

MicroRNAs: Biogenesis, Functions and Potential Biomarkers for Early Screening, Prognosis and Therapeutic Molecular Monitoring of Nasopharyngeal Carcinoma

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Review

MicroRNAs: Biogenesis, Functions and Potential Biomarkers for Early Screening, Prognosis and Therapeutic Molecular Monitoring of Nasopharyngeal Carcinoma

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Abstract: According to reports published, the aberrant expression of microRNAs (miRNAs), a class of 19–25 nucleotide-long small non-coding RNAs, is responsible for human cancers, including nasopharyngeal cancer (NPC). The dysregulation of miRNAs that act either as a tumor suppressor or oncogene, leading to a wide range of NPC pathogenesis pathways, includes the proliferation, invasion, migration as well as the metastasis of NPC cells. This article reviews and highlights recent advances in the studies of miRNAs in NPC, with a specific demonstration of the functions of miRNA, especially circulating miRNAs, in the pathway of NPC pathogenesis. Additionally, the possible use of miRNAs as early screening and prognostic biomarkers and for therapeutic molecular monitoring has been extensively studied.

Keywords: microRNA; circulating microRNA; biomarker; nasopharyngeal carcinoma

1. Introduction

In 1993, Victor Ambros and colleagues discovered the first microRNA (miRNA), namely *lin-4*, in *Caenorhabditis elegans*. Up to date, with in-depth research on microRNA (miRNA), a new era of early diagnosis, prognosis of human cancers as well as cancer treatment has commenced [1,2]. miRNAs are the family of naturally occurring small non-coding RNAs within 19–25 nucleotides (nts) in length. They play multiple key roles in regulating a wide array of biological processes, including cell proliferation, differentiation, metabolism, stress response and apoptosis through the regulation of numerous target genes [3–5]. miRNAs regulate biological processes by binding to sequences in the 3′-untranslated region (3′-UTR) of their target mRNAs, eventually resulting in the degradation and/or repression of mRNA [3–5]. Additionally, miRNAs have been observed to interact with other regions of target genes, including 5′-UTR, as well as promoter and coding regions. Each miRNA is reported to be the mediator of multiple genes by acting at the post-transcriptional levels. Consequently, both the mutation of miRNAs and dysfunction of miRNA biogenesis may lead to various human diseases, including cancers [6]. Growing evidences have indicated that miRNAs are frequently dysregulated in various cancers. Therefore, understanding their profile in cancer may identify them as powerful post-transcriptional biomarkers as well as highlight their great biomarker potential for the early screening, prognosis and therapeutic targets of human cancers.

Cancers are a serious disease to human life and health and have become the second leading cause of human death globally, accounting for an estimated 9.6 million deaths in 2018. It was emphasized that new cases of cancer could reach 23.6 million in 2030 [7]. Among them, nasopharyngeal carcinoma (NPC), a prevalent nasopharyngeal malignant tumor with remarkable differences in distribution and

which gravitates toward Southern Asia, is considered to be the most common head and neck cancer. Even though improvements in nasopharyngeal cancer treatment have been achieved, diagnosis at an advanced stage reduces the success rate of treatment as well as the survival of patients. Thus, early screening and diagnosis represent beneficial opportunities to increase the survival of patients as well as the effects of nasopharyngeal cancer treatment. However, the non-specific symptoms related to the early stage of NPC, as well as the deeply seated location of the nasopharynx, are major obstacles to an early screening of NPC [8]. Therefore, effective biomarkers are truly needed [9]. At present, much effort has been made to identify early biomarkers by focusing on the etiological factors that lead to nasopharyngeal tumorigenesis. In addition to the etiology of Epstein–Barr virus infection, recently, the aberrant expression of miRNAs has been demonstrated to play key roles in the pathogenesis of NPC. Hence, an adequate understanding of the roles of miRNAs in NPC pathogenesis will provide more opportunities as well as better strategies to identify them as effective biomarkers of NPC. Additionally, it will pave the way for a better application of their functions in clinics, i.e., developing them into a promising approach in NPC therapies. In this article, we will summarize the key roles of miRNAs in the pathogenesis of NPC. Additionally, updated miRNA-related research data will be presented. Finally, we will demonstrate the application of miRNAs in NPC early screening, prognosis as well as cancer treatment.

2. Brief Understanding of miRNAs Biogenesis

Mature miRNAs are generated through a two-step processing of primary miRNAs in both the nuclear and cytoplasmic regions. miRNAs can be divided into intronic or intergenic miRNAs (Figure 1) [5,10,11]. Almost half of miRNA genes are located in the intergenic region (between two genes) and may exist either as a cluster of miRNA genes or a single miRNA gene under the control of its own promoter [5,11].

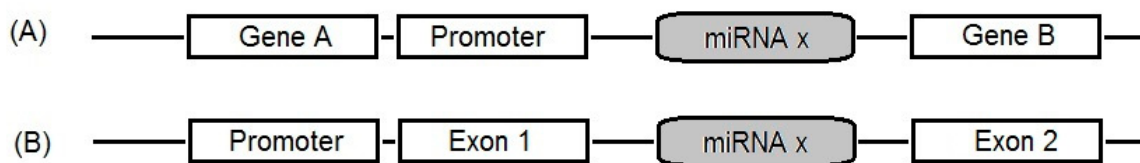


Figure 1. Location of the microRNA (miRNAs) gene in the genome: (A) intergenic miRNAs: miRNAs located between two genes; (B) intronic miRNA: miRNAs located in the region of intron in a gene.

The biogenesis of miRNAs is classified into two categories: the canonical pathway and non-canonical pathway. In the canonical pathway, the primary miRNAs (pri-miRNAs) are transcribed from their genes and cleaved into pre-miRNAs by two main enzymes, Drosha and Dicer [5]. In this dominant pathway, the biogenesis of miRNAs, as well as the mechanism of regulation of their target genes' expression, is summarized in the steps shown in Figure 2. The mature miRNA originates from a long primary miRNA (pri-miRNA) with the structure of 5'-7 methyl-guanosine capped and 3' polyadenylated, and it is transcribed by RNA-polymerase II (RNA-polyII) from its own promoter or the promoter of the host genes in which it is contained; it is controlled by RNA-polyII-associated transcription factors and epigenetic regulators [12–14]. Pri-miRNA contains a hair-spin structure which varies from hundreds to thousands of base pairs in length [10,15]. Pri-miRNA is cleaved at the stem of the hair-spin structure, leading to the release of a ~60–70 nucleotide hair-spin structure, which is termed as the precursor miRNA (pre-miRNA). This process is catalyzed by the microprocessor, which contains the nuclear RNase III-type protein Drosha and its cofactor, the DiGeorge syndrome critical region eight (DGCR8) protein found in humans, and takes place in the nucleus [16]. The pre-miRNA with a stem-loop structure is exported from the nucleus into the cytoplasm for further processing by exportin-5 (EXP 5), originally known as a minor export factor for tRNAs, and the Ras-related nuclear protein guanosine triphosphate (RAN-GTP) [11,15,17]. Then, the terminal loop of the pre-miRNA is removed by RNA III Dicer and its cofactor transactivation-responsive RNA-binding protein (TRBP), thereby releasing a

~20–22 nucleotide miRNA-duplex, which contains two 5' phosphorylated sequence strands with 3' overhangs, named the mature miRNA guide strand (miRNA) and complementary passenger strand (miRNA*) [17,18]. The miRNA-duplex is loaded into an Argonaute protein (Ago protein) to generate a RNA-induced silencing complex (RISC), and the miRNA passenger is degraded. The mature miRNA is incorporated into the miRNA-induced silencing complex (miRISC), which participates in regulating the gene expression via the interaction between a region called the “seed” (2–8 nt), a site located at the 5' part of miRNA (positions 2–7) and the target mRNAs 3'-UTR by a Watson–Crick complementary sequence, leading to the degradation of the mRNA (in case of perfect pairing between the miRNAs/mRNA target) or the blocking of mRNA translation (in case of imperfect pairing (Figure 3)) [3,11,19]. Up to date, some miRNAs are generated by different non-canonical pathways, including: (1) miTrons (pri-miRNAs are encoded in the introns of coding genes); (2) Dicer-independent miRNAs; (3) tRNA-derived miRNAs [5]. These non-canonical pathways use many different combinations of proteins which are involved in another pathway—the canonical pathway, including Dicer, exportin-5 and AGO2. It is noted that the Dicer protein is necessary in both canonical and non-canonical pathways, while Drosha and DGCR8 are only functioned to canonical miRNAs. In other words, the non-canonical miRNAs could be generated in the case of a Drosha and DGCR8 absence [5].

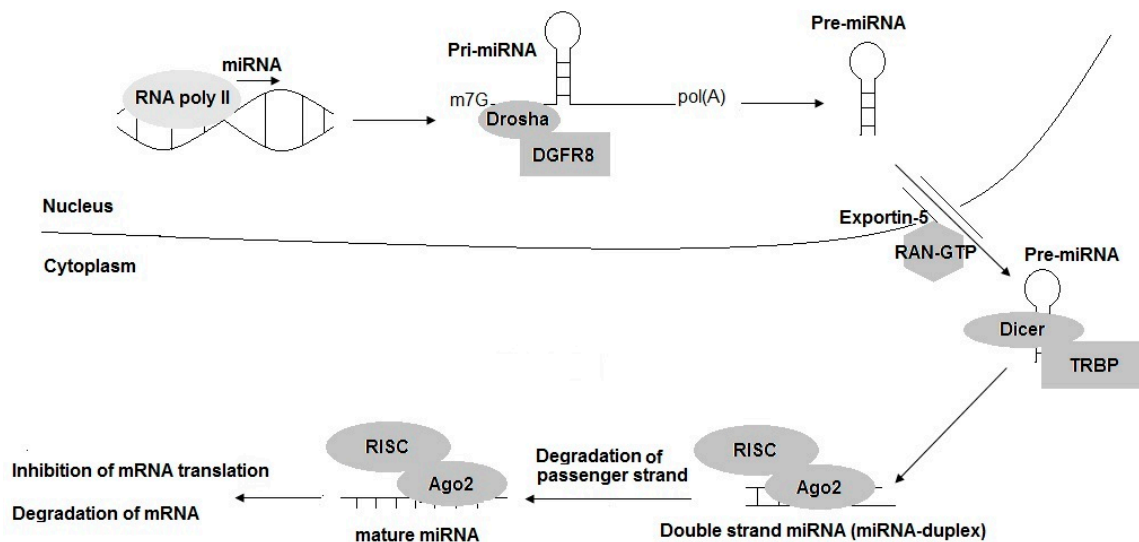


Figure 2. The biogenesis of miRNAs: the canonical pathway. pri-miRNA: primary miRNA; pre-miRNA: precursor miRNA; DGCR8: DiGeorge syndrome critical region 8; RAN-GTP: Ras-related nuclear protein guanosine triphosphate; TRBP: transactivation-responsive RNA-binding protein; Ago: Argonaute protein; RISC: RNA-induced silencing complex; miRISC: miRNA-induced silencing complex.

		Seed region		
		↔		
		1 2 3 4 5 6 7 8 nt		
		miRNA 5'-nNNNNNNNnnnnnnnnnnnnnnnnnn	Interaction types	
mRNA	Pol(A)- 3'-nnnnn	NNNNNNN	6mer-site	
	Pol(A)- 3'-nnnnnnnnn	ANNNNNN	7mer-A1 site	
	Pol(A)- 3'-nnnnnnn	NNNNNNN	7mer-m8 site	
	Pol(A)- 3'-nnnnnnn	ANNNNNN	8mer site	

Figure 3. The interaction types of miRNA–mRNA (target mRNA). Site matching between the seed region of miRNA (at positions 2–8) and the 3'-end of the target mRNA. The character of N represents the single Watson–Crick pairing nucleotide. Pol(A): Poly-A tail; A: Adenine.

3. The Roles of miRNAs in NPC Tumorigenesis: Potential Biomarkers for NPC Early Screening, Prognosis, and Therapy

The first study to reveal the roles of miRNA in nasopharyngeal tumorigenesis was published in 2008 by Sengupta and colleagues [20]. In their report, by using microarray-based approaches, they identified eight miRNAs with significantly different expressions in laser-capture micro-dissected NPC samples compared with normal nasopharyngeal epithelial samples. Among them, six miRNAs, including hsa-miR-29c, hsa-miR-34b/c, hsa-miR-212, hsa-miR-216, and hsa-miR-217, exhibited a lower expression in tumor cells, and two miRNAs, hsa-miR-151 and hsa-miR-192, showed a higher expression in NPC tumor cells. Particularly, the target genes were reported to be associated with the lower expression of hsa-miR-29c, and its 15 target genes' levels, including *FLJ12505*, *COL4A1*, *COL4A2*, *COL5A2*, *COL3A1*, *COL1A2*, *FBN1*, *SPARC*, *COL15A1*, *FUSIP1*, *COL1A1*, *TFEC*, *IFNG*, *LAMC1*, *LAMC1*, showed a two- and six-fold increase in NPC tumors compared with normal nasopharyngeal epithelium. Their abnormal expression was reported to be associated with tumor cell invasiveness, metastasis and metastatic potential, which are prominent characteristics of NPC. Hence, since the first report, growing evidences on miRNA regulatory networks in NPC progression have emerged. Over the years, numerous studies have indicated that a high proportion of miRNAs play a significant role in NPC pathogenesis. The dysregulation of miRNAs that act either as tumor suppressors (down-regulation) or oncogenes (up-regulation) leads to the abnormal regulation of a range of NPC-associated biological pathways, such as cell proliferation, apoptosis, survival and metastasis, which play a crucial role in nasopharyngeal carcinogenesis (Figure 4) [21,22].

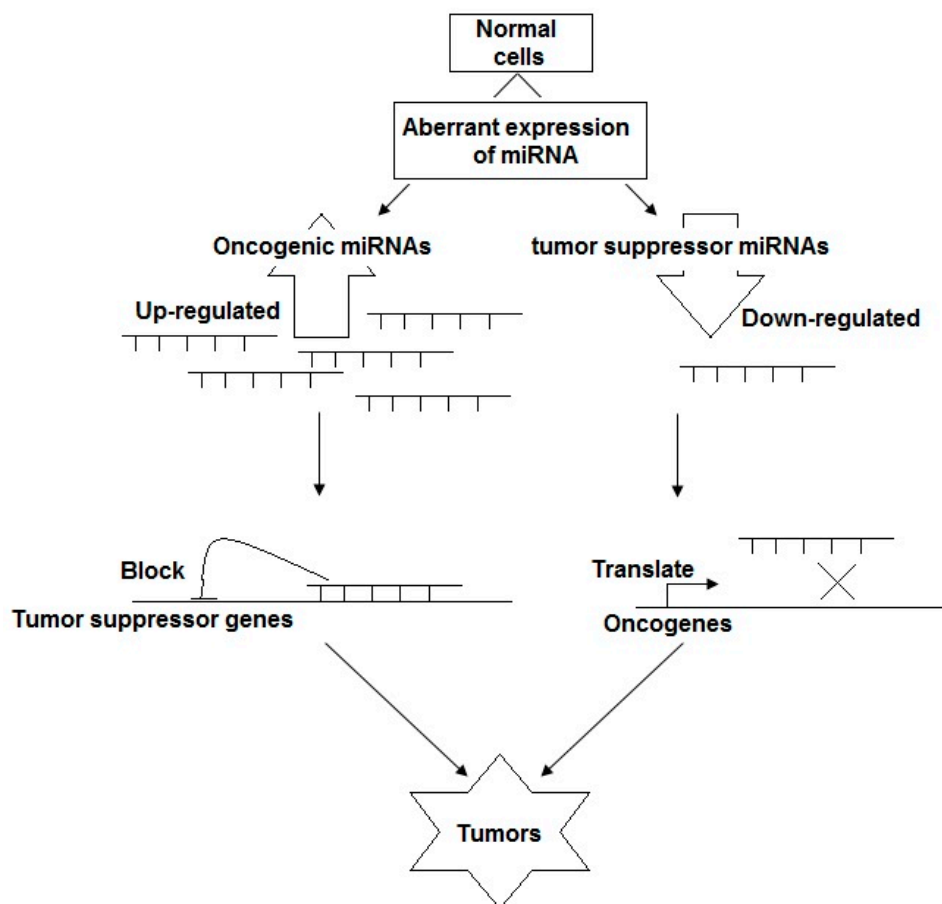


Figure 4. The biological function of miRNAs: tumor suppressors or oncogenic miRNAs.

In terms of the mechanism, miRNAs act as oncogenic and tumor suppressor miRNAs in tumorigenic events. In the function of tumor suppressor miRNAs, miRNAs are down-regulated,

resulting in a potentially enhanced expression of oncogenes, promoting cell proliferation, migration, angiogenesis, invasion, and metastasis, whereas oncogenic miRNAs are over-expressed in nasopharyngeal tumorigenesis, leading to the inhibition of tumor suppressor genes, and, as a result, they increase the proliferation, migration and invasion of NPC cells as well as the loss of cell cycle regulation and they inhibit cell apoptosis.

3.1. miRNAs as Tumor Suppressor Genes

Generally, tumor suppressor miRNAs can down-regulate different oncogenes, which are revealed to promote cell proliferation, migration, angiogenesis, invasion, and metastasis [23]. miRNAs that act as tumor suppressors are reported to be often down-regulated in NPC pathogenesis [22,24,25]. The down-regulation of tumor repressor miRNAs, which are negative regulators of protein-coding genes, leads to an up-regulation of their target genes and the subsequent alterations of the associated cellular pathways in NPC [24]. Many miRNAs (including hsa-Let-7, hsa-miR-9, hsa-miR-26, hsa-miR-29, hsa-miR-30, hsa-miR-34, hsa-miR-101, hsa-miR-200, hsa-miR-218, hsa-miR-223, hsa-miR-331, hsa-miR-429, etc.) are reported to be tumor suppressor genes that play vital roles in nasopharyngeal carcinoma [26–55]. Bioinformatic prediction tools in combination with experimental analysis, including NPC culture cell analysis, case-control studies, etc., have demonstrated that miRNAs could influence multiple steps of tumorigenesis by interacting with target genes (Table 1). Understanding the role of tumor suppressor genes in NPC has the potential to establish the prognostic biomarkers and therapeutic targets of NPC.

Table 1. List of miRNAs that act as tumor suppressor genes in nasopharyngeal carcinoma (NPC).

miRNAs	Functions and Target Genes
Let-7 family (a, -b, -d, -e, -g, and -i)	Promoting the cell proliferation and apoptosis, the epithelial mesenchymal transition by directly regulating the MYC [25], <i>high-mobility group A2 (HMGA2)</i> [26,27], and enhancer of <i>zeste homolog 2 (EZH2)</i> [28].
hsa-miR-9	Inhibiting the nasopharyngeal tumor cell proliferation, migratory and invasion by targeting the 3' untranslated region of chemokine (C-X-C motif) receptor 4 (CXCR4) through activation of the Mitogen-activated protein kinase (MAPK) pathway [29,30]; modulating the immune response through targeting numerous interferon-regulated genes: <i>FI44L</i> , <i>IFI27</i> , <i>PSB9_HUMAN</i> , <i>PSMB8</i> , <i>IRF5</i> , <i>PSMB10</i> , <i>IFIT2</i> , <i>TRAIL</i> , <i>IFIT1</i> , <i>PSB8_HUMAN</i> , <i>IRF1</i> , <i>B2M</i> and <i>GBP1</i> , MHC class I molecules and interleukin (IL)-related genes: <i>IL20RB</i> , <i>GALT</i> , <i>IL7</i> , <i>IL1B</i> , <i>IL11</i> , <i>IL1F8</i> , <i>IL1A</i> , <i>IL6</i> and <i>IL7R</i> [31].
hsa-miR-16	Inhibiting the NPC cell proliferation, migration, invasion, metastatic colonization by targeting fibroblast growth factor 2 (FGF2) via phosphoinositide-3-kinase/AKT (PI3K/AKT) and mitogen-activated protein kinase (MAPK) signaling pathways [32]. Additionally, Knocking-down CDK4 leads to the induction of miR-16, resulting in inhibiting the cell growth [33].
hsa-miR-26	Suppressing the growth of NPC cell as well as the formation of colony by inducing G1 cell-cycle arrest. Additionally, hsa-miR-26 targets the CDK inhibitors p14 (ARF), p21 (CIP1), <i>zeste homolog 2 (EZH2)</i> , T cell lymphoma invasion and metastasis 1 (TIAM1), leading to decrease oncogenic properties of migration, invasion, and cell survival [34,35].
hsa-miR-29c	Suppressing the NPC cells migration and invasion through the hsa-miR-29c/TIAM1 pathway to inhibit the translation of <i>T cell lymphoma invasion and metastasis (TIAM1)</i> [36,37], as well as targeting the multiple mRNAs, which encoded extracellular matrix proteins, includes seven collagens, laminin γ 1, fibrillin, and secreted protein, acidic, cysteine-rich (SPARC) [20]. Additionally, miR-29c can involve to numerous pathways to suppress the proliferation, survival, and motility of NPC cells [21].
hsa-miR-30a	Regulating the invasion and metastasis of nasopharyngeal cancer through epithelial-mesenchymal transition by inhibiting the E-cadherin via targeting 3'-untranslated region (3'-UTR) of <i>E-cadherin</i> [38].
hsa-miR-34b, hsa-miR-449a	Inhibiting the nasopharyngeal malignancy progression through targeting <i>lactate dehydrogenase A (LDHA)</i> [39].
hsa-miR-34c	Suppressing the growth and metastasis of NPC tumor by targeting <i>MET proto-oncogene (MET)</i> through the pathway of hsa-miR-34c/MET pathway [40].
hsa-miR-98, hsa-miR-101	Inhibiting the cellular processes, including cell differentiation, development as well as apoptosis through targeting the expression <i>EZH2</i> [34].
hsa-miR-124	Inhibited cell growth, migration and invasion by repressing Foxq1 expression [41].

Table 1. Cont.

miRNAs	Functions and Target Genes
hsa-miR-138	Suppressing cell proliferation, colony formation and nasopharyngeal tumorigenesis by knocking-down the expression of <i>Cyclin D1 (CCND1)</i> [42].
hsa-miR-142	Suppressing NPC cell proliferation, invasion and metastasis by directly binding to 3'-UTR region of suppressor of cytokine signaling 6 (SOCS6) [43]. Additionally, the hypermethylation of DNMT1 leading to the silence of hsa-miR-142 also promotes the metastasis through targeting zinc finger E-box binding homeobox 2 (ZEB2) [44].
hsa-miR-200b	Inhibiting the NPC cell growth, migration, and invasion. EBV-encoded EB nuclear antigen 1 (EBNA-1) suppresses the expression of hsa-miR-200b, results in upregulating zinc finger E-box binding homeobox 1 and 2 (ZEB1, ZEB2) [38]. Additionally, Notch1 was identified as the direct target gene of hsa-miR-200b [45].
hsa-miR-204	Inhibiting the invasion of NPC. Latent membrane protein 1 (LMP-1) of Epstein-Barr Virus suppresses the expression of miR-204 through activating Stat-3 and enhances cell division cycle 42 (CDC42) to enhance the NPC invasion [46].
hsa-miR-216b	Inhibiting the NPC cell proliferation, invasion and cell growth by targeting KRAS through the inhibition of the KRAS-related AKT and ERK pathways [47], as well as binding to the 3'-untranslated region (UTR) of PKC α [48].
hsa-miR-218	Targeting to enhancer of zeste homolog 2 (EZH2) to inhibit the differentiation, development, and apoptosis [34]. Additionally, causing the significant toxicity in NPC leads to the inhibition of NPC cell growth via the SLIT-ROBO pathway [49].
hsa-miR-223	Inhibiting the proliferation, invasion and epithelial-mesenchymal transition by reducing the expression of <i>structure-specific recognition protein (SSRP1)</i> [50] and <i>MAF BZIP Transcription Factor B (MAFB)</i> [51].
hsa-miR-375	Reducing the cell migration, invasion and tumor formation by targeting the expression of metadherin (MTDH) [52]. Additionally, ROR1-AS1 could act as a sponge for hsa-miR-375 and promote cell migration and invasion by inducing EMT process in NPC [53].
hsa-miR-451	Suppressing the cell growth and invasion targeting MIF through hsa-miR-451/MIF pathway [54]. Collaborator of ARF (CARF) was also identified as the target of hsa-miR-451 [55].

3.2. miRNAs as Oncogenes

Several miRNAs are reported as oncogenes, known as oncogenic miRNAs (onco-miRNAs), which are over-expressed in nasopharyngeal tumorigenesis. Their activities have been found to increase the proliferation, migration and invasion of NPC cells, the loss of cell cycle regulation and inhibition of cell apoptosis [22,24,56]. Many onco-miRNAs (including hsa-miR-10a/b, hsa-miR-17, hsa-miR-18, hsa-miR-21, hsa-miR-93, hsa-miR-141, hsa-miR-144, hsa-miR-155, hsa-miR-205, hsa-miR-214, hsa-miR-378, hsa-miR-421, hsa-miR-663, hsa-miR-3135, etc.) are reported to be associated with nasopharyngeal tumorigenesis (Table 2) [57–92].

Table 2. List of miRNAs as oncogenes in NPC.

miRNAs	Functions and Target Genes
hsa-miR-10a	Fascinating the ability of nasopharyngeal cell transformation via the positively control protein synthesis by stimulating ribosomal protein mRNA translation and ribosome biogenesis [57].
hsa-miR-10b	Promoting the nasopharyngeal carcinoma cells migration and invasion, which related genes, including <i>E-cadherin</i> , <i>Vimentin</i> , and <i>MMP-9</i> , were identified [58]. Additionally, over-expression of hsa-miR-10b also correlated with LMP-1 and Twist1 through the regulation of <i>LMP1/Twist1</i> pathway in NPC malignancy [59].
hsa-miR-17	Promoting the proliferation of nasopharyngeal cell by targeting p21 [60]. Additionally, the over-expression of hsa-miR-17 directly suppresses the expression of <i>PTEN</i> , which is a key regulator of AKT phosphorylation, resulting in enhancing the radio-resistance of NPC via the <i>PTEN/AKT</i> pathway [61].
hsa-miR-18a	Promoting the nasopharyngeal malignant progression by widespread downregulation of the miRNome and regulating Dicer1 expression [62]. Moreover, hsa-miR-18a promotes the progression of NPC through miR-18a/SMG1/mTOR pathway [63].
hsa-miR-20a	Promoting the radio-resistance by targeting Rab27B [64].
hsa-miR-21	Promoting migration and proliferation by inhibiting the <i>B cell CLL/lymphoma 2 (BCL2)</i> expression [65]. Additionally, the expression of STAT3 activates the hsa-miR-21, resulting in inducing the nasopharyngeal carcinoma cell proliferation and suppressing the cell apoptosis through targeting <i>PTEN</i> gene (<i>PTEN/AKT</i> pathway) [66].

Table 2. Cont.

miRNAs	Functions and Target Genes
hsa-miR-30a	Increasing the nasopharyngeal carcinoma cell invasion and metastasis through epithelial-mesenchymal transition by targeting <i>E-cadherin</i> gene via GF-IR-Src-MicroRNA-30a-E-Cadherin Pathway [67,68].
hsa-miR-93	Promoting cell proliferation, invasion and metastasis via the inhibition of <i>transforming growth factor-β receptor II (TGFβRII)</i> through the attenuation of Smad-dependent TGF-β signaling and the activation of PI3K/Akt pathway [69] and <i>disabled homolog-2 (DAB2)</i> [70]. Additionally, hsa-miR-93 enhances the cell proliferation by directly targeting expression of <i>CDKN1A</i> gene [71].
hsa-miR-141	Increasing the cell growth, migration, invasion as well as the regulation of cell cycle, and reducing the cell apoptosis through inhibiting <i>BMI1</i> via hsa-miR-141/BMI1 signaling axis [72], and increasing the tumor formation by targeting <i>phosphatase and tensin homolog (PTEN)</i> via BRD7/hsa-miR-141/PTEN/AKT pathway [73,74].
hsa-miR-144	Promoting the cell proliferation, migration, invasion through the repression of <i>PTEN</i> to active PI3K/Akt pathway [75,76]. Additionally, downregulation of hsa-miR-144 by triptolide enhanced the formation of p85α-PTEN complex, resulting in causing the S phase arrest of NPC cells [77].
hsa-miR-149	Promoting the epithelial-mesenchymal transition, nasopharyngeal cell mobility and invasion was facilitated by LncRNA-LINC00460 through sponging hsa-miR-149-5p [78,79].
hsa-miR-155	Stimulating the NPC proliferation, invasion, migration and colony formation by presence of LMP-1 [80]. Moreover, hsa-miR-155 promoting the cell proliferation and inhibiting apoptosis through targeting PTEN/PI3K/Akt pathway [81] and PI3K/AKT-FOXO3a pathway [82].
hsa-miR-205	Promoting the nasopharyngeal carcinoma cells' proliferation, migration and invasion through regulating the PTEN and AKT signaling. Additionally, over-expression of hsa-miR-205 resulted in the down-regulation of <i>E-cadherin</i> and up-regulation of Snail proteins, led to the NPC cell proliferation, invasion [83]. The repression of apoptosis and stimulation of cell proliferation were also through targeting tumor protein p53-inducible nuclear protein 1 [84].
hsa-miR-214	Promoting the cell proliferation and repressing the cell apoptosis by targeting Bim (Bcl-2-interacting mediator of cell death) [85]. Additionally, the targeting of hsa-miR-214 is responsible for downregulating LTF in the NPC specimens [86].
hsa-miR-378	Promoting the nasopharyngeal cancer cell proliferation, colony formation, and invasion and migration by downregulating the Transducer of ERBB2 (TOB2) expression [87].
hsa-miR-421	Stimulating the cell proliferation and apoptosis resistance via downregulating the expression of FOXO4 [88].
hsa-miR-504	Inducing the radio-resistance in NPC cells through directly downregulating the NRF1 expression [89].
hsa-miR-663	Promoting the nasopharyngeal malignant progression through the targeting <i>EEF1A2</i> and <i>HSPG2</i> [90].
hsa-miR-774	Promoting the nasopharyngeal malignant progression via the regulation of TGF-beta and cyclin B1 [91].
hsa-miR-3182	Associated with the distant metastasis of NPC. The infection of EBV promotes the NPC progression through the disrupting miR-3182 [92].

4. Circulating miRNA: Potential Values in Nasopharyngeal Carcinoma Early Screening, Prognosis and Cancer Treatment

As described above, the over-expression of oncogenic miRNAs or down-expression of tumor suppressor miRNAs are reported to be strongly associated with nasopharyngeal tumorigenesis, progression, tumor colony formation, invasion, metastasis as well as radio/chemical resistance. Notably, recent growing evidence indicates that several miRNAs could be detected in biological fluids, including blood serum/plasma, tears, urine, etc., which reflect the pathophysiological condition of cancer [93–97]. These miRNAs are termed circulating miRNAs (c-miRNAs) or extracellular miRNA (ECmiRNA) [94]. Two major populations of c-miRNAs (including non-vesicle-associated c-miRNAs and vesicle-associated c-miRNAs, which reflect the mechanism of c-miRNAs release) have been identified. However, the mechanism of c-miRNAs release is still unclear [98]. The first profile of c-miRNAs was identified by Chim et al. in 2008 [99]. They discovered the existence of placental miRNAs, including miR-141, miR-149, miR-299-5p, and miR-135b, in maternal plasma using quantitative reverse-transcription real-time PCR [99]. Two months later, Lawrie et al. in 2008 reported that the levels of tumor-related miRNAs, including miR-155, miR-210, and miR-21, were significantly higher in the serum from diffuse large B-cell lymphoma compared with the control sera. Notably, the high expression of miR-21 was associated with relapse-free survival [100]. Hence, the study highlighted

c-miRNAs as non-invasive powerful diagnostic markers for human cancers. Since then, the new class of miRNA, c-miRNAs, has opened up new molecular markers for human cancer monitoring.

Due to their many essential characteristics, c-miRNAs have been considered as valuable biomarkers for the early screening and diagnosis of human cancers, including NPC. c-miRNAs are stable in circulation and resistant to RNase activities in the extracellular environment [93,94]. Additionally, c-miRNAs remain stable with a considerable level of expression even when they are subjected to harsh conditions, including an extreme pH level (high or low pH), extended storage, boiling, and multiple freeze-thaw cycles [93,94,101]. However, the mechanisms by which c-miRNAs maintain their remarkable stability in a RNase-rich extracellular environment as well as in harsh conditions are still not well understood. The levels of c-miRNAs could easily be evaluated by various methods, such as qRT-PCR and oligonucleotide microarray [102,103]. Therefore, c-miRNAs are identified as suitable molecular targets for human cancer early screening, prognosis as well as treatment.

In several reports, interestingly, the potential uses of the c-miRNA expression profile are reported as biomarkers for early screening, and the prognosis and diagnosis of NPC [96,104]. In the study conducted by Zeng et al. in 2012, they performed the evaluation of serum miRNA profiling on the sera of twenty NPC patients and twenty non-cancerous controls. Four serum c-miRNAs, c-miR-223, c-miR-29c, c-miR-20a and c-miR-17, were significantly expressed in NPC patients' sera compared with the expression in the non-cancerous controls. Thus, serum-based biomarkers, especially the four serum c-miRNAs, are potential biomarkers for NPC diagnosis [105]. Yi et al. in 2019 reported that the low expression of c-miR-31-5p was significantly associated with the NPC tumor-node-metastasis (TNM) stage: Stage I + II vs. III + IV, T1 vs. T2 + T3 + T4 and N1 + N3 vs. N0. Moreover, c-miR-31-5p showed a moderate diagnostic performance. Therefore, c-miR-31-5p was concluded as the non-invasive valuable, and as a novel biomarker for the early diagnosis of NPC. Especially, it was reported to be an attractive therapeutic molecular target for NPC treatment [106]. Exosome-associated miRNAs, a type of vesicle-associated c-miRNA, are derived from cancer and could interact with endothelial cells, thereby enhancing proliferation, migration as well as angiogenesis [107]. Exosomal miR-24-3p was reported to be involved in nasopharyngeal pathogenesis by mediating T-cell suppression via the repression of fibroblast growth factor 11 (FGF11), and it may serve as a potential biomarker in NPC [108]. Up to date, exosome-associated miRNAs are still of interest in finding potential biomarkers for NPC. Other exosome-associated miRNAs, such as metastasis-associated miR-23a [109], exosomal miR-9 [107], exosomal miR-34c [110], etc., have been reported. Their data suggested that exosomal miRNAs reflect the pathogenesis of NPC and that there is the possibility of exosome-based therapies for NPC in the future.

5. miRNAs as Novel Molecular Targets for NPC Therapies

As described, strikingly different miRNA expressions have been observed in NPC; therefore, the activation of tumor suppressor miRNAs and/or the inhibition of oncogenic miRNAs may open up a novel approach for the development of therapeutics/treatments for NPC. Up to date, an increasing number of studies have focused on the possibility of miRNAs serving as molecular targets for NPC therapies. In the study conducted by Kang et al. in 2016, they investigated the effects of miR-24 on the radio-sensitivity of NPC cells. They found that the miR-24/SP1 pathway contributed to the reduction in radio-resistance in human NPC [111]. Therefore, the finding of the miR-24/SP1 pathway may help our understanding of radio-sensitivity in NPC and represents a promising therapeutic molecular target. Thus, based on the roles of miRNAs, more and more studies are applying miRNAs to NPC therapy.

6. Conclusions

Since the first discovery of miRNAs, numerous studies have focused on their roles in human tumorigenesis, including NPC. As described in this article, the abnormal expression of miRNAs, especially c-miRNAs, have been shown to play important roles in the hallmarks of NPC by targeting many pathways, including cell proliferation, invasion and migration. Especially, such detectable

changes in non/less invasive samples (plasma, serum, etc.) make them promising non-invasive biomarkers for the early screening, prognosis, and therapeutic molecular target monitoring of NPC.

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References

1. Lee, R.C.; Feinbaum, R.L.; Ambros, V. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell* **1993**, *75*, 843–854. [[CrossRef](#)]
2. Li, K.; Zhu, X.; Li, L.; Ning, R.; Liang, Z.; Zeng, F.; Su, F.; Huang, S.; Yang, X.; Qu, S. Identification of non-invasive biomarkers for predicting the radiosensitivity of nasopharyngeal carcinoma from serum microRNAs. *Sci. Rep.* **2020**, *10*, 5161. [[CrossRef](#)] [[PubMed](#)]
3. Bartel, D.P. MicroRNAs: Genomics, biogenesis, mechanism, and function. *Cell* **2004**, *116*, 281–297. [[CrossRef](#)]
4. Bushati, N.; Cohen, S.M. microRNA functions. *Annu. Rev. Cell Dev. Biol.* **2007**, *23*, 175–205. [[CrossRef](#)] [[PubMed](#)]
5. O'Brien, J.; Hayder, H.; Zayed, Y.; Peng, C. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. *Front. Endocrinol.* **2018**, *9*, 402. [[CrossRef](#)]
6. Stahlhut Espinosa, C.E.; Slack, F.J. The role of microRNAs in cancer. *Yale J. Biol. Med.* **2006**, *79*, 131–140.
7. Si, W.; Shen, J.; Zheng, H.; Fan, W. The role and mechanisms of action of microRNAs in cancer drug resistance. *Clin. Epigenet.* **2019**, *11*, 25. [[CrossRef](#)]
8. Li, M.; Wang, C.; Yu, B.; Zhang, X.; Shi, F.; Liu, X. Diagnostic value of RASSF1A methylation for breast cancer: A meta-analysis. *Biosci. Rep.* **2019**, *39*, BSR20190923. [[CrossRef](#)]
9. Tabuchi, K.; Nakayama, M.; Nishimura, B.; Hayashi, K.; Hara, A. Early detection of nasopharyngeal carcinoma. *Int. J. Otolaryngol.* **2011**, *2011*, 638058. [[CrossRef](#)]
10. Felekis, K.; Touvana, E.; Stefanou, C.; Deltas, C. microRNAs: A newly described class of encoded molecules that play a role in health and disease. *Hippokratia* **2010**, *14*, 236–240.
11. Wong, L.L.; Wang, J.; Liew, O.W.; Richards, A.M.; Chen, Y.T. MicroRNA and Heart Failure. *Int. J. Mol. Sci.* **2016**, *17*, 502. [[CrossRef](#)] [[PubMed](#)]
12. Cai, X.; Hagedorn, C.H.; Cullen, B.R. Human microRNAs are processed from capped, polyadenylated transcripts that can also function as mRNAs. *RNA* **2004**, *10*, 1957–1966. [[CrossRef](#)] [[PubMed](#)]
13. Lee, Y.; Kim, M.; Han, J.; Yeom, K.H.; Lee, S.; Baek, S.H.; Kim, V.N. MicroRNA genes are transcribed by RNA polymerase II. *EMBO J.* **2004**, *23*, 4051–4060. [[CrossRef](#)] [[PubMed](#)]
14. Lao, D.T.; Truong, K.P.; Le, H.A.T. miRNA-141 as the Biomarker for Human Cancers. *AJPRHC* **2018**, *10*, 42–49. [[CrossRef](#)]
15. Peng, Y.; Croce, C.M. The role of MicroRNAs in human cancer. *Signal Transduct. Target. Ther.* **2016**, *1*, 15004. [[CrossRef](#)] [[PubMed](#)]
16. Lee, Y.; Ahn, C.; Han, J.; Choi, H.; Kim, J.; Yim, J.; Lee, J.; Provost, P.; Rådmark, O.; Kim, S.; et al. The nuclear RNase III Drosha initiates microRNA processing. *Nature* **2003**, *425*, 415–419. [[CrossRef](#)]
17. Kim, V.N.; Han, J.; Siomi, M.C. Biogenesis of small RNAs in animals. *Nat. Rev. Mol. Cell Biol.* **2009**, *10*, 126–139. [[CrossRef](#)]
18. Inui, M.; Martello, G.; Piccolo, S. MicroRNA control of signal transduction. *Nat. Rev. Mol. Cell Biol.* **2010**, *11*, 252–263. [[CrossRef](#)]
19. Witkos, T.M.; Koscińska, E.; Krzyżosiak, W.J. Practical Aspects of microRNA Target Prediction. *Curr. Mol. Med.* **2011**, *11*, 93–109. [[CrossRef](#)]

20. Sengupta, S.; den Boon, J.A.; Chen, I.H.; Newton, M.A.; Stanhope, S.A.; Cheng, Y.J.; Chen, C.J.; Hildesheim, A.; Sugden, B.; Ahlquist, P. MicroRNA 29c is down-regulated in nasopharyngeal carcinomas, up-regulating mRNAs encoding extracellular matrix proteins. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 5874–5878. [[CrossRef](#)]
21. Bruce, J.P.; Liu, F.F. MicroRNAs in nasopharyngeal carcinoma. *Chin. J. Cancer* **2014**, *33*, 539–544. [[CrossRef](#)] [[PubMed](#)]
22. Spence, T.; Bruce, J.; Yip, K.W.; Liu, F.F. MicroRNAs in nasopharyngeal carcinoma. *Chin. Clin. Oncol.* **2016**, *5*, 17. [[CrossRef](#)] [[PubMed](#)]
23. Shenouda, S.K.; Alahari, S.K. MicroRNA function in cancer: Oncogene or a tumor suppressor? *Cancer Metastasis Rev.* **2009**, *28*, 369–378. [[CrossRef](#)] [[PubMed](#)]
24. Tan, G.; Tang, X.; Tang, F. The role of microRNAs in nasopharyngeal carcinoma. *Tumour Biol.* **2015**, *36*, 69–79. [[CrossRef](#)] [[PubMed](#)]
25. Wong, T.S.; Man, O.Y.; Tsang, C.M.; Tsao, S.W.; Tsang, R.K.; Chan, J.Y.; Ho, W.K.; Wei, W.I.; To, V.S. MicroRNA let-7 suppresses nasopharyngeal carcinoma cells proliferation through downregulating c-Myc expression. *J. Cancer Res. Clin. Oncol.* **2011**, *137*, 415–422. [[CrossRef](#)] [[PubMed](#)]
26. Liu, Z.; Wu, K.; Yang, Z.; Wu, A. High-mobility group A2 overexpression is an unfavorable prognostic biomarker for nasopharyngeal carcinoma patients. *Mol. Cell Biochem.* **2015**, *409*, 155–162. [[CrossRef](#)]
27. Wu, A.; Wu, K.; Li, J.; Mo, Y.; Lin, Y.; Wang, Y.; Shen, X.; Li, S.; Li, L.; Yang, Z. Let-7a inhibits migration, invasion and epithelial-mesenchymal transition by targeting HMGA2 in nasopharyngeal carcinoma. *J. Transl. Med.* **2015**, *13*, 105. [[CrossRef](#)]
28. Cai, K.; Wan, Y.; Sun, G.; Shi, L.; Bao, X.; Wang, Z. Let-7a inhibits proliferation and induces apoptosis by targeting EZH2 in nasopharyngeal carcinoma cells. *Oncol. Rep.* **2012**, *28*, 2101–2106. [[CrossRef](#)]
29. Lu, J.; Luo, H.; Liu, X.; Peng, Y.; Zhang, B.; Wang, L.; Xu, X.; Peng, X.; Li, G.; Tian, W.; et al. miR-9 targets CXCR4 and functions as a potential tumor suppressor in nasopharyngeal carcinoma. *Carcinogenesis* **2014**, *35*, 554–563. [[CrossRef](#)]
30. Lu, J.; Xu, X.; Liu, X.; Peng, Y.; Zhang, B.; Wang, L.; Luo, H.; Peng, X.; Li, G.; Tian, W.; et al. Predictive value of miR-9 as a potential biomarker for nasopharyngeal carcinoma metastasis. *Br. J. Cancer* **2014**, *110*, 392–398. [[CrossRef](#)]
31. Gao, F.; Zhao, Z.L.; Zhao, W.T.; Fan, Q.R.; Wang, S.C.; Li, J.; Zhang, Y.Q.; Shi, J.W.; Lin, X.L.; Yang, S.; et al. miR-9 modulates the expression of interferon-regulated genes and MHC class I molecules in human nasopharyngeal carcinoma cells. *Biochem. Biophys. Res. Commun.* **2013**, *431*, 610–616. [[CrossRef](#)]
32. Sam, C.K.; Brooks, L.A.; Niedobitek, G.; Young, L.S.; Prasad, U.; Rickinson, A.B. Analysis of Epstein-Barr virus infection in nasopharyngeal biopsies from a group at high risk of nasopharyngeal carcinoma. *Int. J. Cancer* **1993**, *53*, 957–962. [[CrossRef](#)] [[PubMed](#)]
33. Liu, N.; Tang, L.L.; Sun, Y.; Cui, R.X.; Wang, H.Y.; Huang, B.J.; He, Q.M.; Jiang, W.; Ma, J. MiR-29c suppresses invasion and metastasis by targeting TIAM1 in nasopharyngeal carcinoma. *Cancer Lett.* **2013**, *329*, 181–188. [[CrossRef](#)]
34. He, Q.; Ren, X.; Chen, J.; Li, Y.; Tang, X.; Wen, X.; Yang, X.; Zhang, J.; Wang, Y.; Ma, J.; et al. miR-16 targets fibroblast growth factor 2 to inhibit NPC cell proliferation and invasion via PI3K/AKT and MAPK signaling pathways. *Oncotarget* **2016**, *7*, 3047–3058. [[CrossRef](#)] [[PubMed](#)]
35. Jiang, Q.; Zhang, Y.; Zhao, M.; Li, Q.; Chen, R.; Long, X.; Fang, W.; Liu, Z. miR-16 induction after CDK4 knockdown is mediated by c-Myc suppression and inhibits cell growth as well as sensitizes nasopharyngeal carcinoma cells to chemotherapy. *Tumour Biol.* **2016**, *37*, 2425–2433. [[CrossRef](#)] [[PubMed](#)]
36. Alajez, N.M.; Shi, W.; Hui, A.B.; Bruce, J.; Lenarduzzi, M.; Ito, E.; Yue, S.; O'Sullivan, B.; Liu, F.F. Enhancer of Zeste homolog 2 (EZH2) is overexpressed in recurrent nasopharyngeal carcinoma and is regulated by miR-26a, miR-101, and miR-98. *Cell Death Dis.* **2010**, *1*, e85. [[CrossRef](#)]
37. Yu, L.; Lu, J.; Zhang, B.; Liu, X.; Wang, L.; Li, S.Y.; Peng, X.H.; Xu, X.; Tian, W.D.; Li, X.P. miR-26a inhibits invasion and metastasis of nasopharyngeal cancer by targeting EZH2. *Oncol. Lett.* **2013**, *5*, 1223–1228. [[CrossRef](#)]
38. Wang, H.Y.; Li, Y.Y.; Fu, S.; Wang, X.P.; Huang, M.Y.; Zhang, X.; Shao, Q.; Deng, L.; Zeng, M.S.; Zeng, Y.X.; et al. MicroRNA-30a promotes invasiveness and metastasis in vitro and in vivo through epithelial-mesenchymal transition and results in poor survival of nasopharyngeal carcinoma patients. *Exp. Biol. Med.* **2014**, *239*, 891–898. [[CrossRef](#)]

39. Li, H.; Li, X.; Ge, X.; Jia, L.; Zhang, Z.; Fang, R.; Yang, J.; Liu, J.; Peng, S.; Zhou, M.; et al. MiR-34b-3 and miR-449a inhibit malignant progression of nasopharyngeal carcinoma by targeting lactate dehydrogenase A. *Oncotarget* **2016**, *23*, 54838–54851. [[CrossRef](#)]
40. Li, Y.Q.; Ren, X.Y.; He, Q.M.; Xu, Y.F.; Tang, X.R.; Sun, Y.; Zeng, M.S.; Kang, T.B.; Liu, N.; Ma, J. MiR-34c suppresses tumor growth and metastasis in nasopharyngeal carcinoma by targeting MET. *Cell Death Dis.* **2015**, *22*, e1618. [[CrossRef](#)]
41. Peng, X.H.; Huang, H.R.; Lu, J.; Liu, X.; Zhao, F.P.; Zhang, B.; Lin, S.X.; Wang, L.; Chen, H.H.; Xu, X.; et al. MiR-124 suppresses tumor growth and metastasis by targeting Foxq1 in nasopharyngeal carcinoma. *Mol. Cancer* **2014**, *13*, 186. [[CrossRef](#)] [[PubMed](#)]
42. Liu, X.; Lv, X.B.; Wang, X.P.; Sang, Y.; Xu, S.; Hu, K.; Wu, M.; Liang, Y.; Liu, P.; Tang, J.; et al. MiR-138 suppressed nasopharyngeal carcinoma growth and tumorigenesis by targeting the CCND1 oncogene. *Cell Cycle* **2012**, *11*, 2495–2506. [[CrossRef](#)] [[PubMed](#)]
43. Qi, X.; Li, J.; Zhou, C.; Lv, C.; Tian, M. MiR-142-3p Suppresses SOCS6 Expression and Promotes Cell Proliferation in Nasopharyngeal Carcinoma. *Cell Physiol. Biochem.* **2015**, *36*, 1743–1752. [[CrossRef](#)] [[PubMed](#)]
44. Li, Y.; He, Q.; Wen, X.; Hong, X.; Yang, X.; Tang, X.; Zhang, P.; Lei, Y.; Sun, Y.; Zhang, J.; et al. EZH2-DNMT1-mediated epigenetic silencing of miR-142-3p promotes metastasis through targeting ZEB2 in nasopharyngeal carcinoma. *Cell Death Differ.* **2019**, *26*, 1089–1106. [[CrossRef](#)]
45. Wang, L.; Tian, W.D.; Xu, X.; Nie, B.; Lu, J.; Liu, X.; Zhang, B.; Dong, Q.; Sunwoo, J.B.; Li, G.; et al. Epstein-Barr virus nuclear antigen 1 (EBNA1) protein induction of epithelial-mesenchymal transition in nasopharyngeal carcinoma cells. *Cancer* **2014**, *120*, 363–372. [[CrossRef](#)]
46. Yang, X.; Ni, W.; Lei, K. miR-200b suppresses cell growth, migration and invasion by targeting Notch1 in nasopharyngeal carcinoma. *Cell Physiol. Biochem.* **2013**, *32*, 1288–1298. [[CrossRef](#)]
47. Ma, L.; Deng, X.; Wu, M.; Zhang, G.; Huang, J. Down-regulation of miRNA-204 by LMP-1 enhances CDC42 activity and facilitates invasion of EBV-associated nasopharyngeal carcinoma cells. *FEBS Lett.* **2014**, *588*, 1562–1570. [[CrossRef](#)]
48. Deng, M.; Tang, H.; Zhou, Y.; Zhou, M.; Xiong, W.; Zheng, Y.; Ye, Q.; Zeng, X.; Liao, Q.; Guo, X.; et al. miR-216b suppresses tumor growth and invasion by targeting KRAS in nasopharyngeal carcinoma. *J. Cell Sci.* **2011**, *124 Pt 17*, 2997–3005. [[CrossRef](#)]
49. Deng, M.; Liu, J.F.; Gu, Y.X.; Zheng, G.P.; He, Z.M. miR-216b suppresses cell proliferation and invasion by targeting PKC α in nasopharyngeal carcinoma cells. *Zhonghua Zhong Liu Za Zhi* **2013**, *35*, 645–650.
50. Alajez, N.M.; Lenarduzzi, M.; Ito, E.; Hui, A.B.; Shi, W.; Bruce, J.; Yue, S.; Huang, S.H.; Xu, W.; Waldron, J.; et al. MiR-218 suppresses nasopharyngeal cancer progression through downregulation of survivin and the SLIT2-ROBO1 pathway. *Cancer Res.* **2011**, *71*, 2381–2391. [[CrossRef](#)]
51. Gao, L.; Xiong, X. MiR-223 inhibits the proliferation, invasion and EMT of nasopharyngeal carcinoma cells by targeting SSRP1. *Int. J. Clin. Exp. Pathol.* **2018**, *11*, 4374–4384.
52. Yang, W.; Lan, X.; Li, D.; Li, T.; Lu, S. MiR-223 targeting MAFB suppresses proliferation and migration of nasopharyngeal carcinoma cells. *BMC Cancer* **2015**, *15*, 461. [[CrossRef](#)]
53. Hui, A.B.; Bruce, J.P.; Alajez, N.M.; Shi, W.; Yue, S.; Perez-Ordóñez, B.; Xu, W.; O’Sullivan, B.; Waldron, J.; Cummings, B.; et al. Significance of dysregulated metadherin and microRNA-375 in head and neck cancer. *Clin Cancer Res.* **2011**, *17*, 7539–7550. [[CrossRef](#)]
54. Hou, J.; Yan, J.; Ren, X.Y.; Zhu, K.; Du, X.Y.; Li, J.J.; Xu, M. Long noncoding RNA ROR1-AS1 induces tumor metastasis and epithelial-mesenchymal transition by sponging miR-375 in nasopharyngeal carcinoma. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 174–180. [[CrossRef](#)]
55. Liu, N.; Jiang, N.; Guo, R.; Jiang, W.; He, Q.M.; Xu, Y.F.; Li, Y.Q.; Tang, L.L.; Mao, Y.P.; Sun, Y.; et al. MiR-451 inhibits cell growth and invasion by targeting MIF and is associated with survival in nasopharyngeal carcinoma. *Mol. Cancer* **2013**, *12*, 123. [[CrossRef](#)] [[PubMed](#)]
56. Li, L.; Gao, R.; Yu, Y.; Kaul, Z.; Wang, J.; Kalra, R.S.; Zhang, Z.; Kaul, S.C.; Wadhwa, R. Tumor suppressor activity of miR-451: Identification of CARF as a new target. *Sci. Rep.* **2018**, *8*, 375. [[CrossRef](#)] [[PubMed](#)]
57. Kavitha, N.; Vijayarathna, S.; Jothy, S.L.; Oon, C.E.; Chen, Y.; Kanwar, J.R.; Sasidharan, S. MicroRNAs: Biogenesis, roles for carcinogenesis and as potential biomarkers for cancer diagnosis and prognosis. *Asian Pac. J. Cancer Prev.* **2014**, *15*, 7489–7497. [[CrossRef](#)] [[PubMed](#)]
58. Ørom, U.A.; Nielsen, F.C.; Lund, A.H. MicroRNA-10a binds the 5’UTR of ribosomal protein mRNAs and enhances their translation. *Mol. Cell* **2008**, *30*, 460–471. [[CrossRef](#)]

59. Sun, X.J.; Liu, H.; Zhang, P.; Zhang, X.D.; Jiang, Z.W.; Jiang, C.C. miR-10b promotes migration and invasion in nasopharyngeal carcinoma cells. *Asian Pac. J. Cancer Prev.* **2013**, *14*, 5533–5537. [[CrossRef](#)]
60. Allaya, N.; Khabir, A.; Sallemi-Boudawara, T.; Sellami, N.; Daoud, J.; Ghorbel, A.; Frikha, M.; Gargouri, A.; Mokdad-Gargouri, R.; Ayadi, W. Over-expression of miR-10b in NPC patients: Correlation with LMP1 and Twist1. *Tumour Biol.* **2015**, *36*, 3807–3814. [[CrossRef](#)]
61. Chen, C.; Lu, Z.; Yang, J.; Hao, W.; Qin, Y.; Wang, H.; Xie, C.; Xie, R. MiR-17-5p promotes cancer cell proliferation and tumorigenesis in nasopharyngeal carcinoma by targeting p21. *Cancer Med.* **2016**, *5*, 3489–3499. [[CrossRef](#)]
62. Hu, Z.; Zhou, S.; Luo, H.; Ji, M.; Zheng, J.; Huang, F.; Wang, F. miRNA-17 promotes nasopharyngeal carcinoma radioresistance by targeting PTEN/AKT. *Int. J. Clin. Exp. Pathol.* **2019**, *12*, 229–240.
63. Luo, Z.; Dai, Y.; Zhang, L.; Jiang, C.; Li, Z.; Yang, J.; McCarthy, J.B.; She, X.; Zhang, W.; Ma, J.; et al. miR-18a promotes malignant progression by impairing microRNA biogenesis in nasopharyngeal carcinoma. *Carcinogenesis* **2013**, *34*, 415–425. [[CrossRef](#)]
64. Mai, S.; Xiao, R.; Shi, L.; Zhou, X.; Yang, T.; Zhang, M.; Weng, N.; Zhao, X.; Wang, R.; Liu, J.; et al. MicroRNA-18a promotes cancer progression through SMG1 suppression and mTOR pathway activation in nasopharyngeal carcinoma. *Cell Death Dis.* **2019**, *10*, 819. [[CrossRef](#)] [[PubMed](#)]
65. Huang, D.; Bian, G.; Pan, Y.; Han, X.; Sun, Y.; Wang, Y.; Shen, G.; Cheng, M.; Fang, X.; Hu, S. MiR-20a-5p promotes radio-resistance by targeting Rab27B in nasopharyngeal cancer cells. *Cancer Cell Int.* **2017**, *17*, 32. [[CrossRef](#)] [[PubMed](#)]
66. Li, Y.; Yan, L.; Zhang, W.; Wang, H.; Chen, W.; Hu, N.; Ou, H. miR-21 inhibitor suppresses proliferation and migration of nasopharyngeal carcinoma cells through down-regulation of BCL2 expression. *Int. J. Clin. Exp. Pathol.* **2014**, *7*, 3478–3487.
67. Ou, H.; Li, Y.; Kang, M. Activation of miR-21 by STAT3 induces proliferation and suppresses apoptosis in nasopharyngeal carcinoma by targeting PTEN gene. *PLoS ONE* **2014**, *9*, e109929. [[CrossRef](#)] [[PubMed](#)]
68. Wang, R.; Li, H.; Guo, X.; Wang, Z.; Liang, S.; Dang, C. IGF-I Induces Epithelial-to-Mesenchymal Transition via the IGF-IR-Src-MicroRNA-30a-E-Cadherin Pathway in Nasopharyngeal Carcinoma Cells. *Oncol. Res.* **2016**, *24*, 225–231. [[CrossRef](#)]
69. Lyu, X.; Fang, W.; Cai, L.; Zheng, H.; Ye, Y.; Zhang, L.; Li, J.; Peng, H.; Cho, W.C.; Wang, E.; et al. TGF β 2 is a major target of miR-93 in nasopharyngeal carcinoma aggressiveness. *Mol. Cancer* **2014**, *13*, 51. [[CrossRef](#)]
70. Xu, Y.F.; Mao, Y.P.; Li, Y.Q.; Ren, X.Y.; He, Q.M.; Tang, X.R.; Sun, Y.; Liu, N.; Ma, J. MicroRNA-93 promotes cell growth and invasion in nasopharyngeal carcinoma by targeting disabled homolog-2. *Cancer Lett.* **2015**, *363*, 146–155. [[CrossRef](#)]
71. Zhang, Y.; Xu, Z. miR-93 enhances cell proliferation by directly targeting CDKN1A in nasopharyngeal carcinoma. *Oncol. Lett.* **2018**, *15*, 1723–1727. [[CrossRef](#)] [[PubMed](#)]
72. Liu, F.; Wang, W.; Li, S.; Yang, Q.; Hu, J.; Zeng, N.; Gao, C. MicroRNA 141 represses nasopharyngeal carcinoma growth through inhibiting BMI1. *Oncol Lett.* **2018**, *16*, 6479–6487. [[CrossRef](#)] [[PubMed](#)]
73. Liu, Y.; Zhao, R.; Wang, H.; Luo, Y.; Wang, X.; Niu, W.; Zhou, Y.; Wen, Q.; Fan, S.; Li, X.; et al. miR-141 is involved in BRD7-mediated cell proliferation and tumor formation through suppression of the PTEN/AKT pathway in nasopharyngeal carcinoma. *Cell Death Dis.* **2016**, *7*, e2156. [[CrossRef](#)] [[PubMed](#)]
74. Lao, T.D.; Nguyen, T.V.; Nguyen, D.H.; Nguyen, M.T.; Nguyen, C.H.; Le, T.H.A. miR-141 is up-regulated in biopsies from Vietnamese patients with nasopharyngeal carcinoma. *Braz. Oral Res.* **2018**, *32*, e126. [[CrossRef](#)]
75. Zhang, L.Y.; Ho-Fun Lee, V.; Wong, A.M.; Kwong, D.L.; Zhu, Y.H.; Dong, S.S.; Kong, K.L.; Chen, J.; Tsao, S.W.; Guan, X.Y.; et al. MicroRNA-144 promotes cell proliferation, migration and invasion in nasopharyngeal carcinoma through repression of PTEN. *Carcinogenesis* **2013**, *34*, 454–463. [[CrossRef](#)]
76. Song, L.; Chen, L.; Luan, Q.; Kong, Q. miR-144-3p facilitates nasopharyngeal carcinoma via crosstalk with PTEN. *J. Cell Physiol.* **2019**, *234*, 17912–17924. [[CrossRef](#)]
77. Wu, C.W.; Wang, S.G.; Lin, M.L.; Chen, S.S. Downregulation of miR-144 by triptolide enhanced p85 α -PTEN complex formation causing S phase arrest of human nasopharyngeal carcinoma cells. *Eur. J. Pharmacol.* **2019**, *855*, 137–148. [[CrossRef](#)]
78. Kong, Y.G.; Cui, M.; Chen, S.M.; Xu, Y.; Xu, Y.; Tao, Z.Z. LncRNA-LINC00460 facilitates nasopharyngeal carcinoma tumorigenesis through sponging miR-149-5p to up-regulate IL6. *Gene* **2018**, *639*, 77–84. [[CrossRef](#)]

79. Luo, Z.; Zhang, L.; Li, Z.; Jiang, C.; Dai, Y.; Liu, X.; Zheng, Y.; Yu, H.; Xiang, J.; Li, G. miR-149 promotes epithelial-mesenchymal transition and invasion in nasopharyngeal carcinoma cells. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* **2011**, *36*, 604–609. [[CrossRef](#)]
80. Zhu, X.; Wang, Y.; Sun, Y.; Zheng, J.; Zhu, D. MiR-155 up-regulation by LMP1 DNA contributes to increased nasopharyngeal carcinoma cell proliferation and migration. *Eur. Arch. Otorhinolaryngol.* **2014**, *271*, 1939–1945. [[CrossRef](#)]
81. Zuo, W.N.; Zhu, H.; Li, L.P.; Jin, A.Y.; Wang, H.Q. MiR-155 promotes proliferation and inhibits apoptosis of nasopharyngeal carcinoma cells through targeting PTEN-PI3K/AKT pathway. *Eur. Rev. Med. Pharmacol. Sci.* **2019**, *23*, 7935–7942. [[CrossRef](#)] [[PubMed](#)]
82. Wu, S.; Xie, D.L.; Dai, X.Y. Down-regulation of miR-155 promotes apoptosis of nasopharyngeal carcinoma CNE-1 cells by targeting PI3K/AKT-FOXO3a signaling. *Eur. Rev. Med. Pharmacol. Sci.* **2019**, *23*, 7391–7398. [[CrossRef](#)] [[PubMed](#)]
83. Mao, Y.; Wu, S.; Zhao, R.; Deng, Q. MiR-205 promotes proliferation, migration and invasion of nasopharyngeal carcinoma cells by activation of AKT signalling. *J. Int. Med. Res.* **2016**, *44*, 231–240. [[CrossRef](#)] [[PubMed](#)]
84. Nie, G.; Duan, H.; Li, X.; Yu, Z.; Luo, L.; Lu, R.; Ji, Z.; Zhang, W. MicroRNA 205 promotes the tumorigenesis of nasopharyngeal carcinoma through targeting tumor protein p53-inducible nuclear protein 1. *Mol. Med. Rep.* **2015**, *12*, 5715–5722. [[CrossRef](#)] [[PubMed](#)]
85. Zhang, Z.C.; Li, Y.Y.; Wang, H.Y.; Fu, S.; Wang, X.P.; Zeng, M.S.; Zeng, Y.X.; Shao, J.Y. Knockdown of miR-214 promotes apoptosis and inhibits cell proliferation in nasopharyngeal carcinoma. *PLoS ONE* **2014**, *9*, e86149. [[CrossRef](#)]
86. Deng, M.; Ye, Q.; Qin, Z.; Zheng, Y.; He, W.; Tang, H.; Zhou, Y.; Xiong, W.; Zhou, M.; Li, X.; et al. miR-214 promotes tumorigenesis by targeting lactotransferrin in nasopharyngeal carcinoma. *Tumour Biol.* **2013**, *34*, 1793–1800. [[CrossRef](#)]
87. Yu, B.L.; Peng, X.H.; Zhao, F.P.; Liu, X.; Lu, J.; Wang, L.; Li, G.; Chen, H.H.; Li, X.P. MicroRNA-378 functions as an onco-miR in nasopharyngeal carcinoma by repressing TOB2 expression. *Int. J. Oncol.* **2014**, *44*, 1215–1222. [[CrossRef](#)]
88. Chen, L.; Tang, Y.; Wang, J.; Yan, Z.; Xu, R. miR-421 induces cell proliferation and apoptosis resistance in human nasopharyngeal carcinoma via downregulation of FOXO4. *Biochem. Biophys. Res. Commun.* **2013**, *435*, 745–750. [[CrossRef](#)]
89. Zhao, L.; Tang, M.; Hu, Z.; Yan, B.; Pi, W.; Li, Z.; Zhang, J.; Zhang, L.; Jiang, W.; Li, G.; et al. miR-504 mediated down-regulation of nuclear respiratory factor 1 leads to radio-resistance in nasopharyngeal carcinoma. *Oncotarget* **2015**, *6*, 15995–16018. [[CrossRef](#)]
90. Liang, S.; Zhang, N.; Deng, Y.; Chen, L.; Zhang, Y.; Zheng, Z.; Luo, W.; Lv, Z.; Li, S.; Xun, T. Increased Serum Level of MicroRNA-663 Is Correlated with Poor Prognosis of Patients with Nasopharyngeal Carcinoma. *Dis. Markers* **2016**, *2016*, 7648215. [[CrossRef](#)]
91. Yu, Q.; Zhang, F.; Du, Z.; Xiang, Y. Up-regulation of serum miR-744 predicts poor prognosis in patients with nasopharyngeal carcinoma. *Int. J. Clin. Exp. Med.* **2015**, *8*, 13296–13302. [[PubMed](#)]
92. Mo, X.; Yin, W.; Huang, Y.; Guo, W.; Zhou, M.; Ye, H. Expression of miR-3182 and EBV-miR-BART8-3p in nasopharyngeal carcinoma is correlated with distant metastasis. *Int. J. Clin. Exp. Pathol.* **2018**, *11*, 3134–3140. [[PubMed](#)]
93. Ma, R.; Jiang, T.; Kang, X. Circulating microRNAs in cancer: Origin, function and application. *J. Exp. Clin. Cancer Res.* **2012**, *31*, 38. [[CrossRef](#)] [[PubMed](#)]
94. O'Brien, K.P.; Ramphul, E.; Howard, L.; Gallagher, W.M.; Malone, C.; Kerin, M.J.; Dwyer, R.M. Circulating MicroRNAs in Cancer. *Methods Mol. Biol.* **2017**, *1509*, 123–139.
95. Cufaro, M.C.; Pieragostino, D.; Lanuti, P.; Rossi, C.; Cicalini, I.; Federici, L.; De Laurenzi, V.; Del Boccio, P. Extracellular Vesicles and Their Potential Use in Monitoring Cancer Progression and Therapy: The Contribution of Proteomics. *J. Oncol.* **2019**, *2019*, 1639854. [[CrossRef](#)]
96. Sohel, M.H. Extracellular/Circulating MicroRNAs: Release Mechanisms, Functions and Challenges. *Achiev. Life Sci.* **2016**, *10*, 175–186. [[CrossRef](#)]
97. Xu, X.; Lu, J.; Wang, F.; Liu, X.; Peng, X.; Yu, B.; Zhao, F.; Li, X. Dynamic Changes in Plasma MicroRNAs Have Potential Predictive Values in Monitoring Recurrence and Metastasis of Nasopharyngeal Carcinoma. *Biomed. Res. Int.* **2018**, 7329195. [[CrossRef](#)]

98. Wen, W.; Mai, S.J.; Lin, H.X.; Zhang, M.Y.; Huang, J.L.; Hua, X.; Lin, C.; Long, Z.Q.; Lu, Z.J.; Sun, X.Q.; et al. Identification of two microRNA signatures in whole blood as novel biomarkers for diagnosis of nasopharyngeal carcinoma. *J. Transl. Med.* **2019**, *17*, 186. [[CrossRef](#)]
99. Cui, M.; Wang, H.; Yao, X.; Zhang, D.; Xie, Y.; Cui, R.; Zhang, X. Circulating MicroRNAs in Cancer: Potential and Challenge. *Front. Genet.* **2019**, *10*, 626. [[CrossRef](#)]
100. Chim, S.S.; Shing, T.K.; Hung, E.C.; Leung, T.Y.; Lau, T.K.; Chiu, R.W.; Lo, Y.M. Detection and characterization of placental microRNAs in maternal plasma. *Clin. Chem.* **2008**, *54*, 482–490. [[CrossRef](#)]
101. Lawrie, C.H.; Gal, S.; Dunlop, H.M.; Pushkaran, B.; Liggins, A.P.; Pulford, K.; Banham, A.H.; Pezzella, F.; Boultonwood, J.; Wainscoat, J.S.; et al. Detection of elevated levels of tumour-associated microRNAs in serum of patients with diffuse large B-cell lymphoma. *Br. J. Haematol.* **2008**, *141*, 672–675. [[CrossRef](#)] [[PubMed](#)]
102. Mitchell, P.S.; Parkin, R.K.; Kroh, E.M.; Fritz, B.R.; Wyman, S.K.; Pogosova-Agadjanyan, E.L.; Peterson, A.; Noteboom, J.; O'Briant, K.C.; Allen, A.; et al. Circulating microRNAs as stable blood-based markers for cancer detection. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 10513–10518. [[CrossRef](#)] [[PubMed](#)]
103. Lodes, M.J.; Caraballo, M.; Suci, D.; Munro, S.; Kumar, A.; Anderson, B. Detection of cancer with serum miRNAs on an oligonucleotide microarray. *PLoS ONE* **2009**, *4*, e6229. [[CrossRef](#)] [[PubMed](#)]
104. Resnick, K.E.; Alder, H.; Hagan, J.P.; Richardson, D.L.; Croce, C.M.; Cohn, D.E. The detection of differentially expressed microRNAs from the serum of ovarian cancer patients using a novel real-time PCR platform. *Gynecol. Oncol.* **2009**, *112*, 55–59. [[CrossRef](#)]
105. Zeng, X.; Xiang, J.; Wu, M.; Xiong, W.; Tang, H.; Deng, M.; Li, X.; Liao, Q.; Su, B.; Luo, Z.; et al. Circulating miR-17, miR-20a, miR-29c, and miR-223 combined as non-invasive biomarkers in nasopharyngeal carcinoma. *PLoS ONE* **2012**, *7*, e46367. [[CrossRef](#)]
106. Yi, S.J.; Liu, P.; Chen, B.L.; Ou-Yang, L.; Xiong, W.M.; Su, J.P. Circulating miR-31-5p may be a potential diagnostic biomarker in nasopharyngeal carcinoma. *Neoplasma* **2019**, *66*, 825–829. [[CrossRef](#)]
107. Lu, J.; Liu, Q.H.; Wang, F.; Tan, J.J.; Deng, Y.Q.; Peng, X.H.; Liu, X.; Zhang, B.; Xu, X.; Li, X.P. Exosomal miR-9 inhibits angiogenesis by targeting MDK and regulating PDK/AKT pathway in nasopharyngeal carcinoma. *J. Exp. Clin. Cancer Res.* **2018**, *13*, 147. [[CrossRef](#)]
108. Ye, S.B.; Zhang, H.; Cai, T.T.; Liu, Y.N.; Ni, J.J.; He, J.; Peng, J.Y.; Chen, Q.Y.; Mo, H.Y.; Jun-Cui Zhang, X.S.; et al. Exosomal miR-24-3p impedes T-cell function by targeting FGF11 and serves as a potential prognostic biomarker for nasopharyngeal carcinoma. *J. Pathol.* **2016**, *240*, 329–340. [[CrossRef](#)]
109. Bao, L.; You, B.; Shi, S.; Shan, Y.; Zhang, Q.; Yue, H.; Zhang, J.; Zhang, W.; Shi, Y.; Liu, Y.; et al. Metastasis-associated miR-23a from nasopharyngeal carcinoma-derived exosomes mediates angiogenesis by repressing a novel target gene TSGA10. *Oncogene* **2018**, *37*, 2873–2889. [[CrossRef](#)]
110. Wan, F.Z.; Chen, K.H.; Sun, Y.C.; Chen, X.C.; Liang, R.B.; Chen, L.; Zhu, X.D. Exosomes overexpressing miR-34c inhibit malignant behavior and reverse the radioresistance of nasopharyngeal carcinoma. *J. Transl. Med.* **2020**, *18*, 12. [[CrossRef](#)]
111. Kang, M.; Xiao, J.; Wang, J.; Zhou, P.; Wei, T.; Zhao, T.; Wang, R. MiR-24 enhances radiosensitivity in nasopharyngeal carcinoma by targeting SP1. *Cancer Med.* **2016**, *5*, 1163–1173. [[CrossRef](#)] [[PubMed](#)]

