closely associated with pathological and advanced clinical stages of NPC [87]. Moreover, EBV-miR-BART1 affects the expression of mechanism-associated genes in NPC, especially PSAT1 and PHGDH [88]. EBV-miR-BART1 directly downregulates the expression of PTEN [89]. Consequently, EBV-miR-BART1 activates PTEN-dependent pathways including PI3K/Akt, FAK-p130^{Cas} and Shc-MAPK/ERK1/2 signaling [90, 91]. This process induces EMT and increases NPC migration, invasion and metastasis.

EBV-miR-BART6-3p can inhibit cell migration and invasion in NPC. EBV-miR-BART6-3p facilitates EMT by targeting and decreasing the expression of lncRNA LOC553103 [92].

The expression of EBV-miR-BART7 is high in the extracellular environment and in NPC cells and is positively associated with proliferation, migration, and invasiveness of NPC cells [93]. Furthermore, NPC cells that express EBV-miR-BART7 exhibit resistance to cisplatin and radiation treatment [94]. Moreover, EBV-miR-BART7-3p induces c-Myc and c-Jun through stimulation of the PTEN/PI3K/Akt pathway [95].

EBV-miR-BART9, a prometastatic viral miRNA, is highly expressed in all EBV-positive NPC samples. EBV-miR-BART9 specifically represses E-cadherin [96], which can induce the redistribution of β-catenin and promote the metastasis of NPC cells [97, 98]. The ectopic expression of miR-BART9 also induces a mesenchymal-like phenotype, such as the upregulation of multi-

ple MMPs, higher levels of vimentin and lower levels of α-catenin, but the underlying mechanisms are worthy of further analysis [96].

EBV-miR-BART10-3p directly downregulates the expression of the BTRC gene, which encodes β-transducin repeat containing E3 ubiquitin protein ligase. EBV-miR-BART10 facilitates NPC metastasis and EMT through the inhibition of BTRC and then upregulates the downstream substrates β-catenin and Snail [99].

Roles of lncRNAs in the regulation of NPC metastasis

Long noncoding RNAs (lncRNAs) are commonly defined as transcripts more than 200 nucleotides in length without protein-coding function [100]. lncRNAs were once considered junk RNA and transcriptional noise. However, since that time, it has been realized that lncRNA is involved in normal cell metabolism and that it plays a critical role in cancer initiation and progression. This is demonstrated by an increasing number of studies that have focused on lncRNA and the numerous functional lncRNAs that have been discovered. lncRNAs can act as competing endogenous RNAs and antisense RNAs, among others, and were demonstrated to function as either promoters or suppressors in various cancers. The mechanisms include epigenetic, transcriptional, posttranscriptional regulation of relevant genes and the control of cell cycle distribution, cell differentiation, among other processes [101]. We wondered about the association between lncRNA and NPC metastasis, and therefore, we reviewed recent studies and gathered information on the relevant molecules. We found that lncRNAs mostly target miRNAs to mediate their function and that the majority of lncRNAs play oncogenic roles in NPC. However, the mechanisms behind most of the functions of lncRNAs remain to be clarified. Moreover, it is worth mentioning that the regulatory mechanism of lncRNAs is generally unknown. Therefore, this could repre-

sent a new research direction and might provide novel, efficient therapeutic methods for NPC treatment in the future. The introduction of migration-related lncRNAs in NPC is given below.

LINC0086 was found to be decreased in the serum and tissues of NPC patients. This lncRNA is associated with NPC histological grade, lymph node metastasis, and clinical stage. Guo, J., et al [102] demonstrated that LINC0086 acts as a tumor suppressor in NPC via the direct inhibition of miR-214 expression, which plays a carcinogenic role in NPC [103].

LINC00312, also known as NAG7, is positively associated with the adhesive, invasive, and metastatic capabilities of NPC cells as well as with clinical stage and poor prognosis of NPC patients [104]. This lncRNA activates the JNK2/AP-1/MMP1 pathway and the upstream H-Ras/p-c-Raf pathways and inhibits the expression of estrogen receptor α (ER α), which all play a role in the promotion of NPC invasion and migration [105]. However, LINC00312 was found to be negatively correlated with EBV-encoded RNA 1 (EBER-1) in NPC, but the exact mechanism requires further investigation [104].

lncRNA HOX transcript antisense intergenic RNA (HOTAIR) has been shown to be an oncogenic factor in various cancers [106] including NPC. Its expression increases with clinical stage progression and is positively correlated with poor prognosis of NPC [107]. HOTAIR contributes to cancer cell growth through various pathways [108, 109] and mediates the invasion and metastasis of cancer cells [107] via its interactions with Polycomb repressive complex 2 (PRC2); this in turn alters the methylation of histone H3 lysine 27 [110]. In addition, HOTAIR promotes angiogenesis in NPC by the direct induction of vascular endothelial growth factor A (VEGFA) and GRP78-mediated upregulation of VEGFA and Angiopoietin2 (Ang2) expression [111].

Long intergenic nonprotein coding RNA, regulator of reprogramming (LINC-ROR) is likely regulated by pluripotency transcription factors such as Oct4, Sox2 and Nanog in stem cells [112]. Recently, it has been shown to be highly associated with the metastasis and apoptosis of NPC. LINC-ROR promotes NPC invasion and metastasis by advancing EMT [113]. The mechanism

may be the same as that in breast cancer, in which LINC-ROR acts as a competing endogenous RNA to prevent the degradation of miR-205 target genes, including the EMT inducers ZEB1 and ZEB2 [114]. Furthermore, LINC-ROR is a negative regulator of p53, and this inhibition occurs as a result of its interaction with heterogeneous nuclear ribonucleoprotein I (hnRNP I) at the translational level [115]. This causes chemoresistance and protection from apoptosis of NPC cells [113]. Thus, LINC-ROR may serve as a therapeutic target for NPC.

The expression of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is up-regulated in numerous types of tumors. MALAT1 influences tumor cell proliferation, invasion, metastasis and apoptosis and is regulated by various factors [116, 117]. In NPC cells, MALAT1 is involved in a novel MALAT1/miR-124/Capn4 axis to promote invasion and EMT via the de-repression of Capn4 by sponging miR-124 [118]. Excessive expression of MALAT1 downregulates E-cadherin and upregulates N-cadherin and vimentin [118, 119]. Interestingly, in NPC cells, MALAT1 is negatively regulated by miR-25, whose positive upstream regulator RNA binding motif protein 24 (RBM24) is frequently reduced [120].

Actin filament associated protein 1 antisense RNA 1 (AFAP1-AS1) was demonstrated to be a risk factor in the prognoses of various cancers [121, 122]. In NPC, AFAP1-AS1 is involved in the promotion of metastasis by interfering with AFAP1 and then changing the integrity of actin filaments. Moreover, AFAP1-AS1 can also directly target Rho/Rac GTPase family members and actin cytoskeleton signaling pathway proteins. Consequently, changes or disruptions in intercellular junctions and focal adhesion complexes occurs, the actin cytoskeleton extensively reorganizes, and cancer cells acquire metastatic and invasive abilities [123]. In addition, the levels of AFAP1-AS1 were reported to be positively correlated with programmed cell death protein 1 (PD-1) expression in NPC, which would cause immunosuppression and further promote cell migration [124].

H19 is highly expressed and correlated with proliferation, invasion and migration in most types of cancers, while its role in a few cancers is still in dispute [125]. Li, X., et al [126] verified that H19 is involved in NPC metastasis. H19

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Table 5. Summary of migration-related lncRNAs in NPC

IncrRNA	Location	Target	Molecular mechanism	Functional regulation	Reference
Tumor suppressor lncRNAs					
LINC0086	Xq26.3	miR-214	↓miR-214	Pro-apoptosis, metastasis	[102]
ZNF674-1 (LINC01186)	Xp11.3	-	(tumor suppressor)	Pro-apoptosis, invasion, migration	[141]
Oncogenic lncRNAs					
LINC00312 (NAG7)	3p25.3	1. JNK2/AP-1/MMP1 2. H-Ras/p-c-Raf 3. ERa	1. ↑JNK2/AP-1/MMP1 2. ↑H-Ras/p-c-Raf pathways 3. ↓Era	Pro-apoptosis, adhesion, migration and invasion	[105]
HOTAIR	12q13.13	1. PRC2 2. VEGFA 3. GRP78	↑/↓PRC2 thus altering the methylation of histone H3 lysine 27 ↑VEGFA (directly) ↑GRP78-mediated upregulation of VEGFA, Ang2	Migration, invasion, angiogenesis	[110, 111]
LINC-ROR	18q21.31	1. miR-205 2. hnRNP I	1. ↓miR-205 to ↑miR-205 target genes ZEB1 and ZEB2 2. ↑/↓hnRNP I to negative regulate p53	Metastasis, anti-apoptosis, chemoresistance	[114, 115]
MALAT1 (LINC00047)	11q13.1	miR-124	↓miR-124, ↑Capn4, ↓E-cadherin and ↑N-cadherin, vimentin	Invasion, metastasis, EMT, radioresistance	[118, 119]
AFAP1-AS1	4p16.1	1. AFAP1 2. actin filament Rho/Rac GTPase family 3. actin cyokeratin signaling pathway	↑/↓AFAP1 then changing the integrity of actin filament ↑/↓Rho/Rac GTPase family ↑/↓actin cyokeratin signaling proteins	Invasion, migration, immunosuppression, disruption of cell junctions, reorganization of cytoskeleton	[123]
H19 (LINC00008)	11p15.5	miR-630	↓miR-630, ↑EZH2	Invasion, metastasis	[126]
NEAT1 (LINC00084)	11q13.1	miR-204	↓miR-204, ↑ZEB1	EMT, metastasis, radioresistance	[129]
SNHG1 (LINC00057)	11q12.3	miR-145-5p	↓miR-145-5p, ↑NUAK1	EMT, migration, invasion	[133]
FOXCUT	6p25.3	FOXC1	↑FOXC1	EMT, metastasis, angiogenesis	[137]
LOC553103	-	-	(promoting metastasis)	EMT, invasion, migration	[92]
THOR	2q14.2	-	(promoting metastasis)	Cisplatin sensitivity, metastasis	[138]
LINC01420	Xp11.21	-	(promoting metastasis)	Migration, invasion	[139]
XIST	Xq13.2	miR-491-5p	↓miR-491-5p, ↑Notch3	Migration, invasion	[140]
HNF1A-AS	12q24.31	-	(promoting metastasis)	Invasion, metastasis	[142]
ENST00000470135	-	-	(promoting metastasis)	Invasion, metastasis	[143]
LOC84740, ENST00000498296, ENST00000438550	-	-	(show significant difference between metastatic and primary NPC tumors)	Metastasis	[144]
uc010rul	-	ARHGAP42	↑/↓ARHGAP42 and ARHGAP42 activates PI3K/Akt/mTOR signal pathway	Invasion, migration	[145]
CCAT1	8q24.21	-	(promoting metastasis)	Invasion, migration, anti-apoptosis	[146]
ZFAS1	20q13.13	-	(promoting metastasis)	Metastasis, anti-apoptosis	[147]
C22orf32-1 (LINC01315)	22q13.2	-	(promoting metastasis)	Invasion, migration, anti-apoptosis	[148]
LINC00460	13q33.2	miR-149-5p	↓miR-149-5p to upregulate IL-6	(migration, invasion)	[10]

Legends: We use "-" or "()" if the locations, targets, and mechanisms of lncRNAs are currently unknown. The column "location" indicates the location of the DNA that encodes its corresponding lncRNA; the data are selected in the GenBank repository. Tumor suppressor lncRNAs are often downregulated and oncogenic lncRNAs are often upregulated in patients with metastatic NPC.

has de-repression functions to upregulate enhancer of zeste homolog 2 (EZH2) expression via its interaction with miR-630 in a sequence-specific manner. Additionally, EZH2 acts as an inhibitor of E-cadherin, which promotes cell invasion and migration [127].

The overexpression of Nuclear paraspeckle assembly transcript 1 (NEAT1) in several types of solid tumors is associated with a poor prognosis [128]. Lu, Y., et al [129] found a reciprocal repression between NEAT1 and miR-204. ZEB1 is also directly inhibited by miR-204. Therefore, a high level of NEAT1 induces an EMT phenotype and promotes metastasis of NPC cells. Moreover, ZEB1 enhances radioresistance in cancer cells by stabilizing checkpoint kinase 1 (CHK1) [130]. These findings imply that NEAT1 may be a novel therapeutic target in NPC.

A high level of Small nucleolar RNA host gene 1 (SNHG1) was recently considered to be a predictor of enhanced migration capacity and an unfavorable prognosis in a few cancers [131, 132]. In NPC, Lan, X., et al [133] showed that SNHG1 could upregulate NUAK1, an AMPK-related kinase, by inhibiting miR-145-5p, which targets the NUAK1 3'-UTR and subsequently promotes the migration of NPC cells partly through Akt signaling and EMT. In detail, the inhibition of NUAK1 was found to result in the upregulation of E-cadherin and the downregulation of phosphorylated Akt, N-cadherin, MMP-2, MMP-9 and its regulatory factor membrane-type-1 matrix metalloproteinase (MT1-MMP) in CNE and HNE-1 cells.

Forkhead box C1 upstream transcript (FOXCUT) was reported to be associated with metastasis and growth in several cancers [134-137]. Xu, Y. Z., et al [137] validated that FOXCUT would induce forkhead box C1 (FOXC1), a positive EMT-related gene [135], and this induction subsequently contributed to angiogenesis and progression in NPC. Specifically, after knocking down FOXCUT, the expression of MMP7, MMP9, VEGFA and β -catenin was decreased, which conversely showed the angiogenesis- and metastasis-promoting functions of FOXCUT-FOXC1.

LOC553103, a newly discovered lncRNA, was reported to promote EMT and thereby increase the invasive, metastatic capability of NPC cells. The mechanism of the function of LOC553103

in the mediation of EMT is still unknown. But amazingly, LOC553103 is directly downregulated by EBV-encoded EBV-miR-BART6-3p [92]. Therefore, it appears that EBV plays more than only oncogenic roles in NPC.

We have also investigated several lncRNAs related to the metastasis of NPC that are seldom reported in the literature. lncRNA THOR can attenuate cisplatin sensitivity of NPC cells by enhancing cell stemness through the upregulation of YAP transcription. In addition, the inhibition of THOR also depresses the metastasis of NPC [138]. High level of LINC01420 is considered an independent factor for an unfavorable prognosis for it correlates with distant metastasis in NPC patients. Moreover, gender differences were found in the level of LINC01420, as this lncRNA is dramatically high in male patients with NPC [139]. X inactive specific transcript (XIST) and miR-491-5p repress each other, and miR-491-5p is an inhibitor of Notch3. The knockdown of XIST would inhibit the migration and invasiveness of NPC cells in vitro and in vivo [140]. Available information on these lncRNAs is limited, but further studies may help to reveal the mechanism behind the metastasis of NPC and may provide novel, efficient biomarkers and therapies for NPC.

Some other lncRNAs that have not been well studied may also be important, and thus we listed them in **Table 5** together with the above-mentioned molecules.

Roles of cellular miRNAs in the regulation of NPC metastasis

miRNA was first discovered in 1993 in *C. elegans* with the identification of lin-4, which can regulate Lin-14 at the posttranscriptional level [149, 150]. With the development of molecular techniques, the characteristics and functions of miRNA have been revealed. The clinical significance of miRNA, especially concerning tumors, has raised great interest because the deregulation of miRNAs is strongly associated with tumor initiation and progression through a complex regulatory network. Moreover, miRNAs are thought to be highly potential biomarkers for tumor diagnosis and prognosis.

miRNAs are a type of endogenously expressed noncoding RNA that are about 22 nucleotides in length [80]. miRNA can inhibit mRNA expres-

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Table 6. Summary of microRNAs associated with NPC metastasis

miRNA	Location	Targets	Molecular mechanism	Functional regulation	Reference
Tumor suppressor microRNAs					
miR-29c	1q32.2	1. TIAM1	1. ↓TIAM1	Invasion, metastasis	[156]
		2. extracellular matrix	2. ↓extracellular matrix		[157]
		3. DNMT 3a and 3b	3. ↓DNMTs, ↑miR-34c and 449a		[12]
miR-200a	1p36.33	1. ZEB2	1. ↓ZEB2, ↑E-cadherin	EMT	[158]
		2. CTNNB1	2. ↓CTNNB1		[160]
miR-98	Xp11.22	1. MTDH	1. ↓MTDH	EMT, invasion, metastasis	[163]
		2. STAT3	2. ↓STAT3		[164]
		3. EZH2	3. ↓EZH2		[165]
miR-101	1p31.3	1. EZH2	1. ↓EZH2	Overexpress protein kinase, metastasis, escape of apoptosis	[165]
		2. MEK1	2. ↓MEK1/ERK/MAPK		[188]
		3. ITGA3	3. ↓ITGA3		[189]
miR-26a	3p22.2	1. EZH2	1. ↓EZH2	Invasion, metastasis	[166]
		2. cyclin D2	2. ↓cyclin D2		[190]
miR-4288	8p21.1	ELF3	↓ELF3	Invasion, metastasis	[167]
miR-92b	1q22	Smad3	↓Smad3	EMT, metastasis	[168]
miR-122	18q21.31	TRIM29	↓TRIM29, ↓PI3K/Akt signaling	Metastasis	[169]
miR-328	16q22.1	CD44	↓CD44, E-cadherin, ↑N-cadherin, Snail, and vimentin	EMT, metastasis	[170]
miR-342	14q32.2	ZEB1	↓ZEB1	Invasion	[171]
miR-99a	21q21.1	HOXA1	↓HOXA1	Invasion, metastasis	[172]
miR-124	8p23.1	Capn4	↓Capn4, ↓β-catenin, cyclin D1, and c-Myc	Invasion	[118]
miR-185-3p	22q11.21	WNT2B	↓WNT2B	Invasion, metastasis	[174]
miR-324-3p	17p13.1	1. WNT2B	1. ↓WNT2B	Invasion, metastasis, apoptosis	[173]
		2. E-cadherin, Vimentin	2. ↑E-cadherin, ↓Vimentin		[173]
		3. GLI3	3. ↓GLI3		[175]
miR-944	3q28	MACC1	↓MACC1, ↑E-cadherin	EMT, metastasis	[176]
miR-9	1q22	1. CXCR4	1. ↓CXCR4/SDF-1/p38 MAPK pathway	Overexpress protein kinase, invasion, metastasis, EMT	[191]
		2. FN1, ITGB1 and ITGAV	2. ↓FN1, ITGB1 and ITGAV		[192]
		3. immuno-related molecules	3. ↓/↑immune genes expression		[193]
miR-451	17q11.2	MIF	↓MIF	Cell viability, colony formation, invasion, metastasis	[194]
miR-216b	2p16.1	1. KRAS	1. ↓KRAS related Akt and ERK pathways	Invasion, metastasis	[195]
		2. PKCα	2. ↓PKCα		[196]
miR-34c	11q23.1	MET	↓MET	Invasion, metastasis	[197]
miR-16	13q14.2	FMNL1	↓FMNL1, ↑MTA1	EMT, invasion	[198]
miR-143	5q32	ERK-5, caspase 3, KRAS	↓ERK-5, ↑KRAS, caspase 3	Invasion, migration, escape of apoptosis	[199]
miR-148b	12q13.13	MTA2	↓MTA2	Invasion, metastasis	[200]
miR-212	17p13.3	SOX4	↓SOX4	Invasion, metastasis	[201]
miR-425	3p21.31	HDGF	↓HDGF	Viability, invasion	[202]
miR-130a-3p	11q12.1	BACH2	↓BACH2	Viability, invasion, apoptosis	[203]

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miR-203a-3p	14q32.33	LASP1	LASP1	Metastasis	[37]
miR-371-5p	19q13.42	BCL2	↓BCL2	Metastasis	[204]
miR-374a	Xq13.2	CCND1	↓CCND1, ↓PI3K/Akt	Metastasis	[205]
miR-34a	1p36.22	SMAD4	↓SMAD4, ↓TGF-β pathway	EMT, invasion, metastasis	[206]
Oncogenic microRNAs					
miR-200c	12p13.31	PTEN	↓PTEN	Cellular transformation, metastasis	[162]
miR-141	12p13.31	BRD3, UBAP1, PTEN	1. ↓BRD3 regulated Rb/E2F pathway 2. ↓UBAP1 3. ↓PTEN	Invasion, metastasis	[179]
miR-155	21q21.3	JMJD1A & BACH1	↓JMJD1A and BACH1	Clonogenicity, Invasion, metastasis	[181]
miR-30a	6q13	E-cadherin	↓E-cadherin	Metastasis, EMT	[182]
miR-149	2q37.3	1. E-cadherin 2. IL-6	1. ↓E-cadherin 2. ↓IL-6	EMT	[185] [10]
miR-144	17q11.2	PTEN	↓PTEN, ↑PI3K/Akt pathway	Clonogenicity, migration, invasion	[207]
miR-214	1q24.3	LTF Bim	↓LTF, ↑Akt pathway ↓Bim	Metastasis, apoptosis	[208] [209]
miR-93	7q22.1	1. TGFβR2 2. DAB2 3. CDKN1A	1. ↓TGFβR2, ↓Smad-dependent TGF-β signaling and ↑PI3K/Akt pathway 2. ↓DAB2 3. ↓CDKN1A	Invasion, metastasis, EMT	[210] [211] [212]
miR-27a-3p	19p13.12	Mapk10	↓Mapk10	Invasion, metastasis	[213]
miR-18a	13q31.3	STK4	↓STK4	Apoptosis	[214]
miR-346	10q23.2	BRMS1	↓BRMS1	Invasion, metastasis	[215]
miR-663b	2q21.2	TUSC2	↓TUSC2	Invasion, metastasis	[216]

Legends: The column "location" indicates the location of the DNA that encodes its corresponding miRNA; the data are selected in the GenBank repository. Tumor suppressor miRNAs are often expressed at lower levels in metastatic patients while oncogenic miRNAs are often expressed at higher levels, which indicates a poor prognosis.

sion by base-pairing with its complementary sequences in the 3'-UTR within mRNA, thereby represses gene expression in an epigenetic manner [151]. Since perfect binding to mRNA is not necessary and miRNAs are short, a single miRNA may regulate many target mRNAs [152]. Actually, one-third of the human mRNA population is controlled by miRNAs [153]. The evolutionary conservation of miRNA also indicates that they are of great significance in biological processes [154]. Thus, the alterations in miRNA expression may explain the etiology of cancers by inducing tumor cell proliferation, invasion, metastasis, angiogenesis and inhibition of apoptosis. miRNA can act as tumor promoters or suppressors. Variations in the sequence of miRNAs and epigenetic alterations including hypermethylation and histone deacetylation may explain the ways miRNAs are altered [152]. Deregulation of lncRNA and EBV infection can also modulate the expression of oncomirs.

Below, we will discuss miRNAs whose mechanisms in NPC metastasis have been discovered. A summary table (**Table 6**) is shown at the end of the section.

Tumor suppressive miRNAs

The expression of miR-29c is incredibly low in NPC patients, especially in those patients whose tumors have already migrated [155-157]. miR-29c exerts its tumor suppressive functions through the inhibition of several specific genes. One important targeted gene is T cell lymphoma invasion and metastasis 1 (TIAM1), whose ectopic expression has been verified to strongly promote the invasion and metastasis of NPC in vitro and in vivo [156]. Moreover, miR-29c can downregulate DNA methyltransferase (DNMT) 3a and 3b and repress the methylation of the CpG islands of NPC suppressors such as miR-449a and miR-34c [12]. Additionally, decreased levels of miR-29c cause the increased expression of extracellular matrix components such as multiple collagens and laminin γ 1 and consequently facilitate tumor motility [157].

The miR-200 family has 5 members including miR-200a, miR-200b, miR-200c, miR-429 and miR-141 [158]. miR-200a and miR-200b were reported to be downregulated in NPC [159], and miR-200a inhibits NPC invasion and migration. miR-200a can inhibit ZEB2 and β -catenin

[160]. ZEB2 can downregulate E-cadherin, the low expression of which facilitates EMT [158]. β -catenin, which plays a significant role in NPC development [160] was overexpressed in most NPC patients [161]. Interestingly, the miR-200 family does not just repress tumors, but it also plays an oncogenic role. miR-200c, which is activated by c-Myc, promotes NPC invasion and metastasis as a negative regulator of PTEN [162]. miR-141 is also an oncogenic miRNA and will be specifically discussed later in this review. In conclusion, the miR-200 family is similar to a double-edged sword, and its relationship with NPC requires further exploration.

As another tumor suppressor, microRNA miR-98 has recently been demonstrated in vitro to inhibit metadherin (MTDH), and consequently, its low expression results in the overexpression of MTDH and induces alterations in EMT [163]. Additionally, miR-98 can directly inhibit STAT3 to mediate its anticarcinogenic functions [164]. Furthermore, miR-98, along with miR-26a and miR-101, can all downregulate Enhancer of EZH2, which is correlated with NPC metastasis and recurrence [165, 166].

miR-4288 acts as a tumor suppressor and targets E74-like ETS transcription factor 3 (ELF3). miR-4288 has a competing endogenous RNA termed circular homeodomain interacting protein kinase 3 (circHIPK3), which is highly expressed in NPC tissues and can protect ELF3 [167].

In recent years, many novel miRNAs have been confirmed to participate in NPC metastasis. miR-92b can inhibit EMT and metastasis of NPC via the inhibition of Smad3 by binding to its 3'-UTR [168]. miR-122 can suppress tripartite motif-containing protein 29 (TRIM29); this leads to the repression of PI3K/Akt signaling, which is associated with NPC metastasis [169]. miR-328 represses CD44, and this results in the increased expression of E-cadherin and decreased expression of N-cadherin, Snail, and vimentin, which are associated with EMT and metastasis [170]. miR-342 can negatively target ZEB1 and inhibit tumor invasion [171]. miR-99a can repress NPC invasion and metastasis by inhibiting homeobox A1 (HOXA1) [172]. miR-124 can suppress NPC invasion by the downregulation of calpain small subunit 1 (Capn4) and subsequently decreases in β -catenin, cyclin D1, and c-Myc, which are components of

the Wnt/ β -catenin signaling pathway [118]. Both miR-185-3p and miR-324-3p can downregulate Wnt family member 2B (WNT2B) and inhibit NPC invasion and metastasis [173, 174]. The expression of E-cadherin and Vimentin is correlated with miR-324-3p [173]. miR-324-3p also directly targets the gene GLI3 [175]. miR-944 can inhibit NPC EMT and metastasis by downregulating metastasis-associated in colon cancer protein 1 (MACC1) and can consequently cause enhancement of E-cadherin expression and reduction in N-cadherin and vimentin expression [176].

Oncogenic miRNAs

As mentioned above, miRNA-141 is a member of the miR-200 family and has oncogenic functions [177]. miRNA-141 is markedly overexpressed in NPC cells [178] and can negatively regulate several targets including bromodomain containing 3 (BRD3), ubiquitin-associated protein 1 (UBAP1) and PTEN, which are negatively associated with NPC carcinogenesis. The downregulation of PTEN will cause the disinhibition of Akt signaling. Additionally, the JNK2 pathway is also facilitated by miRNA-141. In conclusion, the overexpression of miR-141 will result in NPC cell proliferation, invasion and migration by activation of a few oncogenic pathways [179]. It is worth mentioning that the mechanism of miR-141 regulation has been identified, at least partially. The oncogene c-Myc can upregulate miR-141, while its co-factor, bromodomain containing 7 (BRD7), can downregulate the c-Myc/miR-141 axis by directly targeting c-Myc. Obviously, BRD7 and c-Myc form a negative feedback loop to regulate miR-141, which modulates tumor initiation and progression [178, 180]. Moreover, the re-expression of short palate, lung, and nasal epithelium clone 1 (SPLUNC1) reportedly attenuates miR-141 [179].

The overexpression of miR-155 can induce tumor cell proliferation, migration and invasion by inhibiting its target genes, the Jumonji Domain 1A (JMJD1A) and BTB and CNC homology 1 (BACH1). In EBV-positive NPC tissue samples, LMP1 and LMP2A are closely related to the increased level of miR-155 expression and consequently decrease JMJD1A, which causes a poor prognosis [11, 181].

miR-30a can promote NPC invasion and metastasis via the repression of E-cadherin activity,

which results in a poor prognosis [182]. Insulin-like growth factor I (IGF-I) has been identified as an upstream regulator of miR-30a, which can induce EMT through the IGF-IR-*Src*-miR-30a-E-cadherin pathway [183].

miR-149 mediates the progression and development of NPC [184] through the downregulation of E-cadherin, the same target as miR-30a [185]. In addition, LncRNA-LINC00460 has been validated to function as a competing endogenous RNA for miR-149-5p. This upregulates the IL6 gene and leads to NPC proliferation [10].

miR-20a is overexpressed in NPC cells [155], and we anticipate that its target is deleted in liver cancer-1 (DLC-1) (not yet published). We found that DLC-1 is often downregulated or absent in NPC cells [186] and can negatively regulate EMT by the repression of the EGFR/Akt/NF- κ B pathway [187].

Some other miRNAs that are associated with NPC metastasis along with those already discussed are all shown below in **Table 6**.

Conclusion

In summary, many regulators that are involved in NPC metastasis have been discovered to compose a complicated regulatory network. Thus, they should not be considered alone when we study the molecular mechanisms of metastatic NPC. This inspires us in the sense that when targeted therapies are used, we should consider the interlinked regulatory pathways rather than focus only on a single target. Although the survival rate of patients with NPC is increasing, no effective treatment exists for metastatic tumor cells. However, the continual discovery of the complex genetic regulatory network that operates during NPC metastasis may give us additional inspiration. Further validations on the molecular mechanisms of NPC metastasis should be performed, and molecules such as EBV products, lncRNAs and miRNAs can provide some new targets for targeted therapy and undoubtedly improve the management of NPC.

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None.

Abbreviations

3'-UTR, 3'-untranslated region; AFAP1-AS1, Actin filament associated protein 1 antisense RNA 1; Ang2, Angiopoietin2; ATF2, activating transcription factor 2; BACH1, BTB and CNC homology 1; BART, BamHI fragment A rightward transcript; BCL2, B-cell lymphoma 2; BCR, B-cell receptor; BHRF1, BamHI fragment H rightward reading frame 1; Bim, Bcl-2-interacting mediator of cell death; BRD3, bromodomain containing 3; BRD7, bromodomain containing 7; BRMS1, breast cancer metastasis suppressor 1; BTRC, β -Transducin Repeat Containing E3 Ubiquitin Protein Ligase; Capn4, calpain small subunit 1; CCAT1, colon cancer associated transcript 1; CD109, Cluster of Differentiation 109; Cdc42, Cell division control protein 42 homolog; CDH6, cadherin 6; CDKN1A, Cyclin Dependent Kinase Inhibitor 1A; c-Jun, c-Jun N-terminal kinase; circHIPK3, circular homeodomain interacting protein kinase 3; CHK1, checkpoint kinase 1; Dab2, disabled homolog-2; DcR3, Decoy receptor 3; DLC-1, deleted in liver cancer-1; DNMT, DNA methyltransferase; EBER-1, EBV-encoded RNA 1; EBNA1, Epstein-Barr virus nuclear antigen 1; EBV, Epstein-Barr virus; ELF3, E74-like ETS transcription factor 3; EMT, epithelial-mesenchymal transition; Er α , estrogen receptor α ; ERK, extracellular signal-regulated kinase; EZH2, zeste homolog 2; FAK, focal adhesion kinase; FGD4, FYVE, RhoGEF and PH domain containing 4; FMNL1, formin-like protein 1; FN1, fibronectin 1; Fra-1, AP-1 transcription factors; FOXC1, forkhead box C1; FOXCUT, Forkhead box C1 upstream transcript; GSK3 β , glycogen synthase kinase 3 β ; HIF1 α , Hypoxia-inducible factor-1 α ; HDGF, hepatoma-derived growth factor; HNF1A, Hepatocyte nuclear factor 1A; hnRNP I, heterogeneous nuclear ribonucleoprotein I; HOTAIR, HOX transcript antisense

intergenic RNA; HOXA1, homeobox A1; IGF-I, Insulin-like growth factor I; IL-6, interleukin 6; IL-8, interleukin 8; IRF7, interferon regulatory factor 7; ITAM, immunoreceptor tyrosine-based activation motif; ITG α 6, integrin- α 6; ITGAV, α 5 integrin; ITGB1, integrin β 1; ITGA3, integrin subunit α 3; JMJD1A, Jumonji Domain 1A; JNK/SAPK, c-Jun N-terminal kinase/stress-activated protein kinase; LINC-ROR, Long intergenic non-protein coding RNA, regulator of reprogramming; LMP1, EB-virus Latent Membrane Protein 1; LMP2A, latent membrane protein 2A; lncRNAs, long non-coding RNAs; LTF, lactoferrin; MACC1, metastasis-associated in colon cancer protein 1; MALAT1, Metastasis associated lung adenocarcinoma transcript 1; MAPK, mitogen-activated protein kinase; miRNAs, microRNAs; MEK1, MAPK kinase 1; MIF, migration inhibitory factor; MMP3, matrix metalloproteinase 3; MMP9, matrix metalloproteinase 9; MT1-MMP, membrane-type-1 matrix metalloproteinase; MTA1, metastatic tumor antigen 1; MTA2, metastasis-associated gene 2; MTDH, metadherin; MUC1, Mucin 1; NEAT1, Nuclear paraspeckle assembly transcript 1; NF- κ B, nuclear factor- κ B; NPC, nasopharyngeal carcinoma; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PTEN, phosphatase and tensin homolog; PD-1, programmed cell death protein 1; PI3K, phosphatidylinositol 3-kinase; PRC2, Polycomb repressive complex 2; PTEN, phosphatase and tensin homolog; PY, PPPPY; RAGE, the receptor for advanced glycation end products; RBM24, RNA binding motif protein 24; RUNX2, Runt-related transcription factor 2; S100A4, S100 calcium binding protein A4; S1P, sphingosine-1-phosphate; SNHG1, Small nucleolar RNA host gene 1; SPLUNC1, short palate, lung, and nasal epithelium clone 1; STAT, signal transducer and activator of transcription; STK4, serine/threonine-protein kinase; Syk, spleen tyrosine kinase; SPHK1, sphingosine kinase 1; TES, transformation effector sites; TGF β , transforming growth factor β ; TGF β R2, transforming growth factor- β receptor II; TIAM1, T cell lymphoma invasion and metastasis 1; TIMP-3, tissue inhibitor of metalloproteinase-3; TME, tumor microenvironment; TNFAIP2, tumor necrosis factor α -induced protein 2; TPST-1, tyrosyl protein sulfotransferase-1; TRIM29, motif-containing protein 29; TUSC2, tumor suppressor candidate 2; UBAP1, ubiquitin-associated protein 1; VEGF, vascular endothelial growth factor; VEGFA, vascular endothelial

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growth factor A; XIST, X inactive specific transcript; ZEB1 and ZEB2, zinc finger E-box binding homeobox 1 and 2; ZFAS1, ZNF1 antisense RNA 1.

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