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Long non-coding RNAs in nasopharyngeal carcinoma: biological functions and clinical applications

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Abstract

Nasopharyngeal carcinoma (NPC) is one of the most common head and neck malignancies. It has obvious ethnic and regional specificity. Long non-coding RNAs (LncRNAs) are a class of non-protein coding RNA molecules. Emerging research shows that lncRNAs play a key role in tumor development, prognosis, and treatment. With the deepening of sequence analysis, a large number of functional LncRNAs have been found in NPC, which interact with coding genes, miRNAs, and proteins to form a complex regulatory network. However, the specific role and mechanism of abnormally expressed lncRNAs in the pathogenesis of NPC is not fully understood. This article briefly introduced the concept, classification, and functional mechanism of lncRNAs and reviewed their biological functions and their clinical applications in NPC. Specifically, we described lncRNAs related to the occurrence, growth, invasion, metastasis, angiogenesis, and cancer stem cells of NPC; discussed lncRNAs related to Epstein-Barr virus infection; and summarized the role of lncRNAs in NPC treatment resistance. We have also sorted out lncRNAs related to Chinese medicine treatment. We believe that with the deepening of lncRNAs research, tumor-specific lncRNAs may become a new target for the treatment and a biomarker for predicting prognosis.

Keywords Long non-coding RNAs (lncRNAs) · Nasopharyngeal carcinoma (NPC) · Biological functions · Clinical applications

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor of the head and neck, which originates from the epithelium of nasopharyngeal mucosa, and its distribution is obviously regional and ethnic [1]. NPC is mainly concentrated in Southeast Asia and southern China. The pathogenesis of NPC is closely related to environmental factors, EBV infection, genetic susceptibility, and other factors. The latest data show that there are 129,079 new cases of NPC and 72,987 deaths worldwide. The incidence rate of males is much higher than that of females [2]. At present, the morbidity and mortality of nasopharyngeal carcinoma in my country is relatively high, and it is highly invasive, prone to early metastasis, and has a poor prognosis. The population is mainly middle-aged and elderly. As the population ages, the burden of nasopharyngeal cancer may further increase.

LncRNA (Long non-coding RNA) is a non-coding RNA with a length of more than 200 bp. LncRNA was initially regarded as the "noise" of genomic transcription, which is a by-product of RNA polymerase II transcription and has no biological function. However, recent studies have shown that lncRNA can regulate gene expression at many levels, including epigenetic regulation, transcriptional regulation, post-transcriptional regulation, and regulation of MiRNA [3]. The specific mechanism is very complex and remains to be clarified. According to the position of relative protein-coding genes in the genome, lncRNA can be divided into five categories, named Antisense lncRNA, Sense lncRNA, Intronic transcript, Long intergenic non-coding RNA (lincRNA), and Bidirectional lncRNA [4] (Fig. 1a). The cellular localization of different lncRNA is different. Nuclear lncRNA accounts for the majority of lncRNA, which plays a regulatory role by recruiting chromatin regulatory factors to DNA, or as scaffolding for some ribonucleoprotein. Cytoplasmic lncRNA acts on the level of post-transcriptional regulation of genes, such as MiRNA sponge, which inhibits the effect of miRNA

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on mRNA [5]. In a classic review, Kevin C. Wang et al. distill the myriad functions of lncRNAs into four archetypes of molecular mechanisms, as signals, decoys, guides, and scaffolds [3, 5] (Fig. 1b). LncRNA is widely involved in a variety of biological processes, and the abnormal expression of LncRNA is closely related to a variety of diseases, including cancer.

At present, a large number of studies have confirmed that lncRNA is widely involved in the carcinogenesis, migration and invasion, epithelial-mesenchymal transformation, angiogenesis, and other malignant phenotypes of NPC and mediates radiotherapy resistance and chemotherapy resistance through a variety of pathways, which is an important biomarker for the diagnosis and prognosis of NPC.

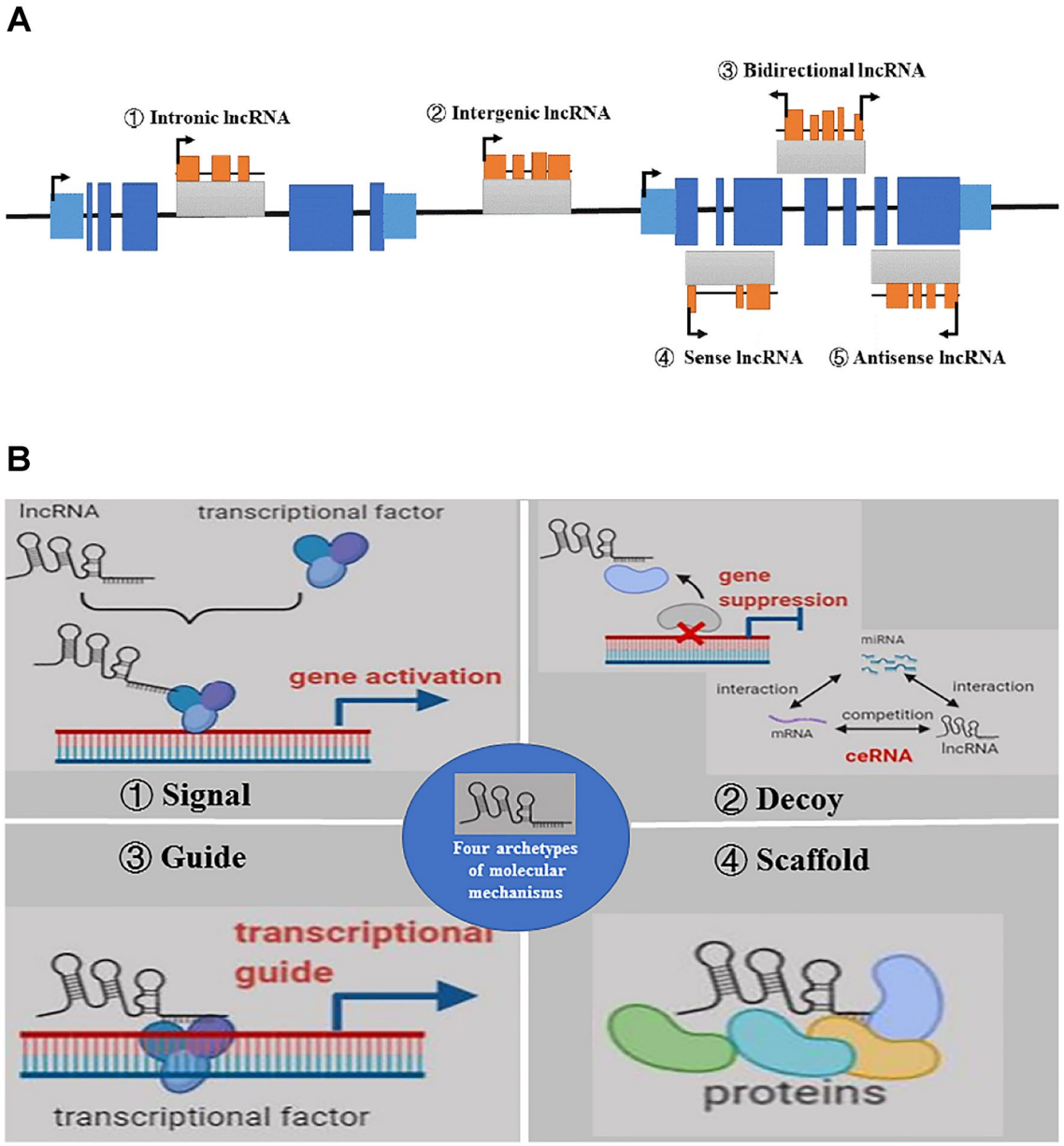

Fig. 1 **a** According to the position of relative protein-coding genes in the genome, lncRNA can be divided into five categories. ①. Intronic lncRNAs: transcribed from introns of protein-coding genes; ②. Intergenic region: transcribed from the intergenic region within two genes; ③. Bidirectional lncRNA: transcribed from different directions and initiated by adjacent coding transcripts on the opposite strand; ④and⑤. Sense or antisense lncRNA: transcribed from the sense or antisense strand of the protein-coding gene and the overlapping exons of the protein-coding gene; **b** The lncRNA mechanisms of action can be divided into four categories: signal, decoy, guide, and scaffold

Biological function of lncRNA in nasopharyngeal carcinoma

Oncogenic lncRNAs

A large number of lncRNA have been reported to be up-regulated in NPC, which are likely to be involved in carcinogenesis, development, proliferation and migration, and other malignant biological phenotypes through different mechanisms as oncogenes. For example, the lncRNA differentiation antagonizing non-protein coding RNA (DANCR) has been reported to play a carcinogenic role in a variety of malignant tumors, including breast cancer [6], hepatocellular carcinoma [7], and osteosarcoma [8, 9]. With more and more in-depth research, the role of DANCR as a metastasis-specific oncogenic lncRNA in NPC has gradually been revealed. Here, we try to briefly summarize the biological functions and molecular mechanisms of carcinogenic lncRNA in NPC (Table 1).

Tumor suppressor lncRNAs

With the further study of lncRNA in tumor, some "beneficial" lncRNA have been widely reported. As tumor suppressors, they can inhibit tumor occurrence, development, migration, and invasion in vivo or in vitro. Maternal expression gene 3 (MEG3) is the first lncRNA [10], with tumor suppressor function [11]. Its low expression can cause head and neck squamous cell carcinoma, breast cancer, and pancreatic ductal adenocarcinoma [12–14]. MEG3 was also identified as a low-expression tumor suppressor lncRNA in nasopharyngeal carcinoma (NPC) [15]. However, the understanding of tumor suppressor lncRNA still has a long way to go. The biological functions and mechanisms of known tumor suppressor lncRNA are summarized below (Table2).

Clinical application of lncRNA in NPC

Through the study of nasopharyngeal carcinoma-related lncRNA, it is not difficult to find that lncRNAs, as an oncogene or suppressor, play an important role in regulating the progression, metastasis, and invasion of NPC. The abnormal expression of LncRNA is closely related to the occurrence, development, and prognosis of NPC. Some of them can be used as effective diagnostic and prognostic markers of human tumors, and some lncRNA are involved in the treatment and resistance of NPC. The study of lncRNA provides a new idea for studying the pathogenesis of tumor and exploring new methods of diagnosis and treatment.

Long non-coding RNAs and Epstein-Barr virus infection in NPC

Epstein-Barr virus infection is a recognized risk factor for NPC. The establishment of EBV latent infection in the epithelium of nasopharyngeal precancerous lesions is considered to be an early and necessary step in the pathogenesis of NPC [16]. The EB virus has three latent infection types, and the NPC cells are expressed as the II latency, and the viral protein associated with NPC is transcribed by viral RNA to the right transfer (BARTS) encoding. This transcription also encodes viruses microRNA and lncRNA [17]. These viral products (EBV-related RNA EBER1 and EBER2) can change the host cell signal, establish a tumor microenvironment and promote the occurrence and development of tumors. BART RNA is usually highly expressed in EBV infection epithelial tumors. The products of these BART RNAs may be miRNAs or lncRNAs [18]. EBV is also the first virus to be discovered that encodes microRNAs [19]. Previous studies have also focused on the regulation of MiRNA's involvement in the occurrence and development of NPC [20]. At present, there is evidence that lncRNA plays an important role in the occurrence, development, and progression of epithelial tumors associated with EBV infection [21–23]. Based on whole-genome RNA sequencing, some researchers have tested the lncRNA expression profiles in four EBV genome-infected 293 cell lines and EBV-negative 293 cells. In the comparative analysis, a series of lncRNAs expression disorders were found [24]. The interaction between EBV and lncRNA has two main aspects: on the one hand, EBV regulates the expression of host lncRNAs, on the other hand, EBV itself encodes lncRNAs that have an impact on host cell-related proteins and signal pathways [25].

EBV-encoded lncRNA

A 2015 study showed that a subset of the changes in gene expression induced by latent EBV infection in AGS cells is due to the expression of the BART nuclear RNAs and suggests that the spliced BART transcripts function as lncRNAs and from this point onward, they are referred to as the BART lncRNA [26]. In NPC, EBV hardly expresses viral proteins, but Bam-HI A right transcript (BARTS) RNA levels are elevated, including viral microRNAs and LncRNAs. BART lncRNAs are located in the nucleus of EBV-infected cells [27]. The knockdown of BART lncRNAs significantly affects the expression of genes related to cell adhesion, oxidoreductase activity, inflammation, and immunity. Bart lncRNAs also participate in the epigenetic regulation of host gene expression in nasopharyngeal carcinoma by interfering with histone methylation and acetylation processes [28]. A study showed that the expression of BARTs is regulated by NF-κB signaling. EBV LMP1

Table 1 Summary of tumorigenic lncRNA known to modulate nasopharyngeal carcinoma

LncRNA	Expression	Targets	Biological functions	Refs
DANCR	Up	HIF-1α mRNA; SOX2 mRNA; PTEN	Promotes NPC cells proliferation and migration	[90–93]
XIST	Up	miR-491-5p; Notch3; miRNA-148a-3p / ADAM17	Promotes hypoxia-induced glycolysis, migration and invasion, and tumor growth in vivo	[94–97]
ZFAS1	Up	miR-135a; miR-892b; PI3K/AKT signaling pathway	Promotes cell proliferation, tumorigenesis, and metastasis	[98–101]
H19	Up	EZH2 / miR-630; miR-675-5p/SFN; let-7	Promotes cell invasion, proliferation, and metastasis	[102–104]
HOTAIR	Up	miR-101/COX-2 axis; VEGFA	Promotes invasion and migration; mediated angiogenesis	[105–107]
SNHG7	Up	miR-140-5p; miR-514a-5p	Promotes proliferation and migration and inhibits apoptosis	[108, 109]
NEAT1	Up	miR-124/NF-κB pathway; miR-34a-5p/ Wnt/β-catenin signaling	Promotes cell proliferation, migration, invasion, and EMT; inhibits apoptosis	[110, 111]
MALAT1	Up	miR-124/Capn4	Promotes cell proliferation, migration, and invasion	[112]
SMAD5-AS1	Up	miR-106a-5p; miR-195	Promotes EMT, cell proliferation, migration, and invasion	[113, 114]
SRRM2-AS	Up	MYLK/cGMP-PKG signaling pathway	Mediated angiogenesis	[115]
FOXD3-AS1	Up	miR-185-3p;	Regulates NPC cell stemness invasion, viability, and migration potentials and apoptosis	[116, 117]
AFAP1-AS1	Up	KAT2B/H3K14ac/TIF1a/RBM3/YAP signaling pathway; miR-423-5p	Promotes proliferation and colony formation in vitro and tumorigenicity in vivo	[118, 119]
Gas5	Up	GAS5/ miR-4465/COX2 axis	Regulates proliferation and promotes apoptosis	[120]
RP11-624L4.1	Up	CDK4/6-CyclinD1-Rb-E2F1 Pathway	Induces tumor proliferation and cycle	[121]
LOC284454	Up	Rho/Rac signaling pathways	Promotes the migration and invasion capacity	[122]
LINC01503	Up	FOSL1	Promotes NPC cells growth, migration, and invasion	[123]
MSC-AS1	Up	miR-524-5p /NR4A2 axis	Promotes cell invasion and EMT process	[124]
AATBC	Up	miR-1237-3p–PNN–ZEB1 axis	Promotes migration, invasion, and metastasis	[125]
DRAIC	Up	microRNA-122/ SATB1 axis	Promotes migration and invasion	[126]
LINC00460	Up	miR-149-5p/ IL6 axis miR-30a-3p/ RAP1A axis	Promotes migration, EMT, invasion, and metastasis	[127, 128]
FAM225A	Up	miR-590-3p/miR-1275 / ITGB3, and activate FAK/PI3K/Akt pathway	Promotes proliferation and metastasis	[129]
HOXC13-AS	Up	miR-383-3p/ HMGA2 axis	Regulates proliferation, migration, and invasion	[130]
SOX2-OT	Up	miR-146b-5p/HNRNPA2B1 pathway	Regulates cell proliferation, cell cycle, and metastasis	[131]
SNHG1	Up	miR-145-5p / NUAK1 axis	Promotes migration, EMT, and invasion	[132]
ANRIL	Up	mTOR signal	Induces the stem cell-like cells; promotes proliferation, colony formation, and transformation ability and reprograms the glucose metabolism	[133]
SWSAT1	Up	miR-326/330-5p / cyclin D1 axis	Promotes viability and growth	[134]

is an effective activator of NF-κB signal. LMP1 can up-regulate the expression of BARTs through NF-κB signal, but miR-BARTs can also down-regulate the expression of LMP1. The authors speculate that abnormal NF-κB signaling and BART expression form an auto-regulatory loop to maintain the EBV latency in NPC cells [29].

Some lncRNAs encoded by EBV, such as BHLF1 and BHF3, can be used as a functional lncRNA to participate in the regulation of the life cycle of EBV [30]. But their role in nasopharyngeal carcinoma remains to be revealed.

EBV regulates the expression of host lncRNAs

The long intergenic non-coding RNA LINC00312, also called NAG7, was found that it could not only inhibit proliferation and induce apoptosis in NPC cells but also stimulate

Table 2 Summary of tumor suppressor lncRNAs known to modulate nasopharyngeal carcinoma

LncRNA	Expression	Targets	Biological functions	Refs
ZNF667-AS1	Down	miR-1290/ ABLIM1 axis	Inhibits the proliferation, migration and invasion abilities, and tumor growth; promotes apoptosis	[135]
NKILA	Down	NF-κB pathway	Inhibits tumorigenesis and metastasis	[136]
LET	Down	MAPK/ERK signaling pathway	Inhibited invasion and proliferation and induced cell apoptosis;	[137, 138]
LINC0086	Down	miR-214	Inhibited proliferation and promoted apoptosis	[139]
MEG3	Down	p53 Pathway	Suppresses cell proliferation and tumorigenicity	[15]
LOC401317	Up	Unknown	Inhibits cell growth and induces apoptosis	[140]

NPC cell invasion [31, 32]. The non-coding ribonucleic acid EBER-1 transcribed by the EBV is abundantly expressed in various cells latently infected with EBV and plays an important role in EBV-mediated tumorigenesis [33]. In a study, the authors analyzed the relationship between LINC00312 and EBER-1 abnormal expression and found that LINC00312 and EBER-1 in nasopharyngeal carcinoma were significantly negatively correlated, suggesting that EBER-1 may regulate the expression of LINC00312 through certain genes and signal pathways [34]. But its exact mechanism needs further study.

EBV can also exert oncogenic or tumor suppressor properties and participate in cancer progression by targeting host genes or its own viral genes by encoding microRNA. A study found that EBV-encoded microRNA, called EBV-miR-BART6-3p, inhibited the migration and invasion of nasopharyngeal carcinoma cells by reversing the epithelial-mesenchymal transition (EMT) process. Through gene chip analysis, the authors found that EBV-miR-BART6-3p down-regulated the expression of a new long non-coding RNA (LncRNA) LOC553103. EBV-miR-BART6-3p inhibits the migration and invasion of NPC cells by down-regulating LncRNA LOC553103 [35]. Subsequently, the team further confirmed through proteomics analysis and luciferase report that Stathmin (STMN1) is affected by EBV-miR-BART6-3p and LOC553103, and that LOC553103 directly binds and stabilizes the 3'UTR region of STMN1 mRNA. STMN1 is an important tubulin, which can inhibit the stability of microtubules, thereby promoting tumor cell proliferation, invasion, and metastasis [36]. These results indicate that the EBV-miR-BART6-3p/LOC553103/STMN1 axis regulates the expression of cell cycle-related proteins, thereby inhibiting the proliferation of EBV-related tumor cells [37].

Long non-coding RNAs and radio-resistance in NPC

The pathological classification of NPC is mainly poorly differentiated squamous cell carcinoma, which accounts for more than 80% of all NPC cases [38]. Studies have shown that poorly differentiated squamous cell carcinoma is extremely sensitive to radiation, and NPC occurs in hidden parts such as the pharyngeal recess and the anterior parietal wall, making it difficult to perform surgery [39, 40]. This determines that the current main treatment for NPC is radiation therapy, supplemented by chemotherapy when necessary [41]. Radiotherapy for early NPC is effective, while radiotherapy for middle and late NPC is less effective, and long-term radiotherapy will lead to changes in certain genes and proteomics, resulting in radiotherapy resistance [42]. Radiation resistance is the main obstacle to radiotherapy, which can lead to relapse and poor prognosis. Therefore, understanding the radio-resistance mechanism and developing new radio-sensitization strategies are of great significance for the treatment of NPC.

Recent research has shown that abnormal expression of lncRNAs in malignant tumor cells before and after radiotherapy may participate in the progression of cancers and affect the radiation sensitivity of malignant tumor cells mediated by specific signaling pathways or cell cycle regulation [43–45]. Similarly, in nasopharyngeal carcinoma, there are many lncRNAs involved in the regulation of radiosensitivity. On the one hand, some lncRNA can induce radiation resistance of nasopharyngeal carcinoma by adsorption with a specific miRNA through sponge. For example, the tumor suppressor FAM133B-2 is highly expressed in radioresistant NPC cells and can target the miR-34a-5p/CDK6 axis to inhibit radiotherapy resistance [46]. There are also many lncRNAs such as ZFAS1 and PVT [47–49] which can also be used to play anti-radiation through ceRNA networks. On the other hand, lncRNA can also modulate the radiation resistance by directly acting in certain cell's signal pathways or key molecules. For example, in one of the latest studies, researchers screened the lncRNA CASC19 as a candidate radiation resistance marker using RNA-SEQ analysis of NPC cell line CNE2 and its radiation resistance cell line CNE2R. The mechanism study found that CASC19 has an important contribution to the radio-resistance of NPC cells by AMPK / mTOR pathway [50]. Evidence that lncRNA inhibits radiotherapy resistance of NPC by regulating DNA damage has also been found. A very important evidence is that Linc00312 directly binds to DNA-PKcs, inhibits the recruitment of Ku80 by DNA-PKcs, inhibits

the phosphorylation of AKT-DNA-PKcs axis, thus inhibits the perception and transduction of DNA damage signals in NHEJ repair pathway, and ultimately inhibits radiation resistance [51].

Radiation resistance is the main obstacle to radiotherapy, which can lead to relapse and poor prognosis. Therefore, understanding the radio-resistance mechanism of NPC and developing new radio-sensitization strategies are of great significance for the treatment of NPC. In this part, we summarize the published studies on lncRNAs in radiotherapy regarding the biological function and mechanism of NPC (Fig. 2).

Long non-coding RNAs and chemotherapy resistance in NPC

Chemotherapy is an effective treatment for advanced NPC. In a randomized controlled trial, through long-term

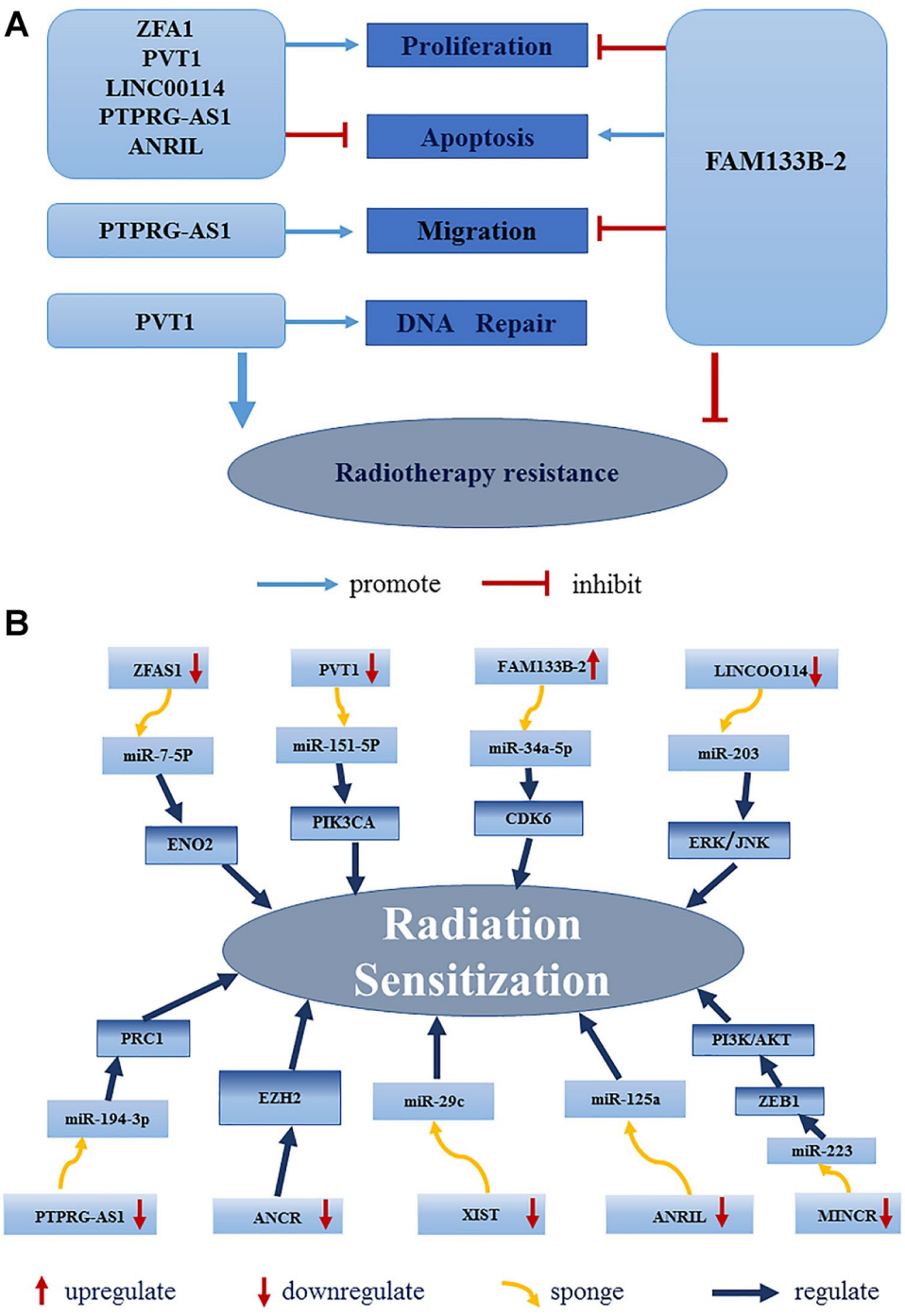

Fig. 2 **a** LncRNA promotes or inhibits radiotherapy resistance; **b** Molecular mechanism of targeting lncRNA to reverse radiotherapy resistance

follow-up, it was found that cisplatin/fluorouracil/docetaxel (TPF) induction chemotherapy (IC) combined with concurrent radiotherapy (CCRT) could significantly improve the survival rate of patients with locally advanced NPC compared with CCRT alone, and there was no significant increase in advanced toxicity [52, 53]. Recently, the first phase 3 trial of recurrent or metastatic nasopharyngeal carcinoma (RMNPC) has identified gemcitabine plus cisplatin (GP) as the standard first-line treatment [54]. Although single or combined chemotherapeutic drugs have a certain effect on recurrent or metastatic cancer, long-term use of chemotherapeutic drugs will produce resistance to chemotherapeutic drugs, which greatly limits the efficacy of chemotherapy.

More and more studies have shown that lncRNAs are new targets for the treatment of drug resistance in NPC. In the early stage, some researchers used next-generation sequencing technology to construct a differential expression profile of lncRNA related to paclitaxel resistance in NPC, and selected lncRNA n375709 with the most significant expression difference for further research, and found that inhibiting lncRNA n375709 can increase the sensitivity of NPC 5-8F and 6-10B cells to paclitaxel [55]. Subsequently, more and more lncRNAs have been confirmed to be involved in regulating the chemotherapy resistance of NPC, such as ROR [56], CCAT1 [57], and THOR [58] [59–63]. One of the most direct evidence comes from the latest research. KcNQ1OT1 significantly inhibited the viability of cisplatin-resistant NPC cells and increased the sensitivity to cisplatin by down-regulating the sponge effect of USP47 on miR-454. It is suggested that KCNQ10T1/miR-454/USP47 axis is involved in the regulation of cisplatin resistance in NPC [64]. At the same time, the researchers found that lncRNA is not only involved in the regulation of chemotherapy resistance, but also is an independent factor predicting the toxicity and efficacy of chemotherapy for NPC. For example, in the report of Youhong Wang et al., it was found that 6 potential SNPs were found in the 5 genes of the lncRNA-p53 regulatory network. They were significantly related to the toxicity and efficacy of CRT in 505 patients with NPC, thereby predicting the efficacy and acute toxicity provides new biomarkers [65]. In addition, the LncRNA Gas5 gene polymorphisms rs2067079 and rs6790 may cause severe bone marrow suppression and severe neutropenia in patients with NPC and may be used as a predictive biomarker for the toxicity of radiotherapy and chemotherapy in NPC patients [66].

In the figure below, we will summarize the lncRNAs related to chemotherapy resistance in NPC and briefly reveal their possible molecular mechanisms (Fig. 3).

Long non-coding RNAs and traditional Chinese medicine in NPC

Traditional Chinese medicine (TCM) has a long history in the treatment of tumors in China and has played an active role in modern tumor treatment due to its low toxicity, strong

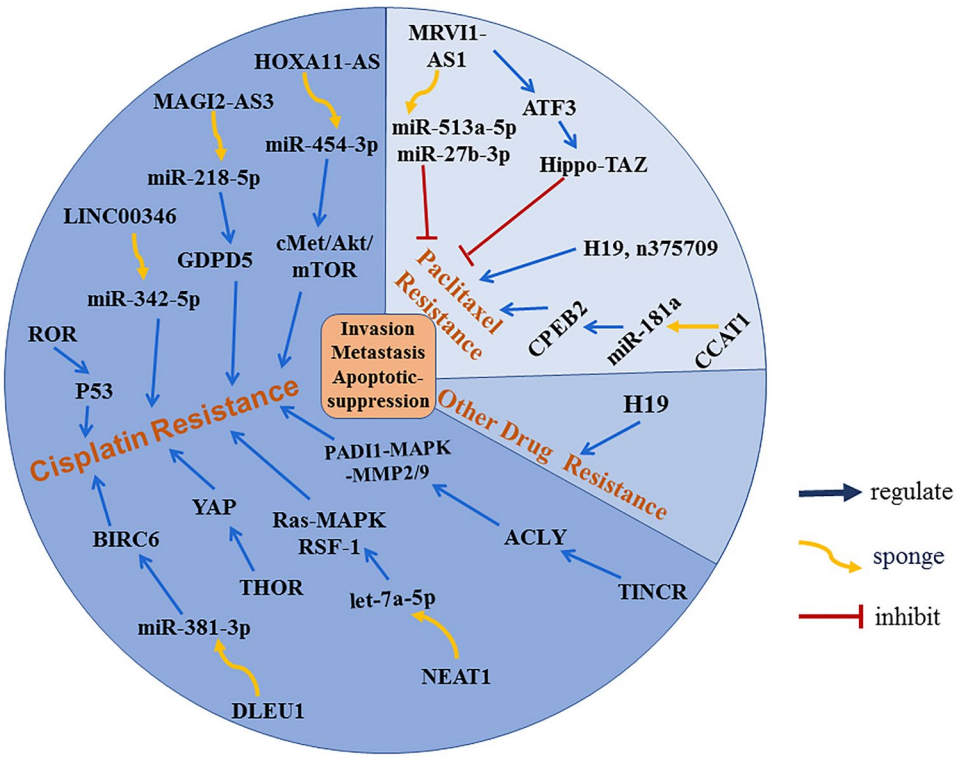

Fig. 3 LncRNA related to chemotherapy resistance in NPC and its molecular mechanisms

specificity, and high curative effect [67]. Recent studies have shown that many TCMs and monomer compounds are effective in breast cancer [68]. It has played a significant antitumor effect in the treatment of cancer. Not only that, compared with radiotherapy and/or chemotherapy alone, TCM and natural products as an adjuvant treatment of radiotherapy and/or chemotherapy have significant effects in improving the quality of life, reducing acute adverse reactions, and enhancing immune regulation [69, 70]. NPC is one of the most common tumors in China, and the application of TMCs is also very extensive. The clinical effect of Chinese medicine in adjuvant treatment of NPC is also definite [71]. So, does lncRNA play a role in the adjuvant treatment of nasopharyngeal carcinoma with Chinese herbal medicine? Some researchers have focused their attention on this issue.

As early as 2013, researchers observed the LncRNA profile of nasopharyngeal carcinoma cells and the effect of curcumin (Cur) on the radiosensitivity of NPC cells [72]. Cur is a kind of polyphenol extracted from turmeric rhizome [73]. In vivo and in vitro experiments have confirmed that Cur has anti-tumor activity that inhibits proliferation and induces apoptosis [73, 74]. In NPC, Cur also has the effect of inhibiting the proliferation and metastasis of NPC cells and enhancing radiosensitivity [75, 76]. In the study of the mechanism of curcumin radio-sensitization, the researchers found that Cur can significantly reverse the changes in lncRNA expression induced by radiotherapy, indicating that Cur can be used as a good radiosensitizer [72]. In modern Chinese medicine, Chinese medicine preparations of Astragalus membranaceus (HangQi) are widely used to assist in the treatment of many diseases [77]. Calycosin is one of the main bioactive components of Astragalus membranaceus [78]. A large number of studies have shown that mullein has anti-tumor effects in a variety of tumors [79, 80]. In NPC, Calycosin affects the growth of NPC cells by regulating lncRNA EWSAT1 and its downstream pathways. In the overexpression of EWSAT1, it was found that the increased expression of EWSAT1 weakened the growth inhibitory effect of Calycosin on NPC cells [81]. There are some other active ingredients of TCM that interact with lncRNA to exert anti-cancer effects in NPC. For example, Triptonide, a small molecule monomer extract from the ancient Chinese herb Tripterygium wilfordii Hook, inhibits human NPC cell growth via disrupting LncRNA THOR-IGF2BP1 signaling [82]. Another evidence is that polyphylloside I, extracted from the natural herb Chonglou, has anticancer activity against nasopharyngeal carcinoma by regulating lncRNA ROR and p53 signaling [83]. In summary, with the deepening of TCMs research, the role and mechanism of lncRNA in TCMs treatment will be gradually revealed. lncRNA is expected to become a new molecular target for TCMs therapy.

Long non-coding RNAs and tumor diagnosis and prognosis biomarkers in NPC

In recent years, the research on diagnostic and prognostic biomarkers related to lncRNA has made great progress. The lncRNAs in circulating serum or plasma have great potential as diagnostic or prognostic markers of diseases, especially in certain types of cancer, because they are stable, available, and closely related to diseases [84]. Compared with classic biopsy, simple molecular biology techniques (PCR, sequencing) can be used for non-invasive detection [85]. In addition, they have different expressions in biological fluids, and their expression is tissue-specific. On this basis, combining different lncRNAs with conventional biomarkers can obtain an effective diagnosis and/or prognosis. The abnormal expression of several lncRNAs is closely related to the prognosis of NPC and can be used as potential prognostic indicators. A 2013 study confirmed that NPC patients with high levels of lncRNA HOTAIR have a poor overall survival prognosis. HOTAIR is an independent prognostic indicator of NPC progression and survival [86]. In addition, the expression level of LINC01420 in NPC tissues were higher than nasopharyngeal epithelial (NPE) tissues [87]. The overall survival rate of NPC patients with high expression of LINC01420 is lower. LINC01420 may play a key role in the progression of NPC and may become a potential prognostic biomarker for NPC patients. One study recruited 101 NPC patients, 20 chronic nasopharyngitis (CN) patients, 20 EBV carriers (EC), and 101 healthy controls. Through qRT-PCR and LncRNADisease database, three NPC diagnostic tools have been established. A profile of three circulating lncRNAs (MALAT1, AFAP1-AS1, and AL359062) was established for NPC diagnosis. The high levels of these three lncRNAs are closely related to late NPC metastasis and EBV infection. After treatment, the serum levels of these three lncRNAs decreased significantly, indicating that circulating MALAT1, AFAP1AS1, and AL359062 may be new serum markers for the diagnosis and prognosis of NPC after treatment [88].

With the deepening of people's understanding of lncRNA as a serum diagnosis and prognostic marker of NPC, more and more studies are focused on screening reliable serum lncRNA for NPC. A new study reveals the role of FOXP4-AS1 as a potential diagnostic marker and independent prognostic factor in NPC patients. The researchers found that the expression of FOXP4-AS1 was related to T stage, lymph node metastasis, tumor histological grade, and clinical stage, and the PFS and OS of patients with high expression of FOXP4-AS1 were lower than those with low expression of FOXP4-AS1 [89].

Conclusion

Nasopharyngeal carcinoma is a common malignant tumor in Guangdong, China and other places. Its onset location is hidden, its early symptoms are not typical, it lacks specific serum diagnostic markers, and it is prone to recurrence and early metastasis, leading to its poor prognosis. The development of high-throughput sequencing technology has greatly promoted the identification and expression profile research of long non-coding RNAs in normal cells and tumor cells. Increasing evidence shows that the abnormal expression of lncRNA in different tumor types is related to the specific biopathological characteristics of the tumor itself, the outcome of the disease, and the response to drug treatment.

This article focuses on the clinical application of lncRNAs in NPC, especially the susceptibility factors (EB virus infection), the potential applications in NPC treatment resistance, and the efficacy and prognosis of traditional natural medicines. EB virus is a tumorigenic virus of nasopharyngeal carcinoma. EB virus can participate in the progression of NPC through its own encoding lncRNA. EB virus can also regulate the malignant biological behavior of NPC by encoding miRNA and then targeting lncRNA of the host. These findings provide potential targets or strategies for new EBV-related cancer treatments, as well as new insights for understanding the carcinogenic mechanisms related to EBV infection. A variety of lncRNAs can promote or inhibit the effects of radiation or chemotherapy on NPC to varying degrees. Some lncRNA induce tumor cells to produce treatment resistance, but some lncRNA can enhance the sensitivity of tumor cells to treatment. Although the mechanism by which lncRNA regulates the sensitivity of treatment is still unclear, related lncRNA can be regarded as a breakthrough for patients with treatment resistance. For example, highly expressed lncRNAs can be specifically silenced for treatment-resistant patients, and related signaling pathways can be monitored to predict the treatment effect and prognosis of cancer patients, so as to more effectively carry out individualized treatment. In China, the active ingredients of traditional natural herbal medicines are used in the treatment of NPC and have shown certain anti-tumor effects and reduce side effects of radiotherapy and chemotherapy. By observing the role of lncRNA in regulating the malignant phenotype of NPC cells by the effective components of Chinese herbal medicine, we believe that lncRNA has played a role in the auxiliary treatment of NPC by Chinese herbal medicine. This view provides a theoretical basis for traditional Chinese medicine to treat tumors, and it also enriches the complex network of lncRNA regulating tumors. LncRNA may be an emerging molecular target for traditional Chinese medicine to treat tumors. The specific expression pattern of lncRNA provides a unique opportunity for fine regulation of lncRNA-targeting therapy for nasopharyngeal carcinoma. The treatment of tumor suppressor lncRNA will also provide a new dawn for the treatment of nasopharyngeal carcinoma. We believe that understanding the role of lncRNAs in the occurrence and development of NPC may help to use it as a diagnostic monitoring tool and a biological target for judging prognosis.

LncRNA has shown complex and powerful functions in NPC, but this is still not the whole truth. The next research plan of nasopharyngeal cancer research will focus on discovering new molecular biomarkers related to prognosis and diagnosis, improving existing screening and treatment strategies, and developing new treatment options for refractory relapsed diseases. lncRNA is considered to have considerable clinical value in oncology, and its potential clinical application is of great significance.

Author contribution YT: Data Curation, Visualization and Writing—Original Draft; XH: Writing—Review & Editing. All authors read and approved the final manuscript.

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Data availability The data used to support the findings of this study are included in the article.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

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