MicroRNA-378 functions as an onco-miR in nasopharyngeal carcinoma by repressing TOB2 expression

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Abstract. Increasing evidence indicates that microRNAs (miRNAs) has been implicated in the progression and metastasis of numerous cancers. In particular, abnormal expression of miR-378 has been observed in various cancers and is associated with cell survival, migration, invasion, angiogenesis and tumor growth. Our previous studies have shown that miR-378 was decreased in nasopharyngeal carcinoma (NPC) plasma and was negatively correlated with NPC progression. However, the tissue expression of miR-378 and its biological function remained unknown in NPC. In this study, we report for the first time that expression level of miR-378 was commonly upregulated in both NPC tissues and NPC cell lines compared to normal healthy nasopharyngeal epithelial samples and human nasopharyngeal epithelial cell lines (NP69), respectively, and was opposite to the reported results in plasma. Functional studies showed that upregulation of miR-378 dramatically promoted cell proliferation, colony formation, migration and invasion in vitro, as well as tumor growth in vivo. Bioinformatics analyses were performed to predict the target genes of miR-378, and the following mechanistic investigations revealed that miR-378 overexpression was able to downregulate the expression of transducer of ERBB2 (TOB2), a potential tumor suppressor, and miR-378 silencing enhanced TOB2 expression. In clinical specimens, TOB2 was widely repressed in tumor tissues accompanied by miR-378 overexpression. Taken together, this study indicates that miR-378 regulates TOB2 and may function as an onco-miR in NPC progression, providing a potential target for gene therapy of NPC.

Introduction

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma derived from epithelial cells lining the nasopharynx with highly malignant local invasion and early distant metastasis, which is rare globally but common in southern China and Southeast Asia (1). However, the cause of this disease is still uncertain while genetic, ethnic and environmental factors could all have a role. Although patients with early stage NPC can achieve excellent local control by radiotherapy alone, the 5-year survival rate is ~35% for patients with stage-IV(A-B) disease (2-4). Once metastasis occurs, the prognosis is even poorer. Therefore, better understanding of the pathogenesis is essential for developing novel therapies for NPC.

MicroRNAs (miRNA) are short non-coding RNAs of 18-24 nucleotides that function as critical gene regulators in mammals and other multicellular organisms. According to the results of bioinformatic analysis, one single miRNA may target up to several hundred mRNAs, indicating its potential influences on almost every biological pathway (5,6). Recent studies have shown that >50% of the miRNAs are frequently located at cancer associated regions and fragile sites (7), playing a role as tumor suppressor genes or onco-genes (8-10). A number of miRNAs have been shown to have different biological effects contributing to the development and progression of NPC (11-16) and combination of some miRNAs is useful in the diagnosis and prognosis of this disease (17,18), suggesting the involvement of miRNAs in NPC tumorigenesis. Our previous studies showed that miR-378 level in plasma was decreased in NPC patients and miR-378 together with other 4 miRNAs may serve as a set of biomarkers in NPC diagnosis (18). Nevertheless, the expression level of miR-378 in NPC tissue and its functional role has not been documented yet.

In this study, we investigated for the first time the potential role of miR-378 in the NPC pathological process. The miR-378 expression in NPC cell lines and tissues were examined and its effects on cell growth, colony formation, cell migration and invasion in vitro were tested. In addition, we investigated the potential role of miR-378 on NPC tumor growth in a murine model. Finally, the effect of miR-378 on its potential target gene transducer of ERBB2 (TOB2) was tested. Our study may provide a new strategy for the therapy of NPC.
Materials and methods

Clinical specimens. The NPC biopsy specimens (n=50) and normal nasopharyngeal epithelium biopsy samples (n=31) were obtained from patients in Nanfang Hospital (Southern Medical University, Guangzhou, China) and were frozen in liquid nitrogen for further study. None of the patients had received radiotherapy or chemotherapy before biopsy sampling. Tumor samples were pathologically confirmed as NPC. Informed written consent was obtained from each patient. The research protocols were approved by the Ethics Committee of Nanfang Hospital and registered in ClinicalTrials.gov (ID: NCT01171235).

Cell culture. The human nasopharyngeal carcinoma cell lines 5-8F; 6-10b, CNE1 and CNE2 were cultured in RPMI-1640 medium (HyClone, Thermo Scientific Inc, USA), supplemented with 10% fetal bovine serum (FBS, HyClone) and 1% penicillin/streptomycin. The primary nasopharyngeal epithelial cell NP69 (Cancer Research Center, Southern Medical University, China) was cultured as the control cell line in Keratinocyte-SFM (Gibco, Life Technologies Corp., USA) according to the manufacturer's instructions. HEK 293T cell line (Cell Bank of Chinese Academy of Science in Shanghai, China) was cultured in DMEM/High glucose medium (HyClone) with 10% FBS (HyClone) and 1% penicillin/streptomycin. All cells were maintained at 37°C with an atmosphere of 5% CO₂.

RNA isolation, reverse transcription, and quantitative real-time PCR. Total RNA was extracted from the samples using RNeasy Plus (Takara, Shiga, Japan) and reversely transcribed to cDNA using the All-in-One First-Strand cDNA Synthesis kit (GeneCopoeia Inc., USA). Quantitative real-time PCR (qPCR) was performed using All-in-One™ qPCR Mix (Applied GeneCopoeia Inc.) on an ABI 7500HT System. U6 (qPCR) was performed using All-in-One™ qPCR Mix (Applied GeneCopoeia Inc.) on an ABI 7500HT System. U6 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) snRNA were used as a miRNA and mRNA endogenous control, respectively. All samples were normalized to the internal control and the relative expression level of miR-378 and TOB2 was calculated using relative quantification assay.

Vector construction and lentivirus transduction. To obtain stable cell lines overexpressing miR-378, pre-miR-378 was cloned into the pLVTHM lentiviral vector (Tronolab). The primers for cloning pre-miR-378 were: forward sequence 5'-CCATCGATGGGAGTTCAAATGGCT and reverse sequence 5'-CGACGCGTCGGGCTGCGAGGAGTGAGCG-3' and 5'-CCATCGATGGGAGTTCAAATGGCT and reverse sequence 5'-CGACGCGTCGGGCTGCGAGGAGTGAGCG-3'. The longest diameter and d = the shortest diameter. The 5-8F and 6-10b transduced by the packaged lentivirus vectors were named lv-control/5-8F and lv-control/6-10B. The stably transduced cells were then selected after transduction with pLVTHM lentiviral vector were named lv-control/6-10B. The stably transduced cells were then selected (all the primers are listed in Table I). Then, the cell lines and miRNA transfected cell lines were separated by flow cytometry. The positive clones with miR-378 overexpression were confirmed by real-time PCR.

Cell proliferation and colony-formation assay. To determine the effect of mir-378 on cell proliferation, the cells with stable overexpression of miR-378 were seeded into 96-wells plates at a density of 1x10⁴ cells/well with 5 replicate wells of each condition. Cell Counting Kit-8 (CCK-8, Kaigene Inc., China) was added to the maintenance cell medium, and all cells were incubated at 37°C for an additional 2 h before being measured. Absorbance values were measured daily for four consecutive days at a wavelength of 450 nm.

In measuring colony-forming activity, cells were counted and seeded into 12-well plates at 100 cells per well. Twelve days after seeding, the numbers of colonies containing >50 cells were counted after dyed crystal violet.

Migration and invasion assays. Transwell migration assays and invasion assays were conducted to determine the functional effects of miR-378 on cell migration and invasion. Briefly, for transwell migration assays, 5x10⁴ cells were plated in the top chamber (24-well insert; pore size, 8 µm; Corning). For invasion assays, 1x10⁵ cells were plated in the top chamber with Matrigel-coated membrane (24-well insert; pore size, 8 µm; BD Biosciences). Cells were then cultured at 37°C for 24 h. After that, the cells on the surface of the upper chamber were swapped with cotton swap and the cells under the surface of the lower chamber were stained with crystal violet (0.1%) and counted under a microscope.

Tumor growth assay. To further investigate the proliferation efficacy of miR-378 in vivo, ten female BALB/C nude mice about four to five-week-old were purchased from Laboratory Animal Center of Southern Medical University. The animal protocol was approved by the Animal Investigation Committee of Southern Medical University. Ten nude mice were randomly divided into two groups. lv-miR-378/5-8F or lv-control/5-8F (1x10⁵) cells were injected into the dorsal flanks of each mouse. Tumor size was measured every other day. Mice were sacrificed and tumors were dissected and weighed. Tumor volumes were calculated as follows: volume = (Dx(d²))/2, where D = the longest diameter and d = the shortest diameter.

miRNA target prediction and validation. Three microRNA target databases (mirBase, PicTar and TargetScan) were utilized to predict mir-378 target genes, and a total of 16 genes were selected (all the primers are listed in Table I). Then, the predicted targets were validated in NPC cell line 5-8F using RT-qPCR.

miRNA transfection and western blotting. MiRNAs were transfected at a working concentration of 80 nmo/l using Lipofectamine 2000 reagent (Invitrogen). The miR-378 mimic, a nonspecific miR control, anti-miR378 and a nonspecific anti-miR control were all purchased from GenePharma (Shanghai, China). Forty-eight hours after transfection, the cells were harvested for protein extraction. Protein lysates extracted from stable cell lines and miRNA transfected cell lines were separated by 10% SDS-PAGE, and electrophoretically transferred to PVDF (polyvinylidene difluoride) membrane (Millipore). Then, the membrane was incubated with goat polyclonal antibody against human TOB2 (Santa Cruz Biotechnology) followed by HRP (horseradish peroxidase)-labeled goat anti-mouse IgG (Santa Cruz Biotechnology) and detected by chemiluminescence. GAPDH was used as a protein loading control. The intensity
of protein fragments was quantified with the Quantity One software (4.5.0 basic, Bio-Rad).

Statistical analysis. Statistical analyses were performed using SPSS 13.0 statistical software. All experiments were performed three times. Two-tailed Student's t-test was used for comparison of two independent groups. MiR-378 expression between tumor and normal samples was analyzed by the Mann-Whitney U test. P-values <0.05 were considered statistically significant.

Results

miR-378 is upregulated in NPC cell lines and clinical specimens. 5-8F, 6-10B, CNE1 and CNE2 cell lines were selected to measure the miR-378 expression level using qRT-PCR. The results showed that the basal expression level of miR-378 was generally upregulated in 4 NPC cell lines compared with the immortalized, but not tumorigenic nasopharyngeal epithelial cell line NP69 (Fig. 1A).

In order to further test and verify the expression level of miR-378, we tested its transcript levels in 50 tumor specimens relative to 31 normal nasopharyngeal tissues. A subsequent analysis confirmed that the expression of miR-378 had a 3.63-fold increase compared with normal tissues (Fig. 1B). On the basis of these results, we focused on miR-378 for further functional studies to evaluate its roles in NPC pathogenesis.

miR-378 enhances the proliferation capacity of NPC cells in vitro. To determine whether miR-378 affected the proliferation of NPC cells, we used lentiviral vectors to stably upregulate the expression level of miR-378 in 5-8F and 6-10B cell lines. The results demonstrated that the expression level of miR-378 was upregulated ~45-fold and 20-fold in 5-8F and 6-10B cells, respectively, after transduced with lentiviral vectors containing miR-378 (Fig. 2A).

CCK-8 was utilized to measure cell proliferation in lv-miR-378/5-8F and lv-miR-378/6-10B cells. The results showed that the proliferation capacity of lv-miR-378/5-8F and lv-miR-378/6-10B cells was increased ~61.6 and 51.9% respectively compared with control cell (Fig. 2B). Colony formation experiment was also performed to evaluate NPC cell proliferation.

<table>
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<th>Gene</th>
<th>Forward sequence (5'-3')</th>
<th>Reverse sequence (5'-3')</th>
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Figure 1. The expression level of miR-378 was reduced in NPC cell lines and clinical specimens. (A) The expression of miR-378 in NPC cell lines. (B) Average expression level of miR-378 in human NPC specimens and normal nasopharyngeal epithelial tissues. *P<0.01.
Similar results indicated that miR-378 increased the colony formation ability by 43.8 and 77% in lv-miR-378/5-8F and lv-miR-378/6-10B than lv-control cell, respectively (Fig. 2C and D). Thus, upregulation of miR-378 plays a crucial role in NPC cell growth, survival and colony formation.

miR-378 promoted the migratory and invasive capacities of NPC cells in vitro. To investigate the effects of upregulated miR-378 in cell invasion and migration, we conducted cell migration and cell invasion assays. We found that upregulated expression of miR-378 significantly promoted the migratory and invasive abilities of lv-miR-378/5-8F cells and lv-miR-378/6-10B cells. The numbers of migrated cells increased by 2.61- and 0.94-fold, respectively (Fig. 3A and C). The numbers of invasive cells increased by 1.32- and 2.47-fold in lv-miR-378/5-8F cells and lv-miR-378/6-10B cells than lv-control cells, respectively (Fig. 3B and D). These results highlighted the vital role of miR-378 in NPC metastasis.

miR-378 accelerates tumor growth in vivo. Given the role of miR-378 in vitro in proliferation, we next determined whether miR-378 could affect tumor growth in vivo. Lv-miR-378/5-8F cells and lv-control cells were used for evaluating the influence of miR-378 overexpression on the growth of tumor xenografts. We implanted lv-miR-378/5-8F or lv-control/5-8F cells subcutaneously in nude mice, respectively (n=5 per group). As shown in Fig. 4, lv-miR-378/5-8F cells resulted in an approximately 2.8-fold increase in tumor size relative to lv-control/5-8F cells (989±327 mm<sup>3</sup> vs. 353±184 mm<sup>3</sup> after 15 days, P<0.05). After the tumors were denuded and weighed, the results of the weight were similar to those of tumor volume. Thus, these results showed that miR-378 accelerated tumor growth in vivo.

TOB2 is decreased in NPC cell lines and tissues and is downregulated by miR-378. By bioinformatic analysis, we focused on 16 possible target genes of mir-378. Primers were designed using Primer-BLAST and the selected targets were validated by RT-qPCR in lv-miR-378/5-8F cells. The result of RT-qPCR showed that the expression level of TOB2 decreased more significantly, compared with other 15 possible target genes (Fig. 5A). To further determine whether miR-378 expression was associated with TOB2 in human NPC tissues, we examined the expression of TOB2 in 50 tumor specimens and 31 normal nasopharyngeal tissues. Notably, the results showed that TOB2 was significantly downregulated in NPC tissues as compared with non-cancer nasopharyngeal tissues (Fig. 5B).

To further investigate the relation between miR-378 and TOB2, we conducted transient transfection in 5-8F cells to enhance or inhibit the expression of miR-378. As a result, up- or downregulation of miR-378 led to a dramatic change in TOB2 mRNA and protein expression (Fig. 5C and E). Moreover, similar results were obtained in the stably transfected cell lv-miR-378/5-8F (Fig. 5D and F).

**Discussion**

MiR-378 was first reported expressed in a number of cancer cell lines and took part in the expression of vascular endothelial...
growth factor (19,20). No biological function of miR-378 was documented until 2007, Lee and his colleges reported that miR-378 overexpression enhanced cell survival, tumor growth and angiogenesis through repression of Sufu and Fus-1, two tumor suppressors (21). Since then, an increasing number of studies were conducted to shed light on the function of miR-378...
in cancers. However, despite the progress that has been made in recent years regarding the role of miR-378 in the pathological process of cancers, our knowledge of miR-378 functions in NPC is limited.

Emerging evidence clearly indicates that miR-378 is abnormally expressed and has been implicated in various tumors such as breast cancer (22), colorectal cancer (23) and diffuse large B-cell lymphoma (24). It was significantly upregulated in the serum of patients with GC and renal carcinoma, indicating its potential role as a serum biomarker in early cancer diagnosis (25,26). Mir-378 was also remarkably elevated in adjacent non-tumorous tissues and decreased in cancer tissues and cell lines in gastric cancer (27-29). Previous functional studies reported that ectopic overexpression of mir-378 can promote cell proliferation, angiogenesis, invasion and induced chemoresistance in a number of solid tumors including glioblastoma, non-small cell lung cancer (NSCLC), and breast cancer (21,22,30,31), suggesting its role as onco-miRNA. On the contrary, however, the expression level of miR-378 in colorectal cancer tissue was significantly decreased and restoration of miR-378 inhibited G1/S transition (23). In the study of miRNA profile in basal cell carcinoma and cutaneous squamous cell carcinoma, mir-378 was also among the downregulated miRNAs (32,33). In addition, miR-378 was abnormally expressed and epigenetically regulated in gastric cancer cell lines and tissues via the suppression of vascular endothelial growth factor (VEGF) signaling (29). These findings indicated that miR-378 may play an important role in certain tumors as tumour suppressors.

Our results showed that miR-378 was overexpressed in NPC cell lines and cancer tissues. Functional studies revealed that overexpression of miR-378 in NPC cell lines was able to enhance cell growth and colony formation in vitro and promote tumorigenesis in a murine model of NPC xenografts. Results of the cell migration and invasion assays showed an enhancement in cell migration and invasion ability in NPC cells overexpressing miR-378. In our murine model of NPC xenografts, tumors derived from lv-miR-378/5-8F cells had a significantly larger volume and weight compared to the control group. These findings revealed the role of miR-378 as onco-miRNA in NPC. These controversial results suggested that the role of mir-378 was possibly tumor specific and highly...
dependent on its targets in different cancer cells. The tissue-dependent expression of miRNAs may influence protein translation during diverse cellular processes. Moreover, the aberrant expression of their target genes affected different biological pathways with diverse functions (34).

It is worth mentioning that in our previous studies (18), miR-378 was found to decrease in the plasma of NPC patients. It increased to a certain extent in patients without relapse but further decreased when cancer relapsed and with metastasis. Compared with the results in the present study, the expression level of miR-378 between NPC patient plasma and tissue changed in the opposite direction. The situation was similar to other studies showing a contrary change of miRNAs between tissues and plasma as well (35,36), suggesting that there may exist a cellular selection mechanism of miRNA intake and release. Thus, we speculate that NPC cells may selectively capture certain miRNAs such as miR-378, resulting an elevated level in tissue. The mir-378 downregulated in tumor tissues showed higher levels in the plasma or serum, thus cancer may selectively secret mir-378 from the cells. Yet the reason why there is such a remarkable difference between extracellular and cellular miRNA expression remains unknown. Clarification of this requires further efforts.

It is well known that a single miRNA can have hundreds of target sites and regulates numerous protein-coding genes, which form a regulatory network (6). To explore the potential target genes of miR-378, three major miRNA databases (miRBase, PicTar and TargetScan) were used to perform bioinformatic prediction. The target genes with the highest context scores were selected and validated in lv-miR-378/5-8F and 5-8F using qRT-PCR. Among the 16 selected target genes, transducer of ERBB2 (TOB2) was top ranked and its mRNA level was the most downregulated one in lv-miR-378/5-8F compared to the control group, whereas, the expression level of TOB2 in tumor specimens was downregulated significantly compared with normal tissues. Additionally, knockdown of miR-378 by transient transfection of miR-378 inhibitor significantly upregulated TOB2 mRNA and protein expression. Therefore, all these results suggested that TOB2 may be a target regulated by miR-378 in NPC.

TOB2 belongs to the anti-proliferative Tob/BTG family proteins (37) which regulate cell cycle progression in a variety of cell types and may have important roles in preventing tumourigenesis and cancer (38,39). It can inhibit cell proliferation through suppressing cell cycle progression from the G0/G1 to S phases (40). Accumulating evidence indicates that TOB2 together with its family members are expressed in various adult tissues and act primarily as transcriptional repressors in several signaling pathways. However, few mechanistic investigations have been conducted on TOB2 function in cancers. Feng et al investigated the interactions between miR-378 and TOB2 and their potential downstream signal pathway in breast cancer. They confirmed that TOB2 was a functional target of miR-378 and its expression was directly inhibited by miR-378. In addition, the candidate tumor suppressor TOB2 achieved its function by transcriptionally repressing the proto-oncogene cyclin D1 (41). As in the present study, overexpression of miR-378 promotes NPC cell proliferation and tumor growth and these may be mediated by downregulation of TOB2. Therefore, we assumed that the function of miR-378 in NPC may be similar to that in breast cancer and TOB2 is probably a direct target gene of miR-378 in NPC. Besides, as our results indicated that miR-378 overexpression could also enhance the migration and invasion ability of NPC cells, it is very possible that miR-378 has multiple target genes and their interactions result in the oncogenic effects in NPC.

In conclusion, this study identified for the first time that miR-378 is upregulated in NPC tissues and cell lines. It can promote cell proliferation, migration, invasion and tumor growth in NPC in vitro and in vivo. The oncogenic effects of miR-378 were probably through downregulation of TOB2. Since miR-378 is overexpressed in NPC, knockdown of this miRNA in tumor tissue may provide us a new therapeutic strategy. Although miRNA-based therapies remain in their infancy, our findings on miR-378 are encouraging and suggest that this specific miRNA may be a potential target for the treatment of NPC.

Acknowledgements

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References

abolishes microRNA miR-378-mediated growth and provides new insights into the mechanisms of microRNA-directed regulation of VEGF and other angiogenic factors under hypoxia.


**YU et al:** miR-378 PROMOTES CELL PROLIFERATION AND INVASION IN NASOPHARYNGEAL CARCINOMA


