

Review Article

The emerging roles of exosomal miRNAs in nasopharyngeal carcinoma

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Abstract: Nasopharyngeal carcinoma (NPC) is a unique subtype of head and neck cancer that is endemic to Southern China and Southeast Asia. Due to the concealed location and intrinsic invasiveness of this disease, majority of NPC patients are diagnosed with advanced stages (III and IV) and poor prognosis. Chemoradiotherapy resistance is a major problem for NPC patients, leading to incomplete local elimination, recurrence and metastasis. Therefore, it is of great significance to seek novel biomarkers and effective therapeutic regimen for clinical management of this deadly cancer. Exosomes are tiny membrane vesicles with a lipid bilayer secreted by most cells in the body, which are widely distributed in various body fluids. They are functionally active in different physiopathological process by carrying and transmitting important signal molecules such as miRNA, mRNA, protein, lipid, etc. Exosomal miRNAs play an important role in tumorigenesis and development of NPC. They are extensively involved in NPC cell proliferation, migration, invasion, neovascularization, radiotherapy resistance and the regulation of tumor immune microenvironment through intercellular communication and control of gene expression. Moreover, exosomal miRNAs can be used as valuable biomarkers for early diagnosis and therapeutic targets of NPC.

Keywords: Exosomes, miRNA, nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is a unique subtype of head and neck cancer that is endemic to Southern China and Southeast Asia [1, 2]. The exact etiology of NPC is obscure yet, however, the known risk factors include Epstein-Barr virus (EBV) infection, genetic predisposition, diet and environmental factors [3, 4]. Due to the concealed location and intrinsic invasiveness of this disease, majority of NPC patients are diagnosed with advanced stages (III and IV) and poor prognosis [5]. Concurrent chemoradiotherapy is the standard therapeutic regimen for NPC [6]. Although the curative effect of chemoradiation is distinct, it would also cause undesirable side-effects, and recurrence and distant metastasis are responsible for the predominant mode of treatment failure. Therefore, it is urgent to develop novel diagnostic biomarkers and improve strategies for the clinical management of this deadly cancer. Currently, exosomes containing specific reper-

toires of proteins, RNAs, and lipids are becoming a useful tool for early diagnosis of various diseases. Exosomal microRNAs (miRNAs) have been reported to be extensively involved in cancer cell proliferation, migration, invasion, neovascularization, radiotherapy resistance and tumor immune microenvironment. Moreover, they can also be used as potential biomarkers, which is of great significance for the early diagnosis and therapeutic targets of cancers. Here, we not only summarize the sorting mechanism of miRNAs into exosomes, but also highlight the emerging roles of exosomal miRNAs in tumorigenesis and progression of NPC (**Figure 1**, **Table 1**).

Exosomes

Exosomes are a homogeneous population of 30- to 120-nm-diameter vesicles secreted by most cells to the extracellular environment.

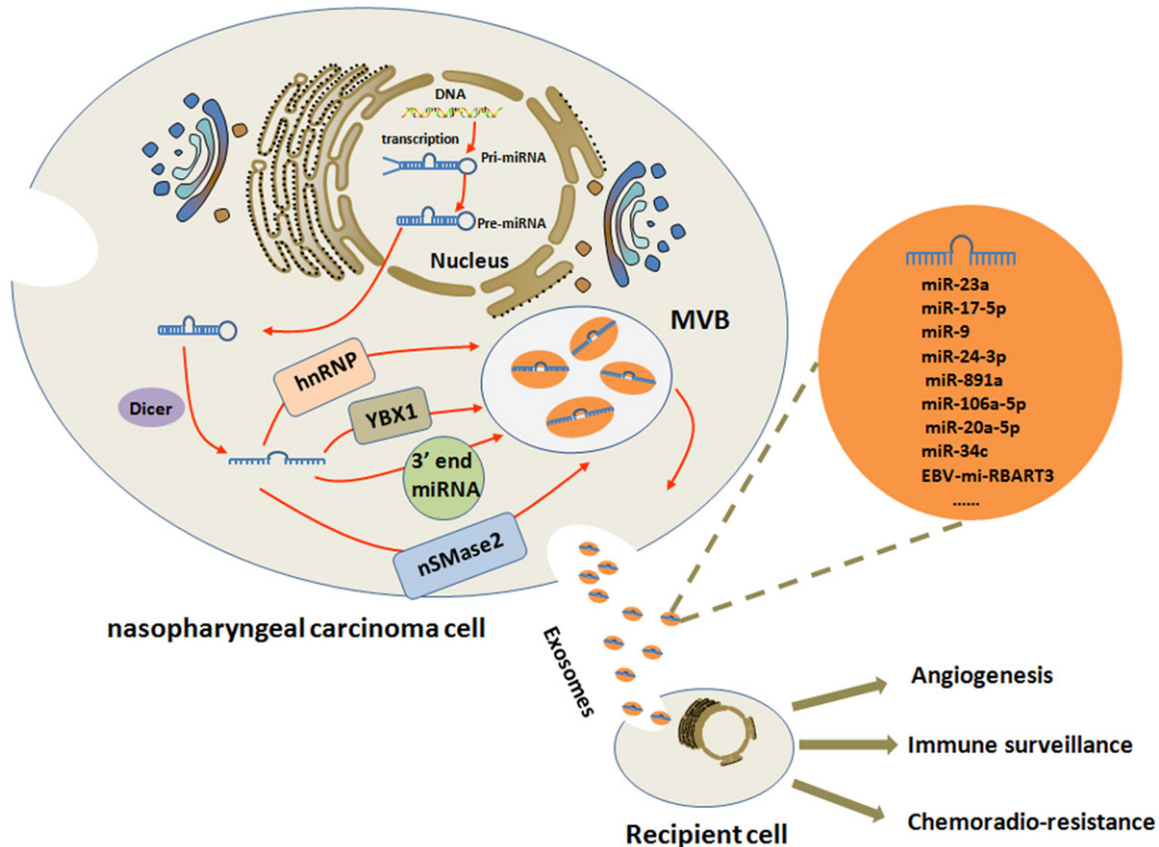


Figure 1. The biogenesis of exosomal miRNA and its role in nasopharyngeal carcinoma progression. Primary miRNA (pri-miRNA) is transcribed in the nucleus by the RNA polymerase II/III. The microprocessor cleaves pri-miRNA into precursor miRNA (pre-miRNA) to form a hairpin structure. The pre-miRNA is transported into the cytosol, which is decomposed by Dicer enzyme to form mature miRNA. Multiple mechanisms are involved in miRNA sorting into exosomes including heterogeneous nuclear ribonucleoprotein (hnRNP), neutral sphingomyelinase 2 (nSMase2), Y-box protein 1 (YBX1) and 3' end miRNA sequence-dependent approaches. By transferring miRNA to recipient cells, exosomes influence the biological behavior of NPC cells as well as stromal cells in NPC tumor microenvironment, thus affecting the tumorigenesis and development of NPC in multiple aspects.

Through sprouting of the endosome membrane, vesicle-filled endosomes are generated, known as multivesicular endosomes (MVEs) or multivesicular bodies (MVBs) [7, 8]. After that, MVEs are fused with the plasma membrane to form exosomes. In addition, MVEs might also be fused with lysosomes as part of degradation pathway [9]. Although exosomes are small in size, they have a complex structure and contain a variety of signaling molecules in the capsule, and the species of which are specific to the donor cells. Secreted exosomes consequently enter into the recipient cells to transmit functional molecules that initiate relevant signaling pathways to exert important biological functions [10-13].

Exosomal miRNAs

miRNAs are a class of endogenous ~22 nt non-coding small RNAs that function in gene expres-

sion suppression through translational repression or mRNA turnover. miRNAs can target mRNAs for cleavage or inhibit their translation by binding to the 3' UTR (untranslated region), thus inhibiting the target gene expressions [14, 15]. The species and amount of miRNA included in the exosomes are dependent on selective sorting process. Although the regulatory mechanism is not fully understood, accumulating documents support that miRNAs might be sorted through four pathways: (1) miRNA motif- and heterogeneous nuclear ribonucleoprotein (hnRNP)-dependent approach. miRNAs that have been loaded into exosomes contain a common short sequence GGAG (EXO sequence), which is mainly distributed at the 3'-terminal of miRNA and can bind specifically to hnRNP2B to be included into exosomes [16]. (2) Neutral sphingomyelinase 2 (nSMase2)-dependent approach. Overexpression of nSMase2 increas-

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Table 1. Regulatory mechanism of exosomal miRNAs associated with nasopharyngeal carcinoma

Function	Exosomal miRNA	Regulatory mechanism	References
Pro-angiogenesis	miR-23a	Enhancing the angiogenesis of HUVECs cells by directly targeting TSGA10	[28]
	miR-17-5p	Targeting BAMBI and AKT/VEGF-A signaling	[29]
	EBV-miR-BART10-5p, miR-18a	Regulating the expression of VEGF and HIF1- α in a Spry3-dependent manner	[59]
Anti-angiogenesis	miR-9	Targeting MDK and PDK/AKT signaling to inhibit the migration and tube formation of HUVEC cells	[30]
Invasion and metastasis	EBV-miR-BART10-3p	Inducing EMT to facilitate the invasion and metastasis of NPC	[58]
Immune regulation	miR-891a, miR-106a-5p, miR-20a-5p, miR-1908	Inducing T cell disorders through inhibition of MARK1 signaling	[32]
	miR-24-3p	Targeting FGF11 p-ERK, p-STAT1, p-STAT3 \uparrow p-STAT5 \downarrow Inhibiting the proliferation of T cells and the differentiation of Th1 and Th17	[33]
	EBV-mi-RBART3	pro-inflammatory cytokine IL-6 \uparrow Targeting IPO7 and Caspase 3 to inhibit host innate immunity	[35-37]
Radiotherapy resistance	miR-34c	Promoting radiosensitivity by Targeting β Catenin to inhibit EMT	[45]
Diagnostic indicator	EBV-miR-BART7-3p, miR-24-3p	Circulating exosomal miRNAs	[57]
Radiation resistance	miR-34c	Promoting radiosensitivity by Targeting β Catenin to inhibit EMT	[45]

BAMBI, bone morphogenic protein and activating membrane-bound inhibitor; ERK, extra-cellular signal-regulated kinase; FGF11, Fibroblast growth factor 11; IPO7, importin-7; MARK1, Microtubule affinity regulating kinase 1; MDK, Midkine; PDK, phosphoinositide-dependent protein kinase; STAT, Signal transducers and activators of transcription; TSGA10, Testis-specific gene antigen 10; VEGF-A, vascular endothelial growth factor-A.

es the content of exosomal miRNA, and vice versa [17]. (3) Y-box protein 1 (YBX1)-associated pathway [18]. (4) 3' end miRNA sequence-dependent pathway. 3' end adenylated miRNAs are mainly present in cells, whereas 3' end uridylylated isoforms appear relatively enriched in exosomes, which suggests that 3' end miRNAs might contain important sorting signals [19]. Considering that exosomes load specific miRNAs reflecting the physiopathological information from cells of origin, exosomal miRNAs might be taken as novel biomarkers and targets for disease diagnosis and therapy.

The role of exosomal miRNAs in NPC progression

By transferring miRNA to recipient cells, exosomes influence the biological behavior of cancer cells as well as stromal cells in the tumor microenvironment, thus affecting the tumorigenesis and development of cancers from multiple aspects. EBV infection prominently contributes to NPC progression. The viral genome resides in the nuclei of infected NPC cells with transcription of a family of viral microRNAs called BART miRNAs (EBV-miR-BARTs). Notably, EBV-miR-BARTs have also been reported to be sorted into exosomes and delivered to the recipient cells.

Exosomal miRNAs in NPC angiogenesis

Angiogenesis plays an essential role in the progression of a variety of solid tumors and a fraction of hematologic malignancies [20-22]. In 1971, Folkman first proposed that "tumor growth depends on angiogenesis" [23] and many types of cancers rely on new blood vessels to provide oxygen and nutrients for sustaining their growth [24-27]. miRNAs loaded in cancer-secreted exosomes have been demonstrated closely associated with the regulation of gene expressions and signal transduction in angiogenesis. Recently, exosomes secreted by NPC cells were found enriched with miR-23a, which significantly enhanced the angiogenesis of human umbilical vein vascular endothelial cells (HUVES) through direct targeting Testis-specific gene antigen 10 (TSGA10) [28]. Moreover, miR-23a depletion substantially inhibited angiogenic process. These observations support the role of miR-23a in NPC angiogenesis. In addition, exosomal miR-17-5p was also reported to promote the angiogenesis of NPC

through targeting bone morphogenic protein and activin membrane-bound inhibitor homolog (BAMBI) as well as regulating AKT/VEGF-A (vascular endothelial growth factor-A) signaling [29]. Dependent on the function of its target gene, exosomal miRNAs can also act as tumor suppressors to inhibit the angiogenesis. A recent study from Lu et al. revealed that exosomal miR-9 derived from NPC cells exerted anti-angiogenesis effect, which is mainly by targeting Midkine (MDK) and PDK (phosphoinositide-dependent protein kinase)/AKT signaling pathway. Midkine (MDK), a heparin-binding growth factor, is recognized as a "pan-cancer" biomarker. The inhibition of MDK as well as PDK/AKT axis induced by exosomal miR-9 led to the blockage of tube formation and migration of HUVEC cells and reduction of microvascular density of NPC [30].

Exosomal miRNAs in immunosuppression of NPC

The tumor immune microenvironment has long played an important role in the development of NPC, which mainly consists of tumor-associated macrophages (TAMs) and T cells [31]. At present, the regulation of exosomal miRNA on tumor immune microenvironment has been principally focused on T cells. Ye et al. [32] revealed that the serum exosomes of NPC patients were enriched with miR-24-3p, miR-891a, miR-106a-5p, miR-20a-5p and miR-1908. Further studies found that these exosomal miRNAs down-regulated the MARK1 (microtubule affinity regulating kinase 1) signaling pathway, thereby inducing T cell disorders and promoting tumor progression. miR-24-3p directly targeted FGF11 (fibroblast growth factor 11) and upregulated the phosphorylated levels of ERK (extra-cellular signal-regulated kinase) as well as STAT1,3 (signal transducers and activators of transcription 1,3), whereas reducing p-STAT5. It consequently resulted in the inhibition of T cell proliferation and the differentiation of T-helper 1 (Th1) and Th17, thus promoting the progression of NPC [33]. Whether exosomal miRNA can affect TAMs has not been reported yet.

During the development of NPC, one of the important strategies is how to avoid host immune surveillance. Exosomes secreted by EBV infected-cells was found containing EBV-miR-BART3, which induces the production of

inflammatory cytokine Interleukin 6 (IL-6) and modulates the host innate immunity by targeting importin-7 (IPO7) and Caspase-3 [34]. This facilitates EBV to evade from host immune monitoring and enable itself latent infection [35-37].

Exosomal miRNAs in radiotherapy resistance of NPC

Despite the clinical application of advanced radiotherapy, the 5-year recurrence rate of NPC is still up to 15% [38]. Chemoradiotherapy resistance is a major problem for NPC patients, leading to incomplete local elimination, recurrence and metastasis [39, 40].

Differential miRNA expression profiles in radioresistant NPC cells and parental cells have been identified by microarray analysis and small RNA sequencing. Over 30 miRNAs, such as miR-30a, miR-125a-3p, miR-130a, miR-196-3p, miR-203, miR-660 and miRNA-4291 are relatively downregulated in radioresistant cells, which suggests that they might contribute to radiotherapeutic sensitivity of NPC cells. While more than 60 miRNAs, such as miR-7, miR-21, miR-193b and miR-205 are up-regulated, and their functions are related to tumor therapeutic resistance [41-43]. Considering that most of them could be detected in the plasma, and packaged into exosomes is a major form for extracellular miRNAs transported in the circulatory system, these miRNAs might be loaded into exosomes and function in the regulation of NPC radioresistance. Besides, miR-34c is well recognized as a tumor suppressor [44] and has been found inclusion in exosomes. Exosomal miR-34c enhances the radiosensitivity of NPC cells mainly through inhibition of epithelial-mesenchymal transition (EMT) by targeting β -Catenin, thus suppressing the malignant development of NPC [45].

Clinical application of exosomal miRNAs in NPC

Exosomal miRNAs in NPC diagnostics

Because of its relatively secluded site and lack of typical symptoms in the early stage, NPC is clinically prone to be misdiagnosed or missed diagnosed. At present, the principal modalities of early detection for NPC include EBV-associated markers screening, imaging and

endoscopy examination. However, due to the sensitivity and specificity of these means are not so ideal, the early detectable rate of NPC is not satisfied. As universal modulators of gene expression and the established role in carcinogenesis and development, miRNAs have been identified as promising candidate diagnostic and prognostic markers for malignancy. To date, miR-9 [46], miR-17, miR-20a, miR-29c, miR-223 [47], miR-125a-5p [48], miR-151 [49], miR-155 [50], miR-204 [51], miR-216b [52], miRNA-324-3p [41], miR-451 [53], miR-483-5p, miR-548q [54], EBV-miR-BARTs [55] and others have emerged as potential indicators of NPC diagnosis and disease outcome.

Exosomes are found abundant in a variety of body fluids including blood, urine, saliva, breast milk and amniotic liquid, which makes it possible that exosomes be taken as non-invasive or minimally invasive approach for early diagnosis of various diseases. Moreover, naked RNA is prone to be degraded, whereas miRNAs packaged to exosomes should be protected and be more stable in body fluids [12, 56]. EBV-miR-BARTs have been demonstrated to be loaded into exosomes secreted by NPC cells *in vivo* and are stable enough to diffuse from tumor tissue to the peripheral blood. A study showed that EBV-miR-BART7-3p was detected in the plasma samples from NPC patients at a significantly higher level than that from control donors [57]. Plasma-derived EBV DNA has been regarded as a classical biomarker of prognosis and response to treatment in clinical management of NPC. Notably, EBV-miR-BART7 is at a high level in the plasma from NPC patients with undetectable EBV DNA in the same sample [57]. This indicates that EBV-miR-BARTs might provide distinct and complementary information for NPC phenotype. Circulating exosomal EBV-miR-BARTs might be valuable blood biomarkers for diagnosis and monitoring of treatment response of NPC patients. Another study showed that miR-24-3p was substantially enriched in serum exosomes from NPC patients compared to the control [33]. miR-24-3p can hinder the function of T cells to facilitate immune escape of NPC cells. Blocking the exosomal miR-24-3p results in the restoration of T cell function. In addition, miR-891a, miR-106a-5p, miR-20a-5p and miR-1908 were also found highly expressed in serum exosomes of NPC patients [32]. In that miRNAs in circulating exo-

somes represent the characteristics of the tumor origin, they might act as compelling screening tools for very early detection of NPC and other diseases.

Exosomal miRNAs in NPC therapy

With the profound understanding of cancer molecular biology and genetics, the mechanism of exosomal miRNAs as molecular therapy targets is gradually unveiled. Studies found that exosomal EBV-miRBART-10-3p induced EMT to facilitate the invasion and metastasis of NPC [58]. EBV-miR-BART10-5p and miR-18a up-regulated the expression of vascular endothelial-derived growth factor (VEGF) and hypoxia inducible factor 1- α (HIF1- α) in a Sprouty3 (Spry3)-dependent manner, which strongly promoted angiogenesis and the growth of NPC [59]. However, exosomal miRNAs also exert anti-tumor effect. miR-34c-overexpression exosomes was reported to reduce the invasion, migration, proliferation and EMT, thus restraining the malignant transformation of NPC [45]. Exosomal miR-9 directly targets MDK to regulate PDK/AKT signaling pathway, thereby inhibiting the angiogenesis of NPC [30]. Moreover, exosomal miR-9 level positively correlates with the overall survival rate of NPC. Hence, identifying the regulatory mechanism of the exosomal miRNAs in tumorigenesis might provide new insights into clinical intervention and treatment strategies for NPC and other EBV-related tumors.

Notably, as inherent therapeutic agents and drug delivery vehicles, exosomes have ascended into the new industrial therapeutic frontiers. Exosomes have phospholipid bilayer membranes decorated with transmembrane proteins and membrane-anchoring proteins that enhance endocytosis, thereby facilitating the delivery of their inclusions in a biologically active form [60, 61]. A number of small-molecule drugs, such as paclitaxel, doxorubicin and curcumin, have been encapsulated into exosomes for the therapy of cancer and other diseases [62-69]. Exosomes are natural vehicles of miRNA that could be explored as an RNA drug delivery system. They have been loaded with let-7a miRNA to target EGFR-expressing xenograft breast cancer tissue and inhibit tumor development *in vivo* [70]. *In vivo* treatment with iRGD-tagged exosomal antagomiRs

(antagomiR-BART10-5p and antagomiR-18a) showed substantial anti-angiogenesis and anti-tumor therapeutic effect on NPC [59]. Exosomes can also deliver exogenous siRNAs for the treatment of diseases [71-79]. Thus, with low immunogenicity and excellent biocompatibility, exosomes loaded with nucleic acid drugs should be exploited therapeutically to target cancerous tissues including NPC.

Conclusion

The most intriguing roles of exosomes are thought to act as the messengers, delivering effectors and signaling macromolecules between specific cells. Through carrying miRNAs and other inclusions to recipient cells, exosomes mediate the informative communication between cells and affect not only the proliferation, invasion, angiogenesis and metastasis, but also the process of immune escape in tumor microenvironment (TME) and chemoradiation resistance of NPC. Moreover, as potential non-invasive biomarkers, they have important clinical value for the early diagnosis of NPC, such as circulating exosomal EBV-miRBARTs and miR-24-3p. In addition, exosomes might also be used as a tool for drug delivery and disease treatment. Exosomes have favorable natural traits that traditional carriers (liposomes and synthetic nanocarriers) do not have: (1) low immunogenicity, exosomes derived from dendritic cells contain major histocompatibility complex(MHC) to avoid being cleared away by immune cells in the body [80]; (2) prolonged half-life time with high expression of CD47 on the surface of exosomes. CD47 protein is a widely expressed integrin-related transmembrane protein and a ligand for signal regulatory protein α (SIRP α). The combination of CD47-SIRP α triggers signaling to inhibit phagocytosis and enhances the half-life of exosomes [81]; and (3) exosomes also have the ability to penetrate the blood-brain barrier and placental barrier [82]. The combination of exosomes with traditional viral vehicles such as adeno-associated virus (AAV) vectors should provide a more efficient delivery tool for gene therapy.

Nonetheless, there are still many questions to be addressed in this field. Tumor suppressive miRNAs such as miR-26a, miR-29c, miR-98, miR-200 family, miR-216b, miR-375 and miR-451 have been found down-regulated in NPC

[53, 83-89]. However, the high expression of onco-miRNAs such as miR-18b, miR-30a, miR-93, miR-141, miR-144, miR-149, miR-155, miR-214 and miR-504 promotes malignant progression of NPC [50, 90-102]. Whether these tumor suppressive miRNAs and oncogenic miRNAs play their roles through exosomes is still unknown and additional investigations will be required. In addition, exosomal miRNAs such as miR-7, miR-21, miR-23a, miR-29a, miR-223 and miR-451 are involved in the immune regulation of diversified cancer types [103-108]. In gastric cancer cells, exosomal miR-451 activates mammalian target of rapamycin (mTOR) signaling pathway to promote T cell differentiation to Th17, inducing inflammatory response in the body and accelerating tumor progression. In ovarian cancer cells, exosomal miR-29a down-regulates STAT3 expression, thereby increasing the expression levels of IL-4, IL-6 and tumor necrosis factor- α (TNF- α), causing an imbalance in the immune microenvironment and promoting the progression of ovarian cancer. In lung cancer cells, miR-21 binds to Toll-like receptors 8 (TLR8) receptors, activates the nuclear factor-kappa B (NF- κ B) pathway, and promotes the formation of inflammatory microenvironment for tumor metastasis. miR-23a reduces the natural killing activity of NK cells and regulates the progression of lung cancer by targeting CD107a. Then, do these exosomal miRNAs involved in tumor immune regulation also participate in the formation of immune microenvironment of NPC? So far, no relevant literature has been reported, and further exploration is needed.

Metabolic reprogramming is one of the hallmarks of cancer [24, 109-112] and exosomal-transferred miRNAs are emerging as a new modulator of metabolic remodeling in TME [113, 114]. Cancer-cell-derived exosomal miR-122 targeted the glycolytic enzyme pyruvate kinase 2 (PKM2) and inhibited glucose uptake by non-tumor cells in pre-metastatic niches, thereby facilitating increasing glucose availability for growing cancer cells [114]. Cancer-cell-secreted exosomal miR-105 activated the oncogenic MYC signalling in cancer-associated fibroblasts (CAFs) to initiate metabolic reprogramming. In case of sufficient nutrients in TME, miR-105-reprogrammed CAFs enhanced glycolysis and glutaminolysis to provide ATP for adjacent cancer cells. When nutrients were

scarce and metabolic wastes accumulated, CAFs enabled detoxification of lactic acid and ammonium to assist tumor growth [115]. Enhanced glycolysis represents a remarkable metabolic feature of Epstein-Barr virus (EBV)-positive NPC [116, 117]. With the theoretical and biotechnological knowledge of exosomes are further explored, the role of exosomal miRNAs in metabolic alteration of NPC microenvironment should be gradually revealed.

Additionally, it should be pointed out that exosomes are generally heterogeneous, and exosome miRNAs from the same cell origin may also differ in number and species, which brings difficulties for the early diagnosis of NPC and may lead to false-negative or false-positive results. As promising diagnostic biomarkers and potential therapeutic modality, exosomal miRNAs remain to be further explored on its regulatory mechanism during tumorigenesis and the development of NPC, due to its diversified species and existing limited cognition.

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Disclosure of conflict of interest

None.

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