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Review Article

MiRNA signatures in nasopharyngeal carcinoma: molecular mechanisms and therapeutic perspectives

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Abstract: Nasopharyngeal carcinoma (NPC) is a prevalent cancerous tumor that affects the head and neck region. Recent studies have provided compelling evidence indicating the significant involvement of microRNAs (miRNAs) in the development and progression of NPC. This review aims to present a comprehensive summary of the current knowledge regarding miRNA signatures in NPC, encompassing their expression patterns, molecular mechanisms, and potential therapeutic implications. Initially, the article outlines the aberrant expression of miRNAs in NPC and elucidates their roles in tumor initiation, invasion, and metastasis. Subsequently, the underlying molecular mechanisms of miRNA-mediated regulation of NPC-associated signaling pathways are discussed. Additionally, the review highlights the potential clinical applications of miRNAs as diagnostic and prognostic biomarkers, as well as their therapeutic potential in NPC treatment. In conclusion, this review underscores the critical involvement of miRNAs in NPC pathogenesis and underscores their promise as novel therapeutic targets for combating this devastating disease.

Keywords: miRNAs, nasopharyngeal carcinoma, molecular mechanisms, miRNA-based diagnosis and therapeutic

Introduction

Nasopharyngeal carcinoma (NPC) is a type of cancer that primarily develops in the nasopharynx, which is the upper part of the throat situated behind the nose [1]. This form of cancer is most commonly observed in Southeast Asia and is strongly associated with infection by the Epstein-Barr virus (EBV) [2, 3]. Due to its nonspecific symptoms like nasal congestion, difficulty swallowing, and hearing loss, NPC is often diagnosed at an advanced stage [1]. Treatment approaches typically involve a combination of chemotherapy, radiation therapy, and, in certain cases, surgery [4, 5]. The prognosis of NPC is dependent on the disease's stage at the time of diagnosis, with early-stage NPC having a more favorable prognosis compared to advanced-stage NPC [4]. In recent years, immunotherapy and targeted therapy have emerged as promising treatment modalities for NPC [6]. Immunotherapy focuses on activating the patient's immune system to identify and attack cancer cells, while targeted therapy employs drugs designed to specifically target cancer cells while sparing healthy cells [6]. Chemotherapy is frequently used in conjunction with radiation therapy for NPC treatment [7], with cisplatin, fluorouracil, and taxanes being the most commonly employed chemotherapy drugs [7]. Cisplatin, in particular, has exhibited notable effectiveness in NPC treatment and is often employed as the primary chemotherapy drug. The timing of chemotherapy administration in relation to radiation therapy is determined by the cancer's stage and extent [8]. Despite the satisfactory survival rates associated with combined chemotherapy and radiation therapy, the development of chemotherapy resistance poses a significant challenge in the treatment of recurrent NPC patients, leading to a poorer prognosis [7].

MicroRNAs (miRNAs) are small RNA molecules that play a critical role in regulating gene expression and various biological processes [9]. Abnormal miRNA expression has been associated with the progression and development of various cancers. Recent studies have identified specific miRNAs that function as either oncogenes or tumor suppressors in different types of cancer. For example, miR-149-5p has been found to regulate signaling pathways involved in the development of several human cancers [10]. In NPC, upregulation of miR-106A-5p has been linked to the suppression of autophagy and the acceleration of malignant characteristics [11], while exosomal miR-301a-3p promotes the proliferation and invasion of NPC cells [12]. Moreover, dysregulation of miR-148a-5p mediated by STAT3 promotes NPC growth and metastasis [13], while miR-129-5p inhibits lymph node metastasis in NPC [14]. Additionally, Increased expression of miR-149 may contribute to the high metastasis of NPC, making it a potential molecular target for anti-metastasis therapy [15]. And let-7i-5p has been associated with advanced stages, recurrence, metastasis, lymph node metastasis, and poor clinical outcomes, underscoring its potential as a therapeutic target for NPC [16]. Overall, miRNAs have emerged as promising targets for cancer treatment [12, 13, 16]. Preclinical studies have shown promising results for miRNA-based therapies, including the use of miRNA mimics and anti-miRNAs [17].

The diagnostic and prognostic potential of miRNAs in cancer has been extensively studied, and some miRNAs have been identified as diagnostic and prognostic biomarkers in NPC [18, 19]. For example, miR-762 provides a potential therapeutic target for the treatment of NPC [20]. MiR-214 provides a novel therapeutic target for the clinical treatment of NPC [21]. miR-342-3p may be a promising therapeutic target [22]. Other miRNAs, such as miR-200c [23] and miR-142-3p [24] also show potential in NPC treatment. In conclusion, miRNA dysregulation is associated with the development and progression of NPC. Identifying miRNAs as potential diagnostic and prognostic biomarkers, as well as therapeutic targets, highlights the potential of miRNA-based therapies for treating NPC [25]. Further research is needed to fully understand the role of miRNAs in NPC and to translate these findings into clinical practice.

Functional mechanisms of miRNAs

miRNAs are synthesized through a multi-step process in eukaryotic cells' nuclei and cytoplasm [26-29]. The miRNA synthesis process begins with the transcription of DNA into Pri-miRNA (primary miRNA) by POL II (RNA polymerase II) [30]. The Pri-miRNA is processed by the Drosha enzyme complex [31], which cleaves the stem-loop structure of the Pri-miRNA to produce a Pre-miRNA (precursor miRNA) [32, 33]. The Pre-miRNA is exported from the nucleus to the cytoplasm by the XPO5 (exportin-5) protein [34]. Then, in the cytoplasm, the Pre-miRNA is further processed by the Dicer enzyme complex [35, 36], which cleaves the Pre-miRNA to produce a short double-stranded RNA molecule known as the miRNA duplex [37-39]. One of the miRNA duplex strands is selected as the mature miRNA, and the other strand, known as the miRNA or passenger strand, is degraded [40]. The mature miRNA is incorporated into RISC complex (the RNA-induced silencing complex), which is composed of Ago (Argonaute proteins) (**Figure 1**) [37, 40, 41].

The miRNA guides the RISC complex to target mRNA (messenger RNA) molecules with complementary sequences in their 3'-UTR [39]. The RISC complex can then induce post-transcriptional regulation of gene expression through mechanisms such as mRNA degradation, translational inhibition, mRNA cleavage, transcriptional regulation and RNA editing [41, 42]. MiRNAs, regulated by genetic and epigenetic events, can potentially regulate every aspect of cellular function including growth, proliferation, differentiation, development, metabolism, infection, immunity, cell death, organellar biogenesis, messenger signalling, DNA repair and self-renewal, among others [43]. Overall, miRNA synthesis is a complex process involving multiple enzymes and proteins that culminates in the production of mature miRNAs that play a critical role in the post-transcriptional regulation of gene expression (**Figure 1**) [43-45]. Aberrant expression of miRNAs may contribute to the development and progression of NPC by modulating the expression of genes involved in cell proliferation, invasion, and survival [46, 47].

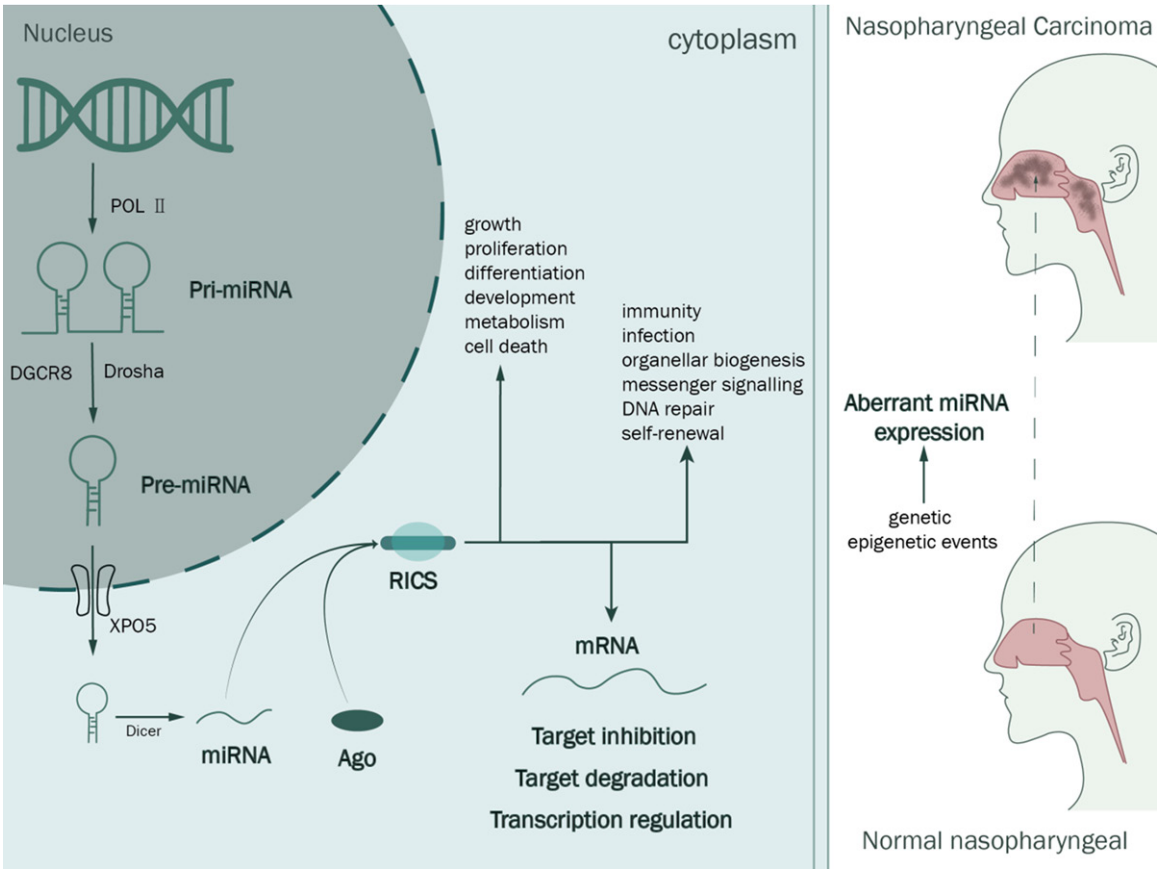

Figure 1. Functional mechanisms of miRNAs. POL II: RNA polymerase II, Pri-miRNA: primary miRNA, Drosha and DGCR8: Microprocessor complex, Pre-miRNA: precursor miRNA, XPO5: exportin-5, Dicer: Dicer enzyme complex, RISC complex: the RNA-induced silencing complex, Ago: Argonaute proteins.

Role and mechanism of miRNA in nasopharyngeal carcinoma

MiRNAs have been confirmed as a significant group of regulators in the pathogenesis of nasopharyngeal carcinoma (NPC). Several miRNAs have been identified as having potential anticancer properties in NPC, as shown in **Table 1**. These miRNAs can inhibit cell proliferation, migration, and invasion, or promote apoptosis of NPC cells by targeting specific proteins. For instance, miR-212 expression levels were significantly decreased in NPC tissues and cell lines [48]. miR-212 was found to inhibit the migration and invasion of NPC cells by targeting SOX4 [48], indicating its potential as an anticancer agent. Several miRNAs have been identified to have oncogenic properties in NPC. For instance, miR-142-3p, miR-29c, and miR-30e have been found to be associated with the overall survival of nasopharyngeal carcinoma patients [49]. Targeting these miRNAs could be a potential strategy for developing novel therapeutic approaches for the treatment of NPC.

Dysregulation of miRNAs has been observed to play a crucial role in the initiation and progression of NPC. Several miRNAs have been reported to be upregulated or downregulated in NPC cell lines or tissue samples, including miR-32 [50], miR-34c [51], miR-449b-5p [52], and miR-194 [53]. The mechanisms underlying miRNA dysregulation involve multiple pathways, including epigenetic modifications, transcription factor regulation, and signaling pathways. In particular, miRNAs have been found to influence the development and progression of tumors by regulating the expression of proteins involved in critical cellular processes, such as cell cycle, apoptosis, and DNA repair. For example, miR-145 [54], miR-148a-3p [55], and miR-449b-3p [56] can promote the malignancy of human nasopharyngeal carcinoma by targeting ADAM17 (**Figure 2**), ADAM17-mediated shed-

Table 1. miRNAs signatures in nasopharyngeal carcinoma

MiRNAs	Direct target	Indirect target	Effects	Role	PMID
miR-338-3p	circZNF609	HRAS	Tumorigenesis	Tumor suppressor	32970285
miR-145	lncRNA mACC1-AS1	Smad2	Stem ability	Tumor suppressor	32058221
microRNA-150-5p	circ-ZNF609	Sp1	Proliferative, migratory, invasive	Tumor suppressor	31002133
miR-24-3p	lncRNA CYTOR	GAD1	Proliferative, migratory, invasive	Tumor suppressor	36814556
miR-1290	lncRNA ZNF667-AS1	*ABLIm1*	Proliferative, migratory, invasive	Oncogene	32606725
miR-1179	lncRNA SNHG5	HmGB3	Proliferation, migration	Tumor suppressor	32131767
miR-514a-5p	lncRNA SNHG7	SNHG7	Proliferation, migration	Tumor suppressor	32370736
miR-892b	lncRNA ZFAS1	LPAR1	Proliferation, migration	Oncogene	31851778
miR-431	lncRNA FBXL19-AS1	PBOV1	Proliferation, migration	Tumor suppressor	34278444
miR-146b-5p	lncRNA SOX2-OT	HNRNPA2B1	Proliferation, migration	Tumor suppressor	31099048
miR-34a-5p	NEAT1	CDCA5	Proliferation, migration	Tumor suppressor	30900419
miR-338-3p	circ-WHSC1	ELAVL1	Proliferation, metastasis	Tumor suppressor	36380666
miR-508-5p	circ_0081534	FN1	Proliferation, invasion	Tumor suppressor	33082297
miR-34c-5p	CircCRIm1	FOSL1	Proliferation, invasion	Tumor suppressor	35484574
miR-582-3p	lncRNA HOXA10-AS	RAB31	Proliferation, invasion	Tumor suppressor	35072529
miR-1278	circ_0000285	FNDC3B	Proliferation, migration, invasion	Tumor suppressor	36738165
miR-577	circ_0008450	CXCL9	Proliferation, migration, invasion	Tumor suppressor	31344361
miR-145	circmYC	mmP2	Proliferation, migration, invasion	Tumor suppressor	35441564
miR-107	circTGFBR2	TGFBR2	Proliferation, migration, invasion	Oncogene	33160003
miR-433-3p	HIF-1α promote	SCD1	Proliferation, migration, invasion	Oncogene	33511729
miR-539-5p	LNC100129148	KLF12	Proliferation, migration, invasion	Tumor suppressor	28328537
miR-18a-5p	lncRNA CASC2	RBBP8	Proliferation, migration, invasion	Oncogene	30569153
miR-630	lncRNA H19	EZH2	Proliferation, migration, invasion	Tumor Suppressor	27040767
miR-193a-5p	lncRNA HEIH	CDK8	Proliferation, migration, invasion	Tumor suppressor	33577031
miR-423-5p	lncRNA AFAP1-AS1	FOSL2	Proliferation, migration, invasion	Tumor suppressor	30326930
miR-3163	lncRNA CRNDE	TWIST1	Proliferation, migration, invasion	Tumor suppressor	34796452
miR-613	lncRNA CYTOR	ANXA2	Proliferation, migration, invasion	Tumor suppressor	31859457
miR-122	lncRNA DRAI	SATB1	Proliferation, migration, invasion	Tumor suppressor	31497998
miR-326/330-5p	lncRNA EWSAT1	CYCLD1	Proliferation, migration, invasion	Tumor suppressor	27816050
miR-33b-5p	lncRNA FLOT2	c-myc	Proliferation, migration, invasion	Tumor suppressor	33744853
miR-185-3p	lncRNA FOXD3-AS1	FOXD3	Proliferation, migration, invasion	Tumor suppressor	33204001
miR-4465	lncRNA GAS5	COX2	Proliferation, migration, invasion	Tumor suppressor	33092435
miR-4465	lncRNA HDAC7	EphA2	Proliferation, migration, invasion	Tumor suppressor	32376822
miR-150-5p	LncRNA IGBP1-AS1	ZEB1	Proliferation, migration, invasion	Tumor suppressor	35402187
miR-129	lncRNA NEAT1	Bcl-2	Proliferation, migration, invasion	Oncogene	32692721
miR-204	lncRNA NEAT1	ZEB1	Proliferation, migration, invasion	Tumor suppressor	27020592
miR-141-3p	lncRNA SNHG15	KLF9	Proliferation, migration, invasion	Tumor suppressor	32633365
miR-588	lncRNA SNHG8	*HmGA2*	Proliferation, migration, invasion	Tumor suppressor	35080988
miR-34a-5p	lncRNA XIST	E2F3	Proliferation, migration, invasion	Tumor suppressor	27461945
miR-381-3p	lncRNA XIST	XIST, NEK5	Proliferation, migration, invasion	Tumor suppressor	32196601
miR-1184	Circ_0000523	COL1A1	Proliferation	Tumor suppressor	35759163
miR-188	circ-ZNF609	ELF2	Proliferation	Tumor suppressor	32273713
miR-140	HCG18	CCND1	Proliferation	Tumor suppressor	31841193
miR-378a-3p	LINC00641	*FOXD1*	Proliferation	Tumor suppressor	32013999
miR-133a-5p	circ-0046263	IGFBP3	Progression	Tumor suppressor	32703944
miR-383-3p	HOXC13-AS	HmGA2	Progression	Tumor suppressor	30536950
miR-328-5p	LNC00210	NOTCH3	Progression	Tumor suppressor	30341249
miR-199a-5p	lncRNA DLX6-AS1	HIF-1α	Progression	Tumor suppressor	31782911
miR-613	FAm225B	CCND2	Migratory, invasive	Tumor suppressor	34255617
miR-135a-3p	circmAN1A2	UBR5	Migration, invasion, EMT	Tumor suppressor	36626032

miR-615-5p, miR-1538	circSETD3	mAPRE1	Migration, invasion	Tumor suppressor	33122825
miR-4649-3p	LINC02570	SREBP1	Migration, invasion	Tumor suppressor	34546840
miR-1237-3p	lncRNA AATBC	PNN	Migration, invasion	Tumor suppressor	32364663
miR-656-3p	lncRNA SNHG8	SATB1	Migration, invasion	Tumor suppressor	32920509
miR-3612	lncRNA ZFPm2-AS1	DTL	Migration, invasion	Tumor suppressor	35276693
microRNA-31	LOC554202	RhoA	Migration, invasion	Tumor suppressor	33155211
miR-486-5p	SLC9A3-AS1	E2F6	Migration, invasion	Tumor suppressor	34165171
miR-490-3p	lncRNA HCG11	mAP3K9	Migration, EMT	Tumor suppressor	35463310
miR-4731-5p	lncRNA ANCR	NmT1	Migration, invasion, EMT	Tumor suppressor	34333213
miR-656-3p	Circ_0028007	ELF2	Migration	Tumor suppressor	35239093
miR-101	lncRNA HOTAIR	COX-2	Migration	Tumor suppressor	30314699
miR-874-3p	Circ_0081534	FmNL3	Malignant	Tumor suppressor	35428519
miR-145-5p	lncRNA SNHG1	NAUK1	Invasion, EMT	Tumor suppressor	29575772
miR-136-5p	LncRNA FOXP4-AS1	MAPK1	EMT	Oncogene	36961080
miR-106a-5p	lncRNA SmAD5-AS1	SmAD5	EMT	Oncogene	31557058

ding of the pro-inflammatory cytokine TNF-α is a critical step in the regulation of the immune response and is involved in the development of several inflammatory diseases. Additionally, ADAM17 activates growth factors and their receptors, which can promote tumor growth and metastasis. While PTEN acts as a negative regulator of the PI3K/Akt pathway by reducing the levels of PIP3, which is a key second messenger in cell growth and survival [57], its reported that miR-141 [58], miR-142 [59], miR-144 [60, 61], miR-155 [62], miR-200c [63], miR-205 [64, 65], miR-21 [66, 67], miR-214 [68, 69], miR-222 [70], miR-513a-3p [71], miR-92a [72] play an oncogenic role by targeting PTEN (**Figure 2**). Besides, miR-103 may significantly impact the development of NPC by targeting TIMP-3 [73], which in turn affects the Wnt/β-catenin pathway. This suggests that miR-103 could play a crucial role in NPC carcinogenesis [73]. Dysregulation of miRNA expression can lead to alterations in the levels of these proteins, ultimately resulting in changes in cell behavior that promote tumor formation and progression. The underlying mechanisms of miRNA dysregulation in NPC involve multiple pathways (**Figure 2**).

The effects of miRNA on the proliferation and apoptosis of nasopharyngeal carcinoma cells

For the regulation of cell proliferation and apoptosis, cyclin-dependent kinases (CDKs) and cyclins (CCND) play a significant role. CDK-cyclin complexes are active during different phases of the cell cycle and phosphorylate various target proteins, facilitating the progression of the cell cycle [74]. CDK4 and CDK6 bind to cyclin D1 and phosphorylate the retinoblastoma protein (Rb), which releases E2F transcription factors that drive the expression of genes required for DNA replication in the S phase [75]. Uncontrolled cell proliferation, one of the mechanisms underlying the excessive proliferation of cancer cells, can result from cells entering a state of excessive proliferation. Several miRNAs have been identified as having potential anticancer properties in NPC by targeting CDKs and CCND. For example, miR-138 [76], miR-140 [77], and miR-613 [78] can suppress NPC growth and tumorigenesis by targeting CCND1/2. miR-188 [79], miR-539 [80], and miR-193a-5p [81] can suppress cell proliferation by targeting CDKs. Additionally, miR-34a-5p [82], miR-432 [83], and miR-486-5p [84] can regulate cell cycle progression, DNA replication, and apoptosis by targeting E2F3. These miRNAs play important roles in tumorigenesis and have the potential to serve as therapeutic targets in NPC.

TP53, P21, and RB1 are essential regulators of cell growth and proliferation in nasopharyngeal carcinoma. TP53, also known as P53, prevents the development of cancer by regulating cell division [85]. P53 can activate genes that initiate apoptosis, preventing damaged cells from proliferating and potentially becoming cancerous, by modulating the expression of P21, RB1, Bax, and NOXA [85]. However, some miRNAs, such as miR-125a [86], miR-34a [87], and miR-205 [88], have been reported to inhibit apoptosis in NPC by targeting p53 mRNA. P21 is a downstream target of the tumor suppressor

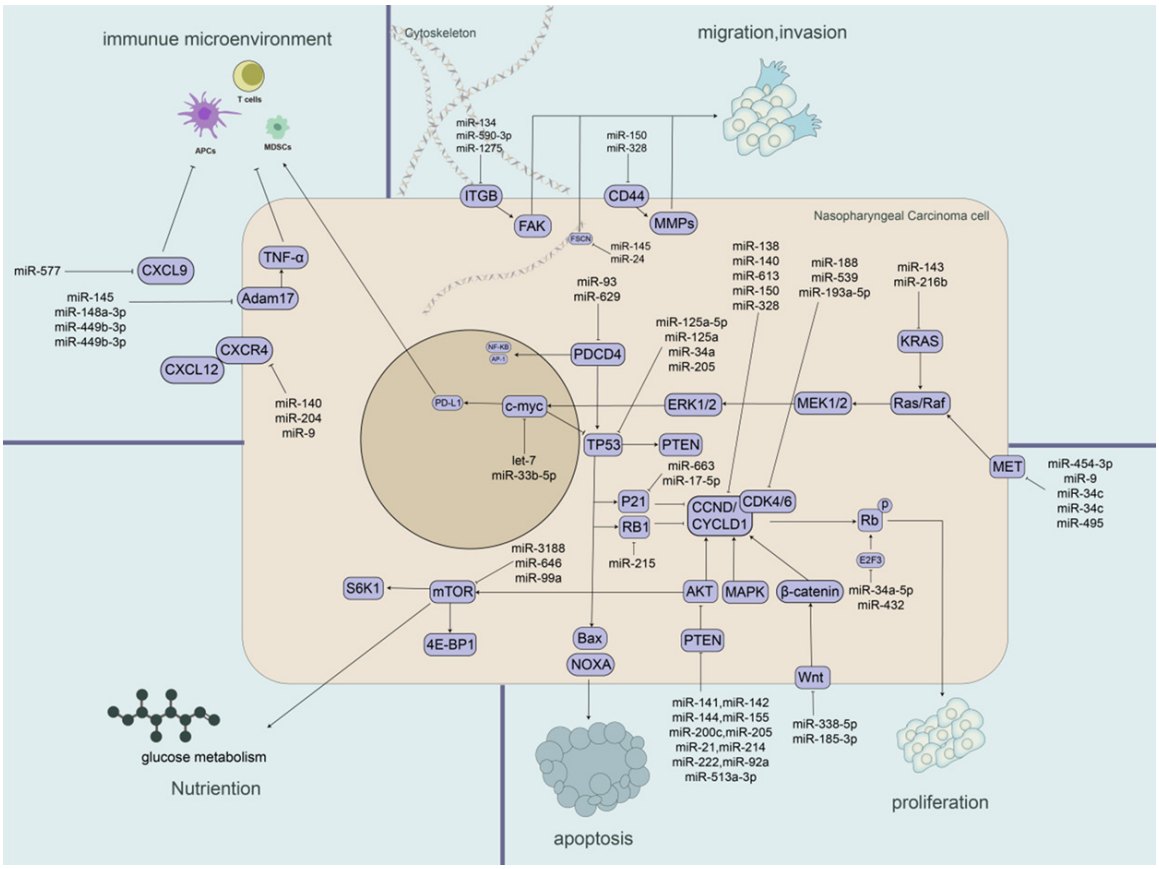

Figure 2. Regulatory pathway diagram of miRNAs in nasopharyngeal carcinoma.

protein p53. P21 functions as a cyclin-dependent kinase inhibitor, which means it binds to and inhibits the activity of CDKs, enzymes that promote the progression of the cell cycle. By inhibiting CDK activity, P21 helps slow the cell cycle, allowing time for DNA repair or other cellular processes [89]. RB1 is also a downstream target of p53 [90]. pRB acts as a negative cell cycle regulator by inhibiting the activity of E2F transcription factors. When pRB is active, it binds to E2F and prevents its transcriptional activity, leading to cell cycle arrest in the G1 phase [90]. miR-215 can promote the progression of nasopharyngeal carcinoma by targeting RB1 [91]. **Table 1** provides a list of other miRNAs identified in nasopharyngeal carcinoma, indicating the potential role of miRNAs in the progression of this disease.

The effects of miRNA on the invasion and migration of nasopharyngeal carcinoma cells

Invasion and migration are critical processes in the progression and metastasis of tumors [92]. These processes involve the movement of cancer cells from the primary tumor site to distant locations in the body [92]. CD44 and ITGB (Integrin beta) have received attention for their involvement in migration and invasion, with ITGB playing a critical role in cell adhesion and signaling. It has been reported that miR-134 [93], miR-590-3p [94], and miR-1275 [94] can reduce the long-distance metastasis of NPC cells by targeting ITGB, representing a promising future direction in the treatment of nasopharyngeal carcinoma. CD44, on the other hand, is a cell surface protein involved in numerous cellular processes, including migration, proliferation, differentiation, and survival. Upregulation of CD44 expression in cancer cells is often associated with poor prognosis, and miR-150 [95] and miR-328 [96] have been suggested as potential prognostic markers and therapeutic targets for NPC through their targeting of CD44. In addition, miR-145 [97] and miR-24 [98] have been identified as novel tumor suppressors in the development and pro-

gression of NPC by targeting FSCN1, a protein that plays a crucial role in the organization of the actin cytoskeleton. FSCN1 is involved in regulating various cellular processes, maintaining cell shape and polarity, and promoting invasiveness and metastasis of cancer cells when overexpressed [99]. These miRNAs have the potential to modulate proteins associated with migration and invasion, indicating their promise as targeted therapies for NPC (**Table 1**).

The effects of miRNA on the immune regulation of nasopharyngeal carcinoma cells

In the early stages of cancer development, the immune system typically identifies and eliminates abnormal cells, thereby inhibiting tumor formation [100]. However, tumor cells employ various strategies to evade detection and attack by the immune system [101]. There exists a profound interplay between the immune system and the tumor microenvironment, playing a pivotal role in cancer development and control [100, 101]. The immune regulation of tumors is a complex interplay between the body's immune system and cancer cells [102]. Tumors often employ various strategies to evade immune surveillance, while the immune system tries to recognize and eliminate cancerous cells [103]. miRNAs also play a crucial role in immune regulation. As mentioned earlier, in addition to miRNAs regulating ADAM17, CXCL9 and CXCR4 also have important roles in immune regulation. CXCL9's primary function is to recruit immune cells to the site of inflammation, including tumors [99]. CXCL9 [104, 105] interacts with its receptor CXCR3, which is expressed on the surface of immune cells, to promote their migration to the tumor site [104], and recognize and eliminate cancer cells [106]. However, high levels of CXCL9 have been associated with poor prognosis in nasopharyngeal carcinoma, likely due to the recruitment of immunosuppressive cells. MiR-577 inhibits cell proliferation and invasion in nasopharyngeal carcinoma by targeting CXCL9 [107]. On the other hand, CXCR4 is frequently overexpressed and is associated with tumor growth, invasion, and metastasis (**Table 1**). In nasopharyngeal carcinoma, miR-140 [108], miR-204 [109], and miR-9 [110] target CXCR4 and function as potential tumor suppressors, providing new insight into the molecular mechanisms that regulate the development and progression of NPC and presenting novel therapeutic targets for NPC.

The effects of miRNA on the glucose metabolism of nasopharyngeal carcinoma cells

Tumor cells often exhibit significant alterations in glucose metabolism compared to normal cells [111]. This metabolic reprogramming, known as the Warburg effect or aerobic glycolysis, plays a crucial role in the growth, survival, and progression of many types of tumors. The mTOR (mammalian target of rapamycin) signaling pathway plays a crucial role in regulating sugar metabolism [112], including glucose metabolism by influencing glucose uptake, glycolysis, anabolic processes and so on, in various types of tumors. This pathway integrates multiple signals, such as growth factors, nutrients, and energy status, to control cell growth, proliferation, and metabolism [113].

It is reported that miR3188 [114], miR646 [115], miR99a [116] can exert regulatory control over the mTOR signaling pathway in nasopharyngeal carcinoma cells. These regulatory effects can subsequently influence sugar metabolism by altering the expression and activity of key enzymes and proteins involved in glycolysis, the pentose phosphate pathway, and other metabolic processes [112, 113]. The specific miRNAs involved and their precise effects may vary among different NPC cases and should be a subject of ongoing research in the field of cancer biology and therapy.

Distinct miRNAs signature for various stages of nasopharyngeal carcinoma

In the context of NPC, miRNA signatures associated with EBV infection and drug resistance provide valuable insights into the disease progression and treatment responses. For patients with NPC, EBV plays a significant role as a causative factor. It infects NPC cells, where it replicates and can significantly alter the expression profiles of specific miRNAs. Additionally, in the course of NPC treatment, some patients may develop resistance to therapies, resulting in suboptimal treatment outcomes. MiRNAs may also be pivotal in these scenarios. It is crucial to recognize that miRNA signatures in NPC can exhibit variations among different cases and patient populations, underscoring

the importance of individualized research and treatment plans.

MiRNAs associated with Epstein-Barr virus (EBV)

Epstein-Barr virus (EBV) is a herpesvirus associated with the development of NPC, and miRNAs are known to be dysregulated in EBV-associated cancers, as shown in **Table 4**. In recent years, there has been a growing interest in identifying miRNAs that are associated with EBV infection and can serve as potential diagnostic and therapeutic targets. Several studies have identified miRNAs that are dysregulated in EBV-associated cancers, including miR-BARTs [117-119]. These miRNAs are encoded by the EBV genome and have been shown to play a role in viral latency and immune evasion. Therefore, miRNAs represent promising diagnostic and therapeutic targets for EBV-associated cancers. In addition to miR-BARTs, other miRNAs, such as miR-1 [120], miR-203 [121], miR-10b [122], miR-204 [123], miR-21 [124, 125], and miR-362-3p [126], have also been implicated in the regulation of cell proliferation, apoptosis, and immune response in EBV-associated NPC, as summarized in **Table 4**.

Epstein-Barr virus (EBV) is a human herpesvirus that infects both B cells and epithelial cells. Its genome is a double-stranded DNA molecule that is approximately 172 kilobases in size [127]. The EBV genome contains several coding sequences that are involved in the regulation of viral gene expression, replication, and packaging of the viral genome [127].

One of the most important genes encoded by EBV is the latent membrane protein 1 (LMP1). LMP1 is a signaling protein that mimics the activity of the CD40 receptor, which is involved in the activation of B cells [128]. By activating signaling pathways that promote cell survival and proliferation, LMP1 can promote the growth and survival of EBV-infected B cells [128]. The dysregulation of miRNAs by EBV can modulate the downstream signaling of LMP1, thereby promoting the development of cancer [129]. Additionally, miR-BART22 has been shown to play a role in modulating LMP2A expression, which may facilitate NPC carcinogenesis by evading the host immune response [130]. Another important gene encoded by EBV is the Epstein-Barr nuclear antigen 1 (EBNA1) gene. EBNA1 is a DNA-binding protein that is required to maintain the EBV genome in infected cells [131]. It plays a crucial role in regulating viral gene expression and replication and is also involved in evading the host immune response [131].

In addition, miRNAs have potential as therapeutic targets for EBV-associated cancers. Several miRNAs, including EBV-miR-BART7-3p [132], EBV-miR-BART1-5P [133], and EBV-miR-BART1 [134], modulate the EMT and metastasis of NPC cells by targeting PTEN, offering new possibilities for targeted therapy for NPC in the future. Another miRNA, EBV-miR-BART11, inhibits its FOXP1 and enhances PD-L1 transcription [135], promoting the immune escape of tumors. This discovery sheds light on potential targets for immunotherapy of EBV-related tumors and could lead to identifying new biomarkers and treatment options for NPC [136]. More studies are necessary to fully understand the involvement of miRNAs in EBV-related cancers and to design diagnostic and therapeutic approaches that target these molecules effectively. It is clear that the miRNAs generated by EBV have significant contributions to the initiation and progression of nasopharyngeal carcinoma. **Table 2** provides more detailed information on the functions of additional miRNAs.

MiRNAs associated with chemotherapy and radiotherapy resistance

Chemotherapy and radiation therapy are common treatments for NPC [137], but drug resistance or radioresistance has become a major challenge in their effectiveness [138]. Chemotherapy drugs kill cancer cells or slow their growth, but some cancer cells can develop resistance to these drugs, making them less effective [139]. This can happen when cancer cells mutate and become resistant to the drugs, or when surrounded by a protective environment that shields them from the effects of the drugs. Radiation therapy uses high-energy radiation to kill cancer cells [140], but the effectiveness of this treatment can also be reduced by drug resistance. Radiation resistance can occur when cancer cells repair themselves faster than the radiation can damage them, or when they activate protective mechanisms that help them survive the treatment [141]. Drug

Table 2. MiRNAs associated with Epstein-Barr virus (EBV)

MiRNAs	Target	Role	PMID	MiRNAs	Target	Role	Pubmed
EBV-miR-BART5-3p	TP53	Angiogenesis	30209170	EBV-miR-BART13	NKIRAS2	Metastasis	30684592
EBV-miR-BART1-5P	PTEN	Angiogenesis	30557400	EBV-miR-BART22	MAP2K4	Metastasis	31594754
EBV-miR-BART	LMP1	Angiogenesis	17911266	miR-204	Cdc42	Metastasis	24613926
EBV-miR-BART11	FOXP1	Angiogenesis	27167345	EBV-miR-BART13-3p	ABI2	Metastasis	31907338
miR-BART19-3p	APC	Angiogenesis	32714979	EBV-miR-BART2-5p	RND3	Proliferation	32060148
EBV-miRNA-BART12	TPPP1	EMT	33094864	EBV-BART10-3p	ALK7	Proliferation	34424090
EBV-miR-BART8-3p	RNF38	EMT	30477559	EBV-miR-BART6-5p	Dicer1	Proliferation Metastasis	33305599
EBV-miR-BART7-3p	PTEN	EMT	25347742	EBV-miR-BART8-3p	ATM/ATR	Radioresistance	31471531
EBV-miR-BART-22	MOSPD2	EMT	35907914	miR-31-5p	WDR5	Suppress tumorigenesis	28042945
EBV-miR-BART7-3p	SMAD7	Cancer stem-like cell	31681406	miR-203	E2F3,CCNG1	Tumor suppressor	22205737
miR-21	PTEN	Enhance cancer stem-like cell	26568302	EBV-miR-BART6-3p	LOC553103	Tumorigenesis	32306460
EBV-miR-BART17-3p	PBRM1	Immune escape	35165282	miR-BART5	PUMA	Viral latency	18838543
EBV-miR-BART22	LMP2A	Immune escape	19881953	H19/miR-675-5p	p53	Viral latency	35674441
EBV-miR-BART11	FOXP1	Immune escape	35165282	let-7a	Dicer	Viral latency	24304932
miR-BART19-3p	WIF1,NLK, APC	Metastasis	28543390	EBV-miR-BART6-5p	Dicer	Viral latency	20716523
EBV-miR-BART1	PTEN	Metastasis	26135619	miR-1	K-RAS		26852690

resistance in cancer chemotherapy is one of the main obstacles to curing this malignant disease, which can be caused by many mechanisms, such as decreased antitumor drug uptake, modified drug targets, altered cell cycle checkpoints, or increased DNA damage repair, among others [142]. In recent years, many studies have shown that miRNAs are involved in the drug and radiotherapy resistance of tumor cells by targeting drug-resistance-related genes or influencing genes related to cell proliferation, cell cycle, and apoptosis [143, 144].

Cisplatin is a widely used chemotherapy drug for NPC treatment. Recent studies have shown that certain miRNAs can sensitize NPC cells to cisplatin by targeting specific genes. For example, miR-1278 enhances cisplatin sensitivity by targeting ATG2B [145], and miR-374a sensitizes NPC to cisplatin by directly targeting CCND1, which is modulated by tumor suppressor PDCD4 [146]. Radiotherapy is also a common treatment modality for NPC. However, some miRNAs have been found to negatively regulate radiosensitivity, while others have been shown to increase radiosensitivity. For instance, miR-210 [147] and miR-101 [148] negatively regulate radiosensitivity of tumor cells, while miRNA-203 reduces NPC radioresistance by targeting IL8/AKT signaling [149] or ZEB2 [150]. In addition, miR-24 enhances radiosensitivity in NPC by targeting SP1 [151], and miRNA-378g by targeting SHP-1 [152]. miR-4270 has been found to modulate the irradiation-sensitivity of nasopharyngeal carcinoma cells by modulating p53, and is lower in radio-sensitive patients [153]. Other miRNAs such as miR-451 [154], miR-183 [155], miRNA-19b-5p [156], miRNA-19b-3p [157], and miRNA-124 [158] have been found to increase the radiosensitivity of NPC cells by targeting RAS. MiR-205 and PTEN have also been identified as potential predictive biomarkers for radiosensitivity in NPC and may serve as targets for successful radiotherapy [159]. Conversely, miRNA-17 [160] promotes NPC radioresistance by targeting PTEN/AKT. These miRNAs described above could be potential therapeutic targets in the radioresistance of NPC treatment. **Table 3** provides additional miRNA profiles in nasopharyngeal carcinoma.

Diagnostic and therapeutic potentials of miRNAs in NPC

In recent years, there has been an increasing interest in exploring the diagnostic and therapeutic potential of miRNAs in NPC. Multiple studies have demonstrated that miRNAs hold promise as potential biomarkers for the early detection and prognosis of NPC. Furthermore, targeting specific miRNAs has shown encouraging outcomes in the treatment of NPC, either alone or in combination with traditional therapies.

MiRNAs are potential biomarkers for the diagnosis and treatment of NPC

MiRNAs have emerged as promising biomarkers for the diagnosis and treatment of nasopharyngeal carcinoma (NPC). It is essential to diagnose and treat NPC early for better patient outcomes. A number of miRNAs have been identified as potential biomarkers for NPC (**Table 4**). For instance, miR-410-3p and miR-34c are markers for early metastasis in NPC and independent prognostic biomarkers [161]. Testing for their expression levels can help predict prognosis and metastasis in patients with this type of cancer [161]. Plasma BART8-3p also shows promise as a biomarker for detecting and predicting the prognosis of NPC [162]. The levels of miR-BART7-3p and EBV DNA in plasma at diagnosis and after radiotherapy could help predict the risk of poor disease-free survival (DMFS) in patients [163]. Moreover, circulating miR-214-3p predicts recurrence or metastasis of nasopharyngeal carcinoma [164]. A combination of circulating miR-17, miR-20a, miR-29c, and miR-223 can be non-invasive biomarkers for detecting NPC [165]. The differential expression of these miRNAs in NPC can serve as a diagnostic or prognostic indicator for early clinical detection. The dysregulation of these miRNAs has been associated with various aspects of NPC, such as tumor growth, invasion, metastasis, and response to therapy (**Table 4**). Hence, miRNAs could serve as diagnostic and prognostic biomarkers for NPC, as well as therapeutic targets.

MiRNAs as promising NPC therapeutic targets

Studies have demonstrated the potential benefits of targeting miRNAs with miRNA inhibitors

Table 3. MiRNAs associated with chemotherapy

MiRns	Role	Expression	PMID	MiRns	Role	Expression	PMID
miR-539	Therapeutic target	Down	26559153	miR-214-3p	Biomarker	Up	31926154
miR-429	Therapeutic target	Down	32894547	miR-214	Biomarker	Up	32101017
miR-34c	Therapeutic target	Down	32586280	miR-214	Biomarker	Up	34612550
miR-29c	Therapeutic target	Down	23142283	miR-214	Biomarker	Up	24465927
miR-296-3p	Therapeutic target	Down	29525743	miR-205	Biomarker	Up	22374676
miR-7	Therapeutic target	Up	20813671	miR-200c	Biomarker	Up	30431444
miR-122-5p	Therapeutic target	Up	34174438	*miR-19a-3p*	Biomarker	Up	35759451
miR-103	Therapeutic target	Up	31038780	miR-17, miR-20a, miR-29c, miR-223	Biomarker	Up	23056289
EBV-miR-BART17-3p	Therapeutic target	Up	36199071	miR-155	Biomarker	Up	31693455
miRNA-150-5p	Biomarker	Down	31002133	miR-135b-5p, miR-205-5p	Biomarker	Up	25292031
miR-9	Biomarker	Down	24327016	EBV-miR-BART8-3p	Biomarker	Up	35380720
miR-613	Biomarker	Down	36061358	EBV-miR-BART7-3p, EBV-miR-BART13-3p	Biomarker	Up	32155300
miR-548q, miR-630, miR-940	Biomarker	Down	30475754	EBV-miR-BART7	Biomarker	Up	22843893
miR-449b-5p	Biomarker	Down	31350893	EBV-miR-BART5-3p	Biomarker	Up	36225172
miR-4262	Biomarker	Down	35220889	EBV-miR-BART2-5p	Biomarker	Up	29971780
miR-204	Biomarker	Down	25752113	miR-410-3p and miR-34c	Biomarker	Up	34817330
miR-194	Biomarker	Down	30652073	miR-378	Biomarker	Up	24481647
miR-1281, miR-6732-3p	Biomarker	Down	32198434	miR-100	Biomarker	Down	29805566
miR-124	Biomarker	Down	32681617	miR-BART19-3p	Biomarker	Up	31958073

Table 4. Diagnostic and therapeutic potentials of miRNAs in NPC

miRNAs	Target	Role	Pubmed	miRNAs	Target	Role	Pubmed
miR-483-5p	DAPK1	Enhance	30664712	miR-7-5p	ENO2	Inhibit	33342344
miR-186	FOXD1	Enhance	32568181	miR-340-3p	FKBP5	Inhibit	36769373
miR-150b	GSK3β	Enhance	29516971	miR-132	FOXA1	Inhibit	36121076
miR-143-5p	HOXA6	Enhance	35176945	miR-495	GRP78	Inhibit	30015969
miR-519d	PDRG1	Enhance	28057028	miR-302c-5p	HSP90AA1	Inhibit	36539366
miR-152	PTEN	Enhance	27840403	miR-206	IGF1	Inhibit	28865599
miR-205	PTEN	Enhance	22374676	miR-203	IL8	Inhibit	26304234
miR-17	PTEN	Enhance	31933738	miR-24	Jab1/CSN5	Inhibit	27157611
miR-181a	RKIP	Enhance	31849491	miR-26b	JAG1	Inhibit	28203521
miR-106a-5p	SOX4	Enhance	35227173	miR-124	JAMA	Inhibit	32681617
miR-34c	SOX4	Enhance	32586280	miR-19b-5p	KRAS	Inhibit	30231694
miR-449b	TGFBI	Enhance	29795279	miR-124-3p	LHX2	Inhibit	35300558
miR-19b-3p	TNFAIP3	Enhance	27919278	miR-342-5p	LINC00346	Inhibit	30928094
miR-155	UBQLN1	Enhance	26698246	miR-125a	lncANRIL	Inhibit	28402230
miR-324-3p	WNT2B	Enhance	23583221	miR-34a-5p	LncXIST	Inhibit	28985197
miR-185-3p	WNT2B	Enhance	25297925	miR-183	MTA1	Inhibit	28631568
miR-1278	ATG2B	Inhibit	32407879	miR-450b-5p	NRF2	Inhibit	32632129
miR-3942-3p	BARD1	Inhibit	35616619	miR-335-5p	PADI4	Inhibit	33593046
miR-125b	Bcl-2	Inhibit	28260044	miR-194-3p	PTPRG-AS1	Inhibit	30993702
miR-182-5p	BNIP3	Inhibit	33313953	miR-451	RAB14	Inhibit	25201065
miR-374a	CCND1	Inhibit	27270423	miR-31-5p	SFN	Inhibit	36520963
miR-195-3p	CDK1	Inhibit	34585634	miR-378g	SHP-1	Inhibit	26473472
miR-29-3p	COL1A1	Inhibit	31034464	miR-338-3p	SMAD5	Inhibit	34387609
miR-138-1-3p	CRIPTO	Inhibit	33850882	miR-24	SP1	Inhibit	26922862
miR-613	DNMT3B	Inhibit	36061358	miR-101	STMN1	Inhibit	25607713
miR-138-5p	EIF4EBP1	Inhibit	28075468	miR-4270	TP53	Inhibit	34078755
miR-147a	circSETD3	Inhibit	35196205	miR-203	ZEB2	Inhibit	27589832

or mimics in NPC treatment. For example, miR-539 plays a significant role in the onset and advancement of NPC by targeting CDK4, and targeting the miR-539/CDK4 pathway could be a promising therapeutic approach [80]. MiR-29c has been shown to improve the efficacy of cisplatin-based chemotherapy and radiotherapy in NPC, suggesting its potential as a therapeutic sensitizer for NPC treatment [166]. MiR-296-3p is negatively regulated by nicotine and promotes the movement of c-Myc into the cell's cytoplasm through MK2, which suppresses chemotherapy resistance and highlights miR-296-3p as a potential therapeutic target for overcoming resistance in NPC [167]. Additionally, a recent study by Zhou H found that pre-administration of antagomiR-122 via nasal delivery can prevent radiation-induced brain injury [168]. These findings indicate the potential of miRNA-targeted therapies as novel therapeutic strategies for NPC treatment (**Table 4**).

Conclusions and perspectives

NPC is a highly prevalent form of head and neck cancer that affects individuals in specific geographical regions worldwide. Recently, miRNA signatures have emerged as critical regulators of gene expression. Their dysregulation has been associated with NPC. miRNA dysregulation plays a crucial role in tumorigenesis, and miRNAs have significant potential as diagnostic, prognostic, and therapeutic targets for cancer treatment. Further research is needed to translate these findings into clinical practice and to develop safe and effective miRNA-based therapies for cancer patients. This review provides a comprehensive overview of the molecular mechanisms underlying miRNA dysregulation in NPC. We have discussed the role of specific miRNAs in NPC initiation and progression, including miRNA-150-5p [169], miR-9 [170], and miR-613 [171], and have highlighted

their potential as diagnostic and prognostic biomarkers for NPC.

Additionally, we have discussed the potential of miRNAs as therapeutic targets in NPC. Several studies have shown promising results using miRNA-based therapies in preclinical and clinical settings, indicating the possibility of miRNAs as a novel therapeutic approach for NPC treatment. In conclusion, miRNA signatures in NPC have provided valuable insights into the molecular mechanisms underlying NPC initiation and progression. Identifying specific miRNAs as diagnostic and prognostic biomarkers for NPC may improve early detection and patient prognosis. Moreover, the use of miRNA-based therapies has the potential to revolutionize NPC treatment, providing a new avenue for developing more effective and targeted therapies. Therefore, further research is warranted to better understand the complex regulatory networks involving miRNAs in NPC and to create safe and effective miRNA-based treatments for NPC patients.

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Disclosure of conflict of interest

None.

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