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REVIEW

Involvement of Non-Coding RNAs in Chemo- and Radioresistance of Nasopharyngeal Carcinoma

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Abstract: The crucial treatment for nasopharyngeal carcinoma (NPC) is radiation therapy supplemented by chemotherapy. However, long-term radiation therapy can cause some genetic and proteomic changes to produce radiation resistance, leading to tumour recurrence and poor prognosis. Therefore, the search for new markers that can overcome the resistance of tumor cells to drugs and radiotherapy and improve the sensitivity of tumor cells to drugs and radiotherapy is one of the most important goals of pharmacogenomics and cancer research, which is important for predicting treatment response and prognosis. Non-coding RNAs (ncRNAs), such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), may play important roles in regulating chemo- and radiation resistance in nasopharyngeal carcinoma by controlling the cell cycle, proliferation, apoptosis, and DNA damage repair, as well as other signalling pathways. Recent research has suggested that selective modulation of ncRNA activity can improve the response to chemotherapy and radiotherapy, providing an innovative antitumour approach based on ncRNA-related gene therapy. Therefore, ncRNAs can serve as biomarkers for tumour prediction and prognosis, play a role in overcoming drug resistance and radiation resistance in NPC, and can also serve as targets for developing new therapeutic strategies. In this review, we discuss the involvement of ncRNAs in chemotherapy and radiation resistance in NPC. The effects of these molecules on predicting therapeutic cancer are highlighted.

Keywords: miRNAs, lncRNAs, nasopharyngeal carcinoma, chemo- and radioresistance

Introduction

Nasopharyngeal carcinoma (NPC) is an epithelial carcinoma that most commonly affects the inner mucosa of the nasopharynx. It is a common malignant tumour of the head and neck, mostly found in the pharyngeal crypt, with a high incidence in Southeast Asia and Southern China, and the non-keratinized subtype associated with EB virus (EBV) infection constitutes the majority of cases (>95%) in endemic areas.[1] Due to its unique anatomical location and high sensitivity to radiotherapy, the main treatment for patients with early and locally advanced nasopharyngeal carcinoma is radiation therapy.[1,2] Multidrug chemotherapy with platinum is the basic treatment option for patients with recurrent nasopharyngeal carcinoma.[3] One of the main problems in the treatment of patients with nasopharyngeal carcinoma is the resistance of cancer cells to radiotherapy and chemotherapy, which tends to lead to unsatisfactory treatment results, tumour recurrence and poor prognosis.[2,4,5] Hence, the main objective of current clinical research is to implement appropriate strategies through which patients can overcome resistance during chemotherapy or radiotherapy.

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Understanding the molecular mechanisms that lead to treatment resistance and identifying new targets to improve treatment efficiency may help oncologists develop personalized directions for cancer treatment.[6,7] Discovering and validating new predictive and prognostic biomarkers may serve as a vital tool to provide better treatment outcomes and directions for patients requiring specific treatment regimens, providing a better approach for tailoring therapy by providing more appropriate treatment options based on particular patients.[8,9] Epstein-Barr virus (EBV)-encoded products, microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) have been identified in existing research as having common signalling pathways that perform many functions in NPC.[10] Non-coding RNAs, including miRNAs and lncRNAs, have powerful biological functions in cancer. The involvement of ncRNAs in the regulation of tumour proliferation, migration and invasion has been demonstrated in many studies[11–13] and is related to chemotherapy resistance and radiation resistance.[14,15]

In this review, the involvement of miRNAs and lncRNAs in chemotherapy and radiotherapy for nasopharyngeal carcinoma will be described, and a preliminary investigation of the molecular mechanisms that may be involved is conducted.

Non-coding RNAs Involved in Radioresistance of NPC

After radiation treatment of tumour cells, the DNA strand is disrupted, and the cells die, losing the ability to proliferate indefinitely. However, the increase in tumour size, decrease in oxygen and dysregulation of various genes can lead to radiation tolerance of tumour cells, resulting in radioresistance and reduced sensitivity to treatment.[16] In radiation resistance, the gene-related causes mainly include the decrease of apoptotic gene expression, the overexpression of proliferation and antiapoptotic genes, the intensification of expression of genes that mediate DNA damage and repair, or the neglect of the expression of cell cycle regulation genes. The most specific reason for this is the decrease in apoptotic cells after radiation exposure.[17–20] ncRNAs have been shown to be aberrantly expressed in a large number of cancers, suggesting a potential role in cancer pathogenesis. miRNAs and lncRNAs, in particular, play an important role in the regulation of drug resistance in NPC by managing the proliferation cell cycle, DNA damage repair, and apoptosis or other key cellular signalling pathways.[21–24]

MiRNAs Affect the Sensitivity of NPC to Radiotherapy

MicroRNAs (miRNAs), which are approximately 22 nucleotides in length, are small non-coding RNA molecules that play an important role in post-transcriptional regulation and thus influence the development of a variety of diseases. Several studies have shown that miRNAs are dysregulated at the expression level in various cancers and that dysregulated miRNAs in turn affect cell proliferation, cell death inhibition, metastasis and angiogenesis in different cancers, which may be related to multiple mechanisms.[25] Several miRNAs have been shown to regulate radiosensitivity in nasopharyngeal carcinoma.

The experimental results of Zhang et al demonstrated that miR-451 overexpression enhanced the radiosensitivity of NPC cells by a mechanism associated with inhibition of the repair of irradiation-induced double-strand breaks (DSBs) and increased apoptosis. Additionally, low expression of RAB14 restored ionizing radiation (IR)-induced miR-451-mediated DSBs. miR-451 directly targets RAB14 to enhance the radiosensitivity of NPC cells, and thus, miR-451 may be a potential marker of radiosensitization. In addition, miR-451 is downregulated in several tumours, including glioma, lung cancer, oesophageal cancer and breast cancer.[26] Wang et al recognized that miR-206 was expressed at low levels in radiation-resistant NPC cells. Furthermore, restoration of miR-206 in CNE2-IR cells increased the radiosensitivity of NPC cells, and inhibition of miR-206 in CNE2 cells decreased the radiosensitivity. The authors concluded that miR-206 sensitizes NPC cells to irradiation by targeting IGF1.[27] Interestingly, miR-206 expression was reduced in a variety of cancers, including breast and lung cancers, and reversed cisplatin resistance in lung adenocarcinoma cells.[28,29] This suggests that in the search for key therapeutic targets in nasopharyngeal carcinoma, we can gain inspiration from key molecules that have been identified in other cancers.

Tian et al demonstrated that JAMA in NPC can be directly targeted by miR-124; thus, stem cell properties are suppressed, and the radiosensitivity of nasopharyngeal carcinoma is improved.[30] It has been reported that COL1A1 induces radioresistance, and in nasopharyngeal carcinoma,

miR-29a targets COL1A1, cell proliferation capacity is inhibited and apoptosis is enhanced after irradiation, reversing COL1A1 radioresistance to some extent; thus, miR-29a can be used as a biomarker for radiosensitization.[31] In addition, a number of studies have demonstrated that a variety of miRNAs play radiosensitization roles in nasopharyngeal carcinoma (Table 1). However, radiation resistance is promoted by other miRNAs. A study showed that miR-193a-3p directly targets the SRSF2 gene, resulting in increased radioresistance in nasopharyngeal carcinoma.[32]

Huang et al demonstrated that miR-150 expression was upregulated and GSK3β protein expression was downregulated in nasopharyngeal carcinoma CNE-2R cells. miR-150 expression was inhibited, and the radioresistance of CNE-2R cells was reversed, whereas the radioresistance of CNE-2 cells was enhanced after overexpression of miR-150. miR-150b was shown to increase the radioresistance of CNE-2 cells by directly targeting GSK3β to elicit these responses.[33] It has also been shown that miR-182-5p upgrades radioresistance in nasopharyngeal carcinoma by directing the expression of BNIP3.[34] Therefore, miRNAs may be a potential target for reversing radioresistance in NPC cells. Therefore, in future studies on nasopharyngeal carcinoma, we can improve the radiosensitivity and reverse radioresistance of nasopharyngeal carcinoma cells by regulating the expression level of miRNA. miRNAs can be used as biomarkers to provide new ideas for the treatment of nasopharyngeal carcinoma.

Mechanisms of miRNAs in Radiotherapy Resistance in Nasopharyngeal Carcinoma

Previous work has shown that miRNAs can affect tumour radioresistance by interfering with multiple pathways,[35] including sensing DNA damage,[36] repairing DNA double-strand breaks (DSBs),[37] and activating the cell cycle

Table 1 ncRNAs Affect the Radiosensitivity of miRNAs in NPC

ncRNAs	Expression	Targets	Functional Regulation	References
miR-451	↑	RAB14	↑Radio-sensitivity	[26]
miR-206	↑	IGF1	↑Radio-sensitivity	[27]
miR-593	↑	MDR1	↑Radio-sensitivity	[109]
miR-124	↑	PDCD6	↑Radio-sensitivity	[30]
miR- 24	↑	SP1	↑Radio-sensitivity	[110]
miR-124	↑	JAMA	↑Radio-sensitivity	[111]
miR-29-3p	↑	COL1A1 3′-UTR	↑Radio-sensitivity	[31]
miR-24-3p	↑	Jab1/CSN5	↑Radio-sensitivity	[112]
miR-9-5p	↑	HK2	↑Radio-sensitivity	[113]
miR-21	↓	*	↑Radio-sensitivity	[114]
miR-483-5p	↑	DAPK1	↓Radio-sensitivity	[115]
miR- BART8-3p	↑	ATM/ATR	↓Radio-sensitivity	[116]
miR-383-5p	↑	RBM3	↑Radio-sensitivity	[117]
miR-139-5p	↑	EMT	↑Radio-sensitivity	[75]
miR-222	↑	PTEN	↓Radio-sensitivity	[118]
miR-181a	↑	RKIP	↓Radio-sensitivity	[119]
miR-193a-3p	↑	SRSF2	↓Radio-sensitivity	[32]
miR-205	↑	PTEN	↓Radio-sensitivity	[43]
miR-203	↑	IL8/AKT	↑Radio-sensitivity	[120]
miR-182-5p	↑	BNIP3	↓Radio-sensitivity	[34]
miR-372	↑	p53	↑Radio-sensitivity	[121]
miR-23a	↓	IL-8/Stat3	↓Radio-sensitivity	[122]
miR-150	↑	Glycogen synthase kinase-3β	↓Radio-sensitivity	[33]
Lnc ANRIL	↓	miR-125a	↑Radio-sensitivity	[24]
Lnc XIST	↓	miR-29c	↑Radio-sensitivity	[123]
Lnc ANCR	↑	PTEN	↓Radio-sensitivity	[59]
Lnc MINCR	↑	miR-223/ZEB1	↓Radio-sensitivity	[60]
Lnc PTPRG-AS1	↑	miR-194-3p	↓Radio-sensitivity	[124]
Lnc PVT1	↑	*	↓Radio-sensitivity	[61]
Lnc MALAT1	↓	miR-1/slug axis	↑Radio-sensitivity	[125]

Notes: ↑ Up-regulated and ↓ down-regulated ncRNAs in NPC, "*" target not specified.

checkpoint,[38] apoptosis,[39] and autophagy.[40] Apoptosis, regulation of DNA damage repair, and regulation of the cell cycle are briefly described below.

Aberrant expression of apoptosis-associated genes can suppress ionizing radiation-induced apoptosis of tumour cells and increase their survival rate, thus promoting NPC radiation resistance.[16] Bcl-2 is a gene that inhibits apoptosis. At least 19 congeners regulate the mitochondria-dependent pathway of apoptosis and control the release of cytochrome c and other cytokines.[41,42] Huang et al showed that the NF-κB, Wnt and P53 signalling pathways are associated with radioresistance and can also regulate apoptosis and the cell cycle. miR-19b-3p may act through these pathways. The apoptosis and cyclic effects of miR-19b-3p were evaluated by flow cytometry. The authors found that the apoptotic percentages of CNE1 and CNE2 cells decreased significantly after miR-19b-3p overexpression. The apoptotic percentages of CNE1 and CNE2 cells with lower miR-19b-3p expression were significantly higher.[18] In addition, miR-125b, miR-205 and miR-21 reduce radiosensitivity in nasopharyngeal carcinoma by targeting Bcl-2 gene family proteins.[43–45]

ATM encodes a protein involved in the cell cycle and DNA damage repair. This protein belongs to the PI3/PI4 kinase family and is an important cell cycle checkpoint kinase that regulates the tumour suppressor proteins p53 and BRCA1, the checkpoint kinase CHK2, the checkpoint proteins RAD17 and RAD9, the DNA repair protein NBS1, and many other downstream proteins.[23,46] Endogenous ATM is the target of EBV-encoded miRNAs (Bart 5–5P, BART7-3p, BART9-3p and BART14-3p).[22,47] When cells are irradiated with nonlethal doses and single- or double-stranded DNA breaks are repaired, cells can survive without apoptosis. This is one of the causes of radiation resistance. JAB1 (c-Jun activation domain binding protein-1) plays an important role in the repair of DNA double-strand breaks; DNA breaks spontaneously due to its deletion and histone γ-H2AX expression increases in response, so JAB1 maintains genomic stability.[21,48,49]

Cell cycle distribution directly affects the radiosensitivity of nasopharyngeal carcinoma (NPC) cells, and thus miRNAs also mediate radiotherapy resistance in NPC through regulation of the cell cycle. Because cells differ in their sensitivity to radiation at different stages, cell cycle proteins, cell cycle protein-dependent cell kinase (CDK) and CDK kinase inhibitors (CDKIs) comprise the cell cycle regulatory system in the available studies. Previous studies have shown that overexpression of miR-188 inhibits cell proliferation, tumour colony formation and G1/S cell cycle transition in human nasopharyngeal carcinoma CNE cells. E2F transcription is downregulated by inhibiting Rb phosphorylation, thereby inhibiting CDK4 and CDK2 mRNA and protein expression, and thus enhancing the radiosensitivity of nasopharyngeal carcinoma cells.[50] Lu et al showed that miR-26a expression was reduced in nasopharyngeal carcinoma tissues and cells. miR-26a targets the EZH2 oncogene and reduces the expression level of EZH2 to inhibit cell growth and cell cycle progression. miR-26a inhibits the expression levels of C-myc, cell cycle proteins D3 and E2, and cell cycle protein-dependent kinases CDK4 and CDK6 while enhancing the expression of the CDK inhibitors p14ARF and p21CIP1 in an EZH2-dependent manner, thereby inducing cell cycle arrest in the G1 phase and acting as a radiosensitizer.[51] It has also been found that miR-663 promotes the proliferation and cell cycle progression of nasopharyngeal carcinoma cells by directly targeting CDKN2A, suggesting that miR-663 may be a potential therapeutic target for the treatment of nasopharyngeal carcinoma.[52]

LncRNAs Affect the Sensitivity of Radiotherapy for NPC

Long noncoding RNAs (lncRNAs) play a key regulatory role in genomic blotting, gene expression, cellular transfer, etc. They are transcripts longer than 200 nucleotides.[53] There is growing evidence that lncRNAs can promote tumour malignancy in many tumours, including nasopharyngeal carcinoma, in addition to exerting an inhibitory effect on tumour growth and metastasis.[54–57] In addition, some studies have confirmed the role of lncRNAs in radiotherapy of nasopharyngeal carcinoma. The research results of Hu et al proved that after low expression of lncRNA ANRIL negatively regulated the expression of miR-125a, the proliferative capacity of NPC cells was reduced, apoptosis was increased, and the sensitivity of NPC to radiation was elevated.[24] Han et al found that the expression of XIST and miR-29c varied inversely in response to irradiation. Mechanistically, the authors validated the direct binding site of miR-29c on XIST. Rescue experiments further revealed that miR-29c inhibition abolished XIST knockdown-induced cell proliferation suppression and radiosensitivity increase in NPC cells, suggesting that XIST knockdown inhibited proliferation and improved radiosensitivity of NPC cells by upregulating miR-29c.[58] Ma et al

demonstrated that lnc ANCR can mediate the functional regulation of the EZH2 and PTEN promoters, thus inhibiting PTEN expression, promoting the proliferative capacity of NPC cells and inducing radioresistance. Thus, it can be hypothesized that low expression of lnc ANCR in nasopharyngeal carcinoma can inhibit radioresistance and play a sensitizing role.[59] The experiments of Zhong et al illustrate that the lncRNA MINCR acts as a ceRNA for miR-223 to positively regulate ZEB1. After low expression of MINCR, the PI3K/AKT axis associated with autophagy is inactivated, and miR-223 can target ZEB1, resulting in enhanced radiosensitivity of NPC. Therefore, we can provide new targets and new perspectives for the effective treatment of NPC by reducing the expression level of miRNAs that promote radioresistance.[60] He et al proved that PVT1 knockdown in NPC cells decreased ATM/Chk2/p53 activation phosphorylation, weakened DNA repair ability, increased tumour apoptosis, and enhanced radiosensitivity.[61] Therefore, lncRNAs can be used as potential biomarkers and therapeutic targets for nasopharyngeal carcinoma, and we can obtain inspiration from lncRNAs to obtain new ideas for reversing the radiation resistance of nasopharyngeal carcinoma.

Mechanisms of lncRNAs in Radiotherapy Resistance in Nasopharyngeal Carcinoma

In current studies, lncRNAs regulate the radiosensitivity of nasopharyngeal carcinoma mainly by mediating DNA damage, regulating the cell cycle, and targeting miRNAs. The expression of lncRNA-PVT1 was elevated in nasopharyngeal carcinoma patients, and low expression of the PVT1 gene promoted the radiosensitivity of nasopharyngeal carcinoma cells in vitro and in vivo, which may be associated with an increased apoptosis rate after IR. In addition, low expression of the PVT1 gene could decrease the phosphorylation levels of ATM, p53 and CHK2, key mediators of the DNA damage response.[61] This suggests that PVT1 knockdown inhibited the repair ability of DSBs. HIF-1α is a key factor in the response to hypoxic stress, and Wang et al further showed that PVT1 increased the stability of HIF-1α in NPC cells.[62] In addition, lncRNAs can also target cyclins to influence radiosensitivity. Wang et al found that IR-induced and Cur-reversed differentially expressed lncRNA AK294004 negatively regulates cell cycle protein D1 (CCND1), suggesting that lnc AK294004 can directly target CCND1. This study demonstrates that Cur enhances the radiosensitivity of NPC cells and that the function of radiation-resistant lncRNAs is reversed, suggesting an important role of lncRNAs in IR-induced radiation resistance.[63] In addition, lncRNAs can modulate the radiosensitivity of nasopharyngeal carcinoma by targeting miRNAs or Mir-mediated signalling axes. It has been shown that lncRNAs and miRNAs can interact with each other in cancer progression.[64,65] Han et al proved that lnc C00114 contributed to the progression and radioresistance of NPC by activating the ERK/JNK signalling pathway by targeting miR-203. Our study provided a novel theoretical basis for NPC treatment and antagonism to radioresistance.[66] Huang et al proved that lncRNA FAM133B-2 represses the radioresistance of nasopharyngeal cancer cells by targeting the miR-34a-5p/CDK6 axis.[67] Lu et al demonstrated that lnc NEAT1 increased radioresistance and induced an EMT phenotype by eliminating the inhibitory effect of miR-204 on ZEB1.[68] Understanding the mechanism of lncRNA radiation sensitization and reverse radiation resistance in nasopharyngeal carcinoma can provide a new direction for the treatment of nasopharyngeal carcinoma, which can be further explored in future studies.

Non-coding RNAs Involved in Drug Resistance of NPC

Nasopharyngeal carcinoma has a relatively high sensitivity to radiation; therefore, radiation therapy (RT) has been used as the first treatment option in the previous clinical management of NPC. However, NPC is not diagnosed until it has progressed to a locally advanced stage. The outcome and prognosis of radiation therapy alone are poor, with a low five-year survival rate. Therefore, the exploration of chemotherapy (CT) has deepened. Current studies have shown that NPC is sensitive not only to radiation but also to chemotherapy, and the use of various chemotherapeutic agents is gradually gaining ground.[69] Therefore, advanced nasopharyngeal carcinoma is usually treated with a combination of radiotherapy and chemotherapy (CRT). Currently, CT is usually combined with RT in most patients with non-metastatic stage III/IV nasopharyngeal carcinoma. Especially since the publication of the results of the 009919 intergroup study, concurrent chemotherapy-radiotherapy (CRT) and adjuvant CT have been widely accepted as the standard of care for the treatment of patients with stage III and IV NPC. For those with recurrent NPC, the standard of care is multidrug chemotherapy with platinum-based agents. However, chemoresistance is a major obstacle to curing patients with

recurrent NPC. Therefore, it is important to clarify the mechanism of chemoresistance in NPC. Modern considerations have shown that ncRNAs, particularly miRNAs and lncRNAs, may play an imperative role in NPC resistance by mediating efflux, death escape, upgrading DNA repair, EMT, CSC, EBV, exosomes, and apoptosis.[5] In addition, ncRNAs can modulate the function of targets of drug action and regulate genes related to drug metabolism and transport.[70] In addition, inactivation of oncogenic miRNAs promoted the expression of target tumour suppressor genes, while activation of tumour suppressor miRNAs suppressed the expression of oncogenes, which may be related to the recovery of drug sensitivity.[71] Therefore, the selection of specific functional ncRNAs can be used as a new therapeutic option to promote prognosis and improve patient survival, reduce the level of drug resistance in cancer cells, and provide inspiration for finding new therapeutic targets.[72]

MiRNAs Affect the Sensitivity of Chemotherapy for NPC

miR-203 interacts with ZBE2, which binds directly to the miR-203 promoter and antagonizes miR-203, increasing cell migration, invasion, stemness and drug resistance; thus, overexpression of miR-203 can promote chemosensitivity.[73] Overexpression of C-myc activates the EMT program and induces the CSC phenotype, therefore promoting drug sensitivity, while miR-200c can negatively feedback with C-myc and inhibit C-myc function, thus promoting chemoresistance.[74] Moreover, Shao et al showed that overexpression of miR-139-5p reversed the progression of EMT in some nasopharyngeal carcinoma cells and improved the chemosensitivity of HNE1 and HNE1/DDP human nasopharyngeal carcinoma cells.[75] Overexpression of miR-BARTs can potentiate the sensitivity to chemotherapeutic agents in some nasopharyngeal epithelial cells.[76] Yang et al revealed for the first time that viral LMP1 triggers the PI3K/Akt/FOXO3a pathway to induce human miR-21 expression, which subsequently decreases the expression of PDCD4 and Fas-L and results in chemoresistance in NPC cells.[77] Zhang et al proved that miRNA-19b contributes to the sensitivity of nasopharyngeal carcinoma to the chemotherapeutic agent cisplatin by targeting KRAS.[78] In addition, Bcl-2 and Mcl-1 are two apoptosis-related targets, and their high expression represents an enhanced antiapoptotic capacity. High levels of miR-29c can inhibit the expression of Bcl-2 and Mcl-1, thus promoting apoptosis and therefore enhancing the sensitivity of NPC cells to radiotherapy and to the chemotherapeutic drug cisplatin.[79] Moreover, miR-132 could enhance the DPP chemosensitivity of nasopharyngeal carcinoma cells by negatively regulating FOXA1 in vitro and in vivo. These data showed that miR-132 is a potential therapeutic target for NPC.[80] It has been reported that mTOR can be a target of miR-3188, and miR-3188 targeting of mTOR can enhance its own expression level and sensitize NPC cells to 5-FU.[81] In addition, a number of studies have demonstrated that a variety of miRNAs play chemosensitization roles in nasopharyngeal carcinoma (Table 2).

Pathways by Which miRNAs Influence Chemotherapy Resistance in NPC

MiRNAs can mediate chemotherapy resistance in nasopharyngeal carcinoma by interacting with EMT-inducing transcription factors. There are many factors associated with tumour chemoresistance, and EMT and tumour stemness signalling are among the most important factors involved.[82–84] In recent studies, miR-203 has been found to be involved in the pathogenesis of a large number of tumours, including nasopharyngeal carcinoma, and plays an inhibitory role in tumours. Jiang et al[73] confirmed that ZEB2 could induce EMT and tumour stemness, and miR-203 inhibited tumour cell progression and improved sensitivity to cisplatin by targeting ZEB2.[85,86] miR-200 has also been reported to regulate the expression of ZEB1 and ZEB2 to suppress the EMT program.[87] The miR-200 family can be regulated by the p53 gene, thereby suppressing EMT and CSC phenotypes.[88,89] miR-200c formed a negative feedback pathway with C-myc, and low expression of C-myc or increased expression of miR-200c promoted chemoresistance.[74] miR-139-5p targets ZEB1 and thereby regulates EMT, inhibits nasopharyngeal carcinoma cell progression, and promotes chemosensitivity to cisplatin.[75,90]

In addition, miRNAs may influence chemotherapeutic sensitivity by regulating cell cycle progression. KRAS can act as a link between upstream and downstream signals and as a transmitter to relay extracellular signals to the nucleus.[91] MiR-19b enhances the sensitivity of nasopharyngeal carcinoma cells to the chemotherapeutic agent cisplatin by targeting KRAS, which is involved in cell cycle regulation.[78] Zhao et al showed that mTOR, PI3K and AKT are associated with autophagy and are also cell cycle factors. mTOR can inhibit the PI3K/AKT signalling pathway, thereby inhibiting the downstream cell cycle factors c-JUN and p-mTOR. miR-3188 inhibits cell cycle

Table 2 ncRNAs Involved in Resistance to Chemotherapy

miRNA	Expression	Drugs	Targets	Functional Regulation	References
miR-203	↑	Cisplatin	ZEB2	↑Chemo-sensitivity	[73]
miR-200c	↑	Cisplatin	c-Myc	↓Chemo-sensitivity	[74]
miR-BARTs	↑	Cisplatin, doxorubicin	BRCA1	↑Chemo-sensitivity	[76]
miR-21	↑	Cisplatin	PDCD4, Fas-L	↓Chemo-sensitivity	[77]
miRNA-19b	↑	Cisplatin	KRAS	↑Chemo-sensitivity	[78]
miRNA-29c	↑	Cisplatin	Mcl-1, Bcl-2	↑Chemo-sensitivity	[79]
miR-139-5p	↑	Cisplatin	EMT	↑Chemo-sensitivity	[75]
miRNA-132	↑	Cisplatin	FOXA1	↑Chemo-sensitivity	[80]
miR-34c	↓	Cisplatin	SOX4	↓Chemo-sensitivity	[126]
miR-96-5p	↑	Cisplatin	CDK1	↑Chemo-sensitivity	[127]
miR-183	↑	Cisplatin	MTA1	↑Chemo-sensitivity	[128]
miR-634	↑	Paclitaxel	*	↑Chemo-sensitivity	[129]
miR-1204	↑	Paclitaxel	*	↑Chemo-sensitivity	[130]
miR-1278	↑	Cisplatin	ATG2B	↑Chemo-sensitivity	[131]
miR-29c	↑	Paclitaxel	ITGB1	↑Chemo-sensitivity	[132]
miR-29a	↑	Paclitaxel	STAT3, Bcl-2	↑Chemo-sensitivity	[133]
miR-3188	↑	5-FU	mTOR	↑Chemo-sensitivity	[134]
Lnc CCAT1	↑	Paclitaxel	miR181a/CPEB2	↑Chemo-sensitivity	[105]
Lnc KCNQ1OT1	↑	Cisplatin	miR-454/USP47 axis	↓Chemo-sensitivity	[100]
Lnc SLC25A21-AS1	↑	Multidrug	miR-324-3p/IL-6 Axis	↓Chemo-sensitivity	[101]
Lnc TINCR	↑	Cisplatin	acetyl-CoA	↓Chemo-sensitivity	[135]
Lnc DLEU1	↑	Cisplatin	BIRC6	↓Chemo-sensitivity	[95]
Lnc HOXA11-AS	↓	Cisplatin	miR-454-3p/c-Met	↑Chemo-sensitivity	[96]
Lnc C00346	↑	Cisplatin	miR-342-5p	↓Chemo-sensitivity	[102]
Lnc MIAT	↑	Cisplatin	HMGB1	↓Chemo-sensitivity	[98]
Lnc NEAT1	↓	Cisplatin	Let-7a-5p	↑Chemo-sensitivity	[99]

Notes: ↑ Up-regulated and ↓ down-regulated ncRNAs in NPC, "*" target not specified.

signalling by targeting mTOR, PI3K/AKT and c-JUN, thereby enhancing the sensitivity of nasopharyngeal carcinoma to the chemotherapeutic agent 5-FU.[81]

The pathway by which miRNAs mediate chemotherapy sensitivity in nasopharyngeal carcinoma is also associated with apoptosis. Zhang et al showed that Bcl-2 and Mcl-1 are important antiapoptotic genes, and the authors found that their expression levels were negatively correlated with those of miR-29c. Loss of miR-29c function may lead to increased expression of NPC Bcl-2 and Mcl-1, and overexpression of miR-29c after cisplatin induction could promote nasopharyngeal carcinoma cell apoptosis and enhance the sensitivity of nasopharyngeal carcinoma to the chemotherapeutic drug cisplatin.[79]

LncRNAs Affect the Chemosensitivity of NPC

Increasing evidence has indicated that abnormal lncRNAs might lead to drug resistance in various types of cancer,[92–94] including NPC.[95,96] Paclitaxel is a classic chemotherapeutic agent in cancer chemotherapy, but with prolonged use and increased dosing, patients develop varying degrees of resistance to the drug. Cell growth assays showed that NPC 5–8F cells are highly tumorigenic and metastatic, 6–10B is a low tumorigenic and minimally metastatic cell line, and low expression of lncRNA n375709 can promote the sensitivity of nasopharyngeal carcinoma cells to the chemotherapeutic drug paclitaxel.[97] Zhu et al proved that the expression levels of lncRNA MIAT and HMGB1 were elevated in drug-resistant NPC cells, and IL6 could activate the JAK2/STAT3 signalling pathway, thus making the tumour resistant. HMGB1 could target IL6 and increase the expression level of IL6, thus promoting chemoresistance of the tumour, and lncRNA MIAT could positively regulate, thus forming the lncRNA MIAT/HMGB1/JAK2/STAT3 signalling axis, which plays a role in chemoresistance of tumours. Therefore, lncRNA MIAT can be used as a target, and inhibition of lncRNA MIAT expression can reverse chemoresistance in nasopharyngeal carcinoma to some extent.[98] The authors found that lnc NEAT1 interacted with let-7a-5p, and the two were negatively correlated. Let-7a-5p inhibited chemoresistance and improved

chemosensitivity in nasopharyngeal carcinoma. Overexpression of NEAT1 regulates Rsf-1 expression and the Ras-MAPK pathway by inhibiting let-7a-5p, thereby rendering nasopharyngeal carcinoma cells resistant to the chemotherapeutic agent cisplatin.[99] Existing research results indicated that KcNQ1OT1 enhanced DDP resistance in NPC cells via the miR-454/USP47 axis, suggesting a potential therapeutic target for patients with DDP-resistant NPC.[100] Wang et al demonstrated elevated expression levels of lncRNA SLC25A21-AS1 in NPC tissues and cells. In addition, high expression of SLC25A21-AS1 could target miR-324-3p and thus mediate IL-6, resulting in enhanced proliferation and multidrug resistance in NPC cells.[101] It has been reported that lnc C00346 targets miR-342-5p and reduces the sensitivity of nasopharyngeal carcinoma cells to cisplatin.[102] In addition, a variety of lncRNAs may be involved in the regulation of chemotherapy sensitivity in nasopharyngeal carcinoma (Table 2).

The existence of multiple lncRNAs that can inhibit or enhance sensitivity to radiotherapy and chemotherapy in nasopharyngeal carcinoma can serve as inspiration for the direction of treatment for drug-resistant patients. In future studies, we can find a breakthrough in reversing drug resistance by suppressing lncRNAs that are highly expressed in cells that develop drug resistance or upregulating lncRNAs that are expressed at low levels in drug-sensitive cell lines to achieve the desired therapeutic effect and patient survival.[103] This study provides a new idea and a new direction for reversing chemotherapy resistance in nasopharyngeal carcinoma.

Pathways by Which lncRNAs Regulate Chemotherapy Resistance in NPC

After a long period of research and exploration, the following mechanisms can be identified for lncRNAs to regulate drug resistance in tumours: directly targeting miRNAs or interacting with miRNAs, mediating signalling pathways and regulating protein function, inhibiting or enhancing apoptosis, and regulating autophagy.[104] In nasopharyngeal carcinoma, lncRNAs mainly exert their influence by regulating miRNAs and targeting signalling pathways and apoptosis-related proteins, among which various regulatory pathways also interact with each other.

LncRNAs can target miRNA-related signalling axes or interact with miRNAs to regulate chemotherapy sensitivity in nasopharyngeal carcinoma. Yuan et al suggested that lncRNA KcNQ1OT1 facilitated cell viability and DDP resistance in NPC cells by regulating the miR-454/USP47 axis. Therefore, KcNQ1OT1 might serve as a potential target for overcoming DDP resistance in NPC chemotherapy.[100] Wang et al showed that miR-181a could enhance the sensitivity of nasopharyngeal carcinoma cells to paclitaxel by promoting apoptosis, while in nasopharyngeal carcinoma, lncCCAT1 could directly bind to miR-181a, thus inhibiting the biological function of miR-181a and making nasopharyngeal carcinoma cells less sensitive to paclitaxel.[105] In addition, lnc SLC25A21-AS1 regulates IL-6 by targeting miR-324-3p, making nasopharyngeal carcinoma resistant to multiple chemotherapeutic agents.[101] Li et al revealed that lnc DLEU1 inhibits miR-381-3p, resulting in increased expression of BIRC6 and increased resistance of nasopharyngeal carcinoma to the chemotherapeutic agent cisplatin.[95] Lin et al demonstrated that silencing lncRNA HOXA11-AS can inhibit the c-Met/AKT/mTOR pathway by specifically upregulating miR-454-3p, thus promoting cell apoptosis and enhancing the sensitivity of cisplatin-resistant NPC cells to cisplatin.[96] Long noncoding RNA LINC00346 contributes to cisplatin resistance in nasopharyngeal carcinoma by repressing miR-342-5p.[102]

In addition, lncRNAs can also influence drug resistance in nasopharyngeal carcinoma by mediating signalling pathways. Zhu et al proved that lncRNAs MIAT and HMGB1 are upregulated in cisplatin-resistant nasopharyngeal carcinoma cells, are biological targets that promote cisplatin resistance, and can initiate the JAK2/STAT3 pathway by promoting the expression level of self-IL6, further increasing cisplatin resistance in nasopharyngeal carcinoma cells.[98] Moreover, Ras-MAPK is an important intracellular signalling pathway that regulates apoptosis, the cell cycle and many other cellular processes. Low expression of NEAT1 inhibited the expression level of let-7a-5p, which reduced the activity of the Ras-MAPK signalling pathway and increased the sensitivity of NPC cells to cisplatin.[99]

In tumours, proapoptotic and antiapoptotic proteins regulate each other to stabilize the intratumour environment, with Bcl-2 being the classical antiapoptotic protein. The apoptotic ability of cells is a key factor in assessing the effect of tumour chemotherapy, and chemotherapeutic drugs can mediate apoptosis-related proteins and promote apoptosis to achieve a desirable chemotherapeutic effect.[106] Thus, low expression of the antiapoptotic protein Bcl-2 can promote tumour sensitivity to chemotherapeutic agents.[107] Xue et al found that low expression of lncRNA-ROR can promote apoptosis in NPC cells, indicating that

we can use inhibitors of lncRNA-ROR to promote apoptosis and restore the sensitivity of nasopharyngeal carcinoma to chemotherapy.[108]

Conclusions and Future Perspectives

The World Health Organization classifies nasopharyngeal carcinoma into three pathological subtypes: keratinizing squamous carcinoma, non-keratinizing squamous carcinoma, and basal-like squamous carcinoma. Non-keratinizing nasopharyngeal carcinoma can be divided into differentiated and undifferentiated tumours, and the non-keratinizing subtype associated with EB virus (EBV) infection constitutes the majority of cases (>95%) in endemic areas. Therefore, this type deserves our focused attention. In this article, the effects and mechanisms of miRNAs and lncRNAs in the resistance to radiotherapy and chemotherapy in nasopharyngeal carcinoma are summarized and analyzed. miRNAs can affect tumour radioresistance by interfering with multiple pathways. In addition, a large number of studies have shown that miRNAs can affect chemotherapy resistance in nasopharyngeal carcinoma by regulating apoptosis, cell cycle and EMT-related signalling. We speculate that the same regulatory pathway may exist between radiotherapy resistance and chemotherapy resistance in nasopharyngeal carcinoma, or that there may be miRNAs that can affect both radiotherapy and chemotherapy in nasopharyngeal carcinoma: this remains to be investigated. Interestingly, miR-206 and miR-451 and multiple miRNAs were found to be downregulated in a variety of cancers other than nasopharyngeal carcinoma. This suggests that we can be inspired by key molecules already identified in other cancers to find key therapeutic targets for nasopharyngeal carcinoma. In current studies, lncRNAs regulate the radiosensitivity of nasopharyngeal carcinoma mainly by mediating DNA damage, regulating the cell cycle, and targeting miRNAs. LncRNAs mainly play a role in regulating the effects of chemotherapy resistance in nasopharyngeal carcinoma by regulating miRNAs, targeting signalling pathways and apoptosis-related proteins, in which various regulatory pathways also interact with each other. This suggests that lncRNAs can interact with miRNAs through multiple pathways and molecules, and that there may be common regulatory pathways.

LncRNAs and miRNAs contained in ncRNAs have powerful biological functions. In nasopharyngeal carcinoma cells resistant to radiotherapy, elevated expression levels of some lncRNAs and miRNAs can be found, and interestingly, most of these lncRNAs and miRNAs are silently expressed in cells sensitive to radiotherapy. We can speculate that inhibiting their expression in resistant cells or upregulating lncRNAs and miRNAs with functions related to promoting apoptosis and inhibiting proliferation and metastasis can reverse the radiation resistance. Most of the current data on ncRNAs related to chemoresistance and radioresistance in nasopharyngeal carcinoma focus on miRNAs and lncRNAs, which indicates that miRNAs and lncRNAs have been studied in some contexts, but that circRNAs, which are included among ncRNAs, have not been fully studied in nasopharyngeal carcinoma at present because of their numerous types and complex functions. circRNAs can act as ceRNAs for miRNAs and disrupt the inhibitory effects of miRNAs on target genes, thus exerting their anticancer or cancer-promoting effects. There are fewer studies on circRNAs affecting tumour progression through other pathways and molecular mechanisms, which is a possible breakthrough point for future treatment and prognosis improvement in nasopharyngeal carcinoma, thus developing individualized treatment for nasopharyngeal carcinoma patients and benefiting more patients. Current research data demonstrate that miRNAs and lncRNAs are useful biomarkers for predicting treatment outcomes or monitoring treatment response, but most studies are still in the preclinical stage and have not been clinically tested. In addition, only a small fraction of ncRNAs are stably present in body fluids, so future studies could use non-invasive liquid biopsy methods. It is noteworthy that some studies assessing the potential of ncRNAs as biomarkers in different cancers have yielded conflicting results. More clinical data should be mined to reconcile these controversies.

It is hoped that in the near future, specific ncRNA signalling may provide new insights into the mechanisms of chemotherapy and radiation resistance that may arise in nasopharyngeal carcinoma patients before starting treatment, while the regulation of specific ncRNA expression may provide new tools for overcoming acquired resistance. In conclusion, the identification of candidate non-coding RNAs that regulate drug resistance in nasopharyngeal carcinoma and the study of their molecular mechanisms can help aid the design of new and targeted non-coding RNA-based therapeutic strategies and provide new ideas for improving clinical outcomes in patients with nasopharyngeal carcinoma. miRNAs and lncRNAs are considered to have considerable clinical value in oncology, and their potential clinical application is of great significance.

Disclosure

The authors report no conflicts of interest in this work.

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