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Research Progress on Long Non-Coding RNAs in the Regulation of Malignant Biological Behavior of Nasopharyngeal Carcinoma

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Abstract

Nasopharyngeal carcinoma (NPC) is a malignant tumor originating from the nasopharyngeal epithelium, characterized by a distinct geographic distribution, with high incidence in southern China and Southeast Asia. Although radiotherapy and chemotherapy have advanced considerably, distant metastasis and resistance to chemoradiotherapy remain the leading causes of death in NPC patients. Long non-coding RNAs (lncRNAs) are RNA molecules longer than 200 nucleotides that do not encode proteins; they regulate gene expression at the epigenetic, transcriptional, and post-transcriptional levels and participate in the initiation and progression of various malignancies. In recent years, a growing body of evidence has shown that lncRNAs play pivotal regulatory roles in the malignant biological behaviors of NPC, including proliferation, migration and invasion, resistance to chemoradiotherapy, apoptosis and autophagy, and metabolic reprogramming. This review systematically summarizes the research advances on lncRNAs in NPC, covering their regulatory mechanisms, signaling pathways, value as clinical biomarkers, and prospects as therapeutic targets, and discusses the current limitations and future directions of the field, with the aim of providing a theoretical basis for the early diagnosis, prognostic evaluation, and targeted therapy of NPC.

Keywords

Nasopharyngeal Carcinoma, Long Non-Coding RNA, Tumor Metastasis, Competing Endogenous RNA

1. Introduction

NPC is a malignant tumor arising from the nasopharyngeal mucosal epithelium,

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and histologically the non-keratinizing undifferentiated carcinoma is the most common subtype. NPC exhibits marked epidemiological features: its incidence shows pronounced geographic variation, with high-incidence regions in southern China (especially Guangdong, Guangxi, and Hunan provinces) and Southeast Asia, where the annual incidence can reach 20 - 30 per 100,000, whereas in Europe and North America it is typically below 1 per 100,000 [1]. The pathogenesis of NPC involves the combinatorial action of multiple factors, among which Epstein-Barr virus (EBV) infection, genetic susceptibility, and environmental factors (e.g., N-nitroso compounds in preserved foods) are considered the most important etiological factors [2]. Currently, the primary treatment for NPC is radiotherapy combined with chemotherapy. With the widespread adoption of intensity-modulated radiotherapy (IMRT) and the optimization of chemotherapy regimens, the 5-year survival rate of early-stage NPC has exceeded 90%; however, the prognosis of locally advanced and metastatic NPC remains unsatisfactory [3]. Distant metastasis and resistance to chemoradiotherapy are the main causes of treatment failure and mortality in NPC patients. Therefore, elucidating the molecular mechanisms underlying the malignant biological behavior of NPC and identifying novel diagnostic biomarkers and therapeutic targets are of great scientific and clinical significance.

Only about 2% of the human genome encodes proteins, while the vast majority of transcriptional output consists of non-coding RNAs. lncRNAs are RNA molecules longer than 200 nucleotides that lack a significant open reading frame and are transcribed widely across the genome. Based on their positional relationship with neighboring protein-coding genes, lncRNAs can be classified as: 1) antisense lncRNAs, transcribed from the antisense strand of a protein-coding gene; 2) long intergenic ncRNAs (lincRNAs), located between two protein-coding genes; 3) intronic lncRNAs, derived from the intronic regions of protein-coding genes; 4) enhancer lncRNAs, transcribed from enhancer regions; and 5) bidirectional lncRNAs, transcribed in the opposite direction to a neighboring protein-coding gene [4]. lncRNAs exert diverse biological functions, and their molecular mechanisms of gene expression regulation can be summarized into the following modes (**Figure 1**): 1) signal—lncRNAs serve as molecular signals for transcriptional regulation, being transcribed under specific spatiotemporal conditions to reflect the transcriptional status of genes; 2) decoy—lncRNAs bind transcription factors or other RNA-binding proteins, sequestering them away from target genes and thereby inhibiting their function; 3) guide—lncRNAs guide chromatin-modifying complexes (e.g., PRC2) to specific genomic loci to regulate epigenetic modifications; 4) scaffold—lncRNAs act as molecular scaffolds that assemble multiple proteins into functional complexes; and 5) competing endogenous RNA (ceRNA)—lncRNAs "sponge" microRNAs (miRNAs), relieving miRNA-mediated repression of target mRNAs [5] [6]. Among these, the ceRNA mechanism has attracted considerable attention in cancer research and represents one of the principal modes by which lncRNAs regulate the malignant biological behavior of tumors.

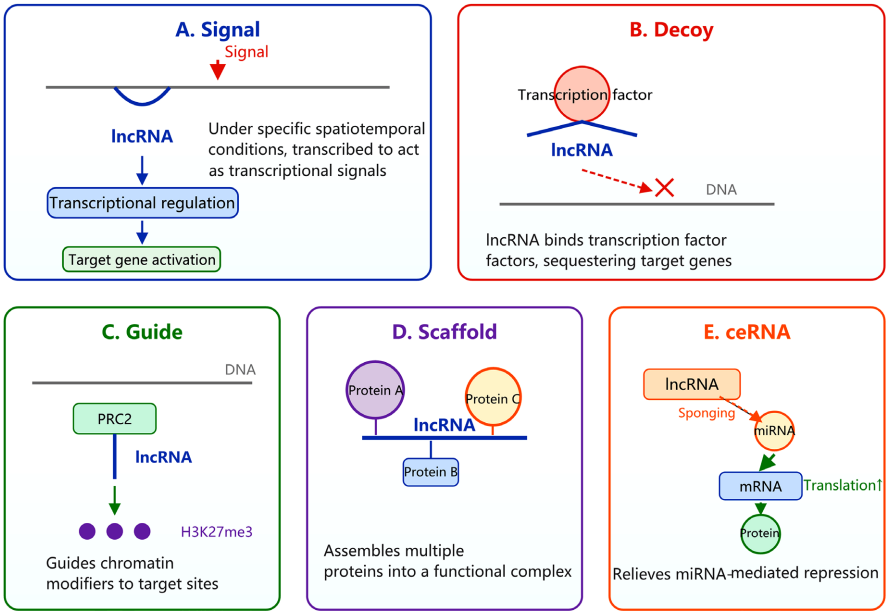

Figure 1. Schematic of the regulatory mechanisms of lncRNAs in nasopharyngeal carcinoma. A: Signal mode; B: Decoy mode; C: Guide mode; D: Scaffold mode; E: Competing endogenous RNA (ceRNA) mode.

Since the functions of classical lncRNAs such as MALAT1 and HOTAIR in cancer were elucidated, the role of lncRNAs in malignancies has become a major research focus in the life sciences. Studies have shown that lncRNAs exert key regulatory functions in multiple processes of tumorigenesis, including proliferation, apoptosis, migration, invasion, angiogenesis, metabolic reprogramming, and immune evasion [5]. In head and neck squamous cell carcinoma, aberrant expression of various lncRNAs (e.g., HOTAIR, H19, and UCA1) is closely associated with tumor progression and poor prognosis. In recent years, with the rapid development of high-throughput sequencing technologies and bioinformatics analysis, a large number of differentially expressed lncRNAs in NPC have been identified, and substantial progress has been made in elucidating their functions and mechanisms. This review aims to systematically summarize the regulatory roles of lncRNAs in the malignant biological behaviors of NPC (including proliferation, migration, invasion and metastasis, resistance to chemoradiotherapy, apoptosis and autophagy, and metabolic reprogramming), to integrate their molecular mechanisms and signaling networks, to evaluate the candidate role of lncRNAs as diagnostic and prognostic biomarkers and therapeutic targets in NPC (although most such applications remain preclinical), and to discuss current problems and future directions, thereby providing a reference for basic research and clinical translation in NPC.

2. lncRNAs Regulating NPC Cell Proliferation

Uncontrolled cell proliferation is one of the most fundamental biological hallmarks of malignancies. In NPC, multiple lncRNAs promote or inhibit cell proliferation through distinct mechanisms, providing potential intervention targets for

NPC therapy. Table 1 summarizes the major lncRNAs regulating NPC proliferation and their mechanisms.

Table 1. Summary of studies on lncRNAs regulating NPC cell proliferation.

lncRNA	Expression	Mechanism /Pathway	Key Finding	Ref No.
ROR	↑	Inhibition of p53 signaling	Promotes proliferation, metastasis, and chemoresistance	[6]
n326322	↑	-	Promotes NPC cell proliferation and invasion	[7]
DANCR	↑	-	Promotes NPC cell proliferation and migration	[8]
Lnc-MRPL39-2:1	↑	HuR/beta-catenin mRNA stability	Binds HuR to stabilize beta-catenin mRNA	[9]
LINC00491	↑	PURA/ANXA1/PI3K-AKT	Promotes proliferation & metastasis; activates PI3K/AKT	[10]
HOTTIP	↑	HOXA13	Promotes proliferation via HOXA13 regulation	[11]
LINC01503	↑	SFPQ-FOSL1 axis	AR-induced; promotes proliferation and metastasis	[12]
AFAP1-AS1	↑	Actin filament integrity/small GTPases	Upregulated in NPC; associated with metastasis and poor prognosis	[13]
LUADT1	↑	miR-1207-5p/TEAD1/Hippo-YAP	Sponges miR-1207-5p to promote proliferation	[14]
EWSAT1	↑	miR-326/-330-5p	Sponges miRNAs to promote NPC cell growth	[15]
LINC00173	↑	miR-765/GREM1	Acts as ceRNA upregulating GREM1	[16]
LncRNA 319	↑	miR-1207-5p/KLF12	Promotes carcinogenesis via miR-1207-5p/KLF12 axis	[17]

2.1. Pro-Proliferative lncRNAs

Li *et al.* [6] found that lncRNA-ROR is markedly upregulated in NPC tissues, and its overexpression is closely linked to proliferation, migration and invasion, and apoptosis of NPC cells. Mechanistic studies revealed that lncRNA-ROR promotes malignant progression of NPC by inhibiting the p53 signaling pathway and plays a key role in chemoresistance. Since p53 is a classic tumor suppressor, the repression of the p53 pathway by lncRNA-ROR may be an important mechanism by which NPC cells acquire a proliferative advantage and chemoresistance. This study was the first to reveal the oncogenic function of lncRNA-ROR in NPC and provided new insights into combination therapies targeting the p53 pathway. Du *et al.* [7] identified a novel lncRNA, n326322, which is highly expressed in NPC tissues and cell lines, and whose knockdown significantly suppresses NPC cell

proliferation and invasion. Hao *et al.* [8] reported that DANCR is upregulated in NPC and promotes cell proliferation and migration. Tian *et al.* [9] found that Lnc-MRPL39-2:1 is upregulated in NPC and promotes NPC cell growth and invasion by binding the RNA-binding protein HuR and stabilizing beta-catenin mRNA.

Beyond the lncRNAs described above, several additional pro-proliferative lncRNAs have been identified in NPC. LINC00491 is upregulated in NPC and promotes cell proliferation and metastasis through the PURA/ANXA1-mediated PI3K-AKT signaling axis [10]. HOTTIP facilitates NPC cell proliferation by regulating HOXA13 [11]. The androgen-receptor-induced lncRNA LINC01503 promotes NPC proliferation and metastasis via the SFPQ-FOSL1 axis [12]. AFAP1-AS1 is also upregulated in NPC and promotes proliferation by modulating actin filament integrity and small-GTPase activity, and its high expression is further associated with metastasis and poor prognosis [13].

2.2. lncRNAs as ceRNAs Regulating Proliferation

The ceRNA mechanism is among the most frequently reported modes by which lncRNAs regulate NPC proliferation; however, a proposed lncRNA-miRNA-mRNA ceRNA axis should be interpreted cautiously and ideally supported by evidence for sufficient expression abundance, subcellular co-localization of the interacting partners, direct miRNA binding (e.g., via CLIP or reporter assays), and target-gene rescue experiments. In this mechanism, lncRNAs competitively bind miRNAs through shared miRNA response elements (MREs), thereby relieving miRNA-mediated translational repression of target genes. Jiang *et al.* [14] found that LUADT1 is significantly highly expressed in NPC tissues and cells, and that it acts as a sponge for miR-1207-5p, thereby relieving the latter's repression of TEAD1. TEAD1 is a transcription factor whose activity is constrained by the Hippo pathway; its upregulation promotes NPC cell proliferation and invasion, implicating Hippo/YAP signaling. Nude mouse tumorigenesis assays further confirmed that LUADT1 knockdown significantly reduced tumor volume and weight. This study revealed the oncogenic role of the LUADT1/miR-1207-5p/TEAD1 axis involving Hippo/YAP signaling in NPC. Song *et al.* [15] demonstrated that EWSAT1 promotes NPC cell growth by targeting miR-326 and miR-330-5p. Wang *et al.* [16] reported that LINC00173 upregulates GREM1 expression by binding miR-765, and promotes NPC progression both *in vitro* and *in vivo*. Song *et al.* [17] also reported that lncRNA 319 promotes NPC carcinogenesis through the miR-1207-5p/KLF12 axis, revealing that the same miRNA (miR-1207-5p) can be competitively bound by multiple lncRNAs and suggesting the existence of a complex ceRNA regulatory network in NPC.

In summary, pro-proliferative lncRNAs are generally highly expressed in NPC tissues, and their regulatory mechanisms frequently involve ceRNA networks-although the strength of evidence for individual axes varies-while also engaging classic signaling pathways including p53, Wnt/beta-catenin, and Hippo/YAP. Notably, several lncRNAs (e.g., AFAP1-AS1, ROR, and LUADT1) concurrently affect

both proliferation and cell migration/invasion, suggesting their pleiotropic roles in NPC malignant progression.

3. lncRNAs Regulating NPC Migration, Invasion, and Metastasis

Distant metastasis is one of the leading causes of death in NPC patients. Epithelial-mesenchymal transition (EMT) is a critical process through which tumor cells acquire migratory and invasive capacities, and lncRNAs play important roles in EMT regulation. Figure 2 illustrates the global signaling network by which lncRNAs regulate the malignant biological behavior of NPC.

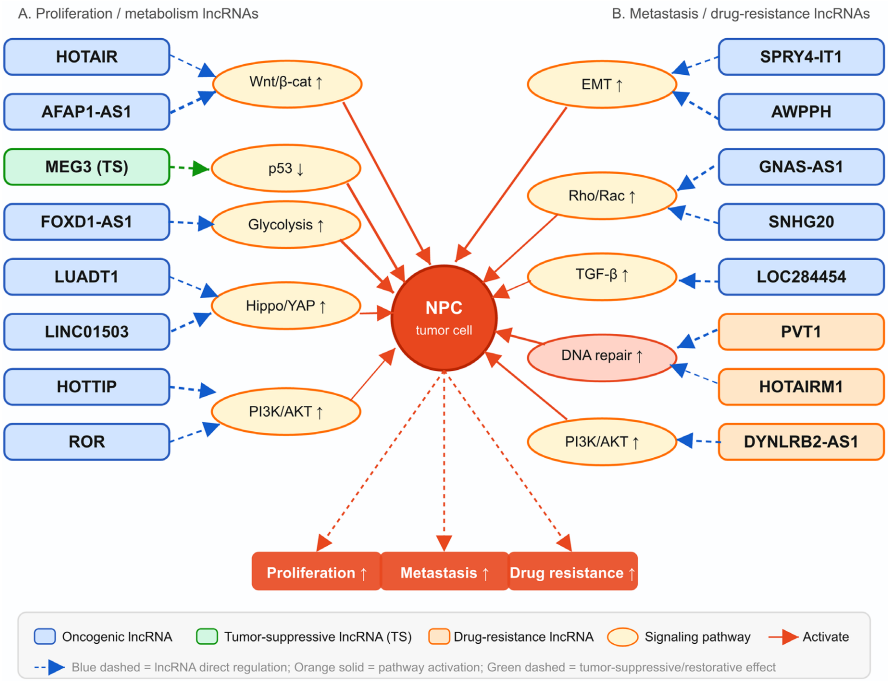

Figure 2. Network of signaling pathways by which lncRNAs regulate the malignant biological behavior of nasopharyngeal carcinoma. Blue boxes represent oncogenic lncRNAs, green boxes represent tumor-suppressive lncRNAs, orange boxes represent drug-resistance-related lncRNAs, yellow ellipses represent signaling pathways, and the red box at the bottom represents malignant biological outcomes. Blue dashed lines indicate direct regulatory relationships, orange solid lines indicate pathway activation, and green dashed lines indicate tumor-suppressive effects.

3.1. lncRNAs and Epithelial-Mesenchymal Transition

SPRY4-IT1 is an lncRNA that has attracted attention in NPC EMT research in recent years. Li *et al.* [18] found that SPRY4-IT1 is significantly upregulated in multiple NPC cell lines (6-10B, CNE-2, and HONE-1) compared with the human immortalized nasopharyngeal epithelial cell line NP69. Knockdown of SPRY4-IT1 inhibited NPC cell proliferation, migration, and invasion, and induced G2/M phase arrest and apoptosis. Western blot analysis showed that SPRY4-IT1 knockdown increased E-cadherin (an epithelial marker) and decreased Vimentin (a

mesenchymal marker), together with reduced Snail and Twist1 (EMT transcription factors), indicating that SPRY4-IT1 expression promotes EMT and enhances the malignant phenotype of NPC.

3.2. lncRNAs Regulating Key Signaling Pathways to Promote Metastasis

Liu *et al.* [19] found that the lncRNA ANRIL suppresses NPC cell migration and invasion through a positive-feedback loop involving lncRNA ANRIL/miR-339-5p/ZBTB7A and the SREBP1-FASN axis. Tao *et al.* [20] reported that DNASE1L3 acts as an important suppressor of NPC cell migration and invasion by attenuating MYH9/beta-catenin/c-Jun/lncRNA-KDM4A-induced ubiquitination and degradation of E-cadherin. These two studies suggest the existence of an lncRNA network regulating NPC cell motility and invasion with both pro- and anti-tumor functions; in addition, as mentioned above, LINC00491 also promotes NPC cell migration and invasion by activating the PI3K/AKT pathway [10].

lncRNAs regulate NPC metastasis through multidimensional mechanisms, including EMT regulation, cytoskeletal rearrangement (Rho/Rac pathway), activation of classic signaling pathways (Wnt/beta-catenin, TGF-beta, PI3K/AKT), and epigenetic modifications (LSD1/EZH2-mediated silencing of PTEN). Several lncRNAs (HOTAIR, ILF3-AS1, and FOXD1-AS1) have been proposed as candidate biomarkers for metastasis prediction and prognostic evaluation.

4. lncRNAs Regulating Chemoradiotherapy Resistance in NPC

Resistance to chemoradiotherapy is a key reason for treatment failure in NPC. In recent years, the role of lncRNAs in NPC chemoradiotherapy resistance has attracted increasing attention. **Table 2** summarizes the lncRNAs associated with NPC chemoradiotherapy resistance.

4.1. lncRNAs and Radioresistance

Radiotherapy is the preferred treatment for NPC, but the development of radioresistance severely limits its efficacy. He *et al.* [21] were the first to demonstrate that PVT1 is highly expressed in NPC, and that patients with high PVT1 expression had significantly shortened progression-free survival (PFS) and overall survival (OS). Functional assays showed that PVT1 knockdown inhibits NPC cell proliferation and promotes apoptosis while increasing radiosensitivity. Mechanistic studies revealed that PVT1 knockdown induces post-irradiation apoptosis by affecting the DNA damage repair pathway. Mi *et al.* [22] identified HOTAIRM1 as a key regulator of radioresistance in NPC. HOTAIRM1 promotes NPC radioresistance by regulating the acetylation-dependent alternative splicing of the FTO protein, which affects the expression of CD44 splice variants. With over 38 citations, this study revealed a novel mechanism by which lncRNAs regulate radioresistance through RNA modification and alternative splicing, providing a new tar-

get for overcoming radioresistance in NPC. Jiang *et al.* [23] combined weighted gene co-expression network analysis (WGCNA) with validation in 40 pre-radiotherapy NPC biopsy specimens and found that RHPN1-AS1 is significantly associated with radiosensitivity. *In vitro* and *in vivo* experiments showed that silencing RHPN1-AS1 inhibits NPC cell proliferation, migration, and invasion, upregulates DNA double-strand break markers (gamma-H2AX and 53BP1), induces DNA damage, and promotes apoptosis; mechanistically, RHPN1-AS1 negatively regulates CELF2, which in turn affects radiosensitivity through the MAPK pathway. This study provides new evidence for the mechanism by which lncRNAs regulate radiosensitivity in NPC.

Table 2. Summary of studies on lncRNAs regulating NPC chemoradiotherapy resistance.

lncRNA	Resistance type	Mechanism/Pathway	Key Finding	Ref No.
ROR	Chemoresistance	Inhibition of p53 signaling	Enables NPC cells to evade chemotherapy-induced apoptosis	[6]
PVT1	Radioresistance	DNA damage repair/apoptosis	High expression shortens PFS and OS; knockdown sensitizes to radiation	[21]
HOTAIRM1	Radioresistance	FTO acetylation/CD44 alternative splicing	Promotes radioresistance via FTO-dependent CD44 splicing	[22]
RHPN1-AS1	Radioresistance	CELF2/MAPK	Negatively regulates CELF2 to reduce radiosensitivity via MAPK	[23]
DYNLRB2-AS1	Gemcitabine resistance	DHX9 ubiquitination/degradation	Inhibits DHX9 degradation to enhance DNA repair	[24]
H19	Paclitaxel sensitivity	-	Silencing H19 + paclitaxel inhibits NPC progression	[25]

4.2. lncRNAs and Chemoresistance

As mentioned above, lncRNA-ROR contributes to NPC chemoresistance by inhibiting the p53 signaling pathway [6]. Chemotherapeutic agents kill tumor cells by inducing DNA damage and activating p53-dependent apoptotic pathways, whereas ROR-mediated inhibition of p53 enables NPC cells to evade chemotherapy-induced apoptosis. Chen *et al.* [24] found that DYNLRB2-AS1 promotes gemcitabine resistance in NPC by inhibiting the ubiquitination-dependent degradation of the DHX9 protein. DHX9 is an RNA helicase involved in DNA repair and RNA metabolism. DYNLRB2-AS1 maintains DHX9 protein stability and enhances DNA repair capacity, thereby mediating chemoresistance. Chen *et al.* [24] published this work in a high-impact journal specialized in drug resistance, suggesting that targeting the DYNLRB2-AS1/DHX9 axis may reverse gemcitabine resistance. Zhu *et al.* [25] found that silencing H19 combined with paclitaxel treatment significantly inhibits NPC progression. H19 is a classic imprinted-gene-derived lncRNA that is highly expressed in various tumors. This study provides experimental evidence for combination strategies involving lncRNA targeting and

chemotherapy.

lncRNAs mediate NPC chemoradiotherapy resistance through mechanisms such as regulation of DNA damage repair (PVT1, DYNLRB2-AS1), evasion of apoptosis (ROR/p53), and RNA modification and alternative splicing (HOTAIRM1/FTO/CD44). Preclinical evidence suggests that targeting specific lncRNAs can reverse the resistant phenotype and improve NPC treatment outcomes, representing one of the most promising directions for future clinical translation in this field.

5. lncRNAs Regulating Apoptosis and Autophagy in NPC

Apoptosis and autophagy are important processes for maintaining cellular homeostasis, and their dysregulation is a key mechanism in tumor development. lncRNAs regulate NPC apoptosis in a bidirectional manner: oncogenic lncRNAs mostly inhibit apoptosis, whereas tumor-suppressive lncRNAs promote it.

5.1. Tumor-Suppressive lncRNAs Promoting Apoptosis

Lin *et al.* [26] found that MEG3 is downregulated in NPC and exerts tumor-suppressive functions. MEG3 promotes NPC cell autophagy and apoptosis by binding miR-21 to upregulate PTEN expression. miR-21 is a classic oncogenic miRNA that is highly expressed in various tumors and promotes tumor progression by repressing tumor suppressors such as PTEN. As a ceRNA for miR-21, MEG3 relieves miR-21-mediated repression of PTEN, thereby restoring the tumor-suppressive function of PTEN. Chak *et al.* [27] also confirmed the downregulation of MEG3 in NPC, further supporting its tumor-suppressive role. Zhang *et al.* [28] found that RGMB-AS1 is downregulated in NPC and suppresses NPC progression by binding the transcription factor FOXA1, exerting a tumor-suppressive function.

5.2. Oncogenic lncRNAs Inhibiting Apoptosis

As mentioned above, knockdown of SPRY4-IT1 upregulates cleaved PARP and cleaved caspase-3 expression, suggesting that SPRY4-IT1 inhibits apoptosis in NPC [18]. Zhang *et al.* [29], in a 2026 study, identified a novel lncRNA, LINC-AC092535.5, which directly regulates MICAL2 mRNA at both transcriptional and post-transcriptional levels, enabling MICAL2 to promote p53 nuclear translocation and recruit the E3 ubiquitin ligase MDM2 to mediate p53 ubiquitination and degradation, thereby suppressing p53-mediated ferroptosis and promoting NPC progression. Zhu *et al.* [30], in a 2025 study, reported that HELLPAR promotes NPC progression through the miR-448/ADAM10 axis, and that interfering with HELLPAR or upregulating miR-448 inhibits the malignant phenotype of NPC. Jiang *et al.* [31] elucidated the role of the H19/miR-423-5p/DTX3L axis in the malignant phenotype of NPC: H19 acts as a molecular sponge for miR-423-5p, relieving its repression of DTX3L and enhancing the proliferation, migration, and invasion of NPC cells, indicating that, beyond effects on chemosensitivity, H19 also promotes NPC malignant progression through ceRNA mechanisms in a mul-

tidimensional manner.

The regulation of NPC apoptosis by lncRNAs exhibits a bidirectional pattern - oncogenic lncRNAs inhibit apoptosis whereas tumor-suppressive lncRNAs promote it. The role of autophagy in NPC is complex, capable of either promoting cell survival or inducing cell death, and the mechanisms by which lncRNAs regulate autophagy remain sparsely studied, with the MEG3/miR-21/PTEN axis being among the few clearly reported. Future work should deeply explore the specific mechanisms by which lncRNAs regulate autophagy and ferroptosis and their therapeutic implications in NPC.

6. lncRNAs Regulating Metabolic Reprogramming in NPC

Metabolic reprogramming of tumor cells is one of the hallmarks of malignancy. The Warburg effect (aerobic glycolysis) also occurs in NPC, and the role of lncRNAs in metabolic regulation has only recently begun to receive attention. The study by Wang *et al.* [32] was the first to link lncRNAs to glycolysis in NPC. FOXD1-AS1 is overexpressed in NPC and promotes cell proliferation, migration, invasion, and glycolysis by upregulating FOXD1 protein expression. Further studies revealed that FOXD1 directly transcriptionally upregulates the expression of key glycolytic genes, including hexokinase 2 (HK2), lactate dehydrogenase A (LDHA), and pyruvate kinase M2 (PKM2), thereby enhancing aerobic glycolysis in NPC cells. This study revealed the regulatory role of the lncRNA-FOXD1-glycolytic gene axis in NPC metabolic reprogramming and provided a preclinical therapeutic target for tumor-metabolism-directed therapies.

Currently, research on lncRNAs regulating lipid metabolism and amino acid metabolism in NPC is still in its infancy. In other tumors, lncRNAs have been reported to regulate lipid synthesis (e.g., ACACA and FASN), glutamine metabolism, and one-carbon metabolism. Given the unique EBV-associated metabolic features of NPC, in-depth exploration of the role of lncRNAs in the comprehensive metabolic reprogramming of NPC is of great scientific significance. In addition, the association between metabolic reprogramming and chemoradiotherapy resistance is also a worthwhile direction - enhanced glycolysis can mediate radioresistance by maintaining ATP levels and reducing the production of reactive oxygen species (ROS).

7. Association between lncRNAs and Epstein-Barr Virus

EBV infection is one of the most important etiological factors in NPC, with over 90% of non-keratinizing NPC cases associated with EBV. In recent years, the role of lncRNAs in EBV-associated tumorigenesis has gradually attracted attention. Zhang *et al.* [33] reviewed the involvement of lncRNAs in EBV infection and tumorigenesis. EBV itself encodes various non-coding RNAs, including EBV-encoded miRNAs (e.g., miR-BARTs) and EBV-encoded lncRNAs (e.g., RPMS1 and BART); these EBV-derived non-coding RNAs can modulate host gene expression and have been implicated in NPC initiation and progression. Moreover, EBV la-

tent infection can alter the host lncRNA expression profile, generally inducing upregulation of oncogenic lncRNAs and downregulation of tumor-suppressive lncRNAs. At the mechanistic level, EBV latent gene products (e.g., LMP1, LMP2A, and EBNA1) are known to activate transcription factors such as NF-kappaB, STAT3, and AP-1, which could in turn regulate the transcription of host lncRNAs; for instance, LMP1 has been reported to upregulate certain lncRNAs through the NF-kappaB pathway in EBV-associated models. However, direct, primary NPC studies that mechanistically link specific EBV latent proteins to the regulation of individual host lncRNAs-and to NPC cell migration, invasion, and proliferation-remain limited. Therefore, many of these host-lncRNA links should currently be regarded as proposed mechanisms rather than established NPC-specific pathways, and the interaction network between EBV miRNAs and host lncRNAs awaits further elucidation in NPC models.

8. lncRNAs as Diagnostic and Prognostic Biomarkers in NPC

8.1. lncRNAs as Diagnostic Biomarkers

The aberrant expression of lncRNAs is tissue-specific and stage-dependent, making them ideal candidate tumor biomarkers. For NPC diagnosis, detection of lncRNAs in serum and plasma (liquid biopsy) offers the advantages of being non-invasive and repeatable. Although research on liquid-biopsy lncRNAs for NPC is currently insufficient, differential diagnosis based on tissue lncRNA expression profiles has shown promising prospects. For example, HOTAIR is 5.2- to 48.4-fold higher in NPC tissues than in normal tissues [34], and AFAP1-AS1 is significantly upregulated in NPC [13]; these differentially expressed lncRNAs hold promise as candidate molecular biomarkers for the auxiliary diagnosis of NPC. Nevertheless, their diagnostic utility remains to be confirmed by independently validated discrimination measures and clinically defined thresholds before routine clinical application.

8.2. lncRNAs as Prognostic Biomarkers

Multiple studies have reported that lncRNA expression levels are significantly associated with the TNM stage and prognostic predictive value of NPC (**Table 3**).

HOTAIR was among the first lncRNAs identified as an independent prognostic marker in NPC. Nie *et al.* [34], by *in situ* hybridization analysis of 160 paraffin-embedded NPC biopsy tissues, found that 56.87% of samples showed high HOTAIR expression. HOTAIR expression level was significantly correlated with tumor size ($P = 0.021$), clinical stage ($P = 0.012$), and lymph node metastatic burden ($P = 0.005$). HOTAIR expression in fresh tissues was 5.2- to 48.4-fold higher than in non-cancerous tissues. More importantly, multivariate analysis showed that HOTAIR is an independent prognostic factor for overall survival in NPC. Bo *et al.* [13] found that high AFAP1-AS1 expression is significantly associated with NPC metastasis and poor prognosis. He *et al.* [21] confirmed that NPC patients with high PVT1 expression had significantly shortened PFS and OS. Yang *et al.*

[35] found that high ILF3-AS1 expression predicts poor prognosis in NPC patients and is positively correlated with cellular metastatic capacity. Wang *et al.* [32] confirmed that FOXD1-AS1 is overexpressed in NPC cells and tissues; FOXD1-AS1 promotes cell proliferation, migration, invasion, and glycolysis while inhibiting apoptosis by upregulating FOXD1, acting as a multifunctional oncogenic lncRNA that is significantly negatively correlated with patient survival. Dynamic monitoring of lncRNA expression levels after treatment may aid in efficacy assessment and recurrence warning; however, like the prognostic associations described above, this remains to be validated by large-scale, independently replicated prospective clinical studies with clinically defined thresholds.

Table 3. Summary of studies on lncRNAs as prognostic biomarkers in NPC.

lncRNA	Prognostic value	Sample size	Key statistical result	Ref No.
AFAP1-AS1	Poor prognosis	12 cases + validation	Significantly associated with metastasis and poor prognosis	[13]
PVT1	Shortened PFS and OS	-	High expression significantly shortens survival	[21]
FOXD1-AS1	Negative correlation with survival	-	Overexpression significantly negatively correlates with survival	[32]
HOTAIR	Independent OS prognostic factor	160 cases	Significantly associated with tumor size, stage, lymph-node metastasis	[34]
ILF3-AS1	Poor prognosis	-	High expression predicts poor prognosis	[35]

9. Prospects of lncRNAs as Therapeutic Targets in NPC

9.1. Strategies for Targeting lncRNAs

With advances in nucleic-acid drug technology, therapeutic strategies targeting lncRNAs have become increasingly mature, mainly comprising the following four categories, all of which have been validated as proof-of-concept in different tumor models: Many of the aforementioned NPC functional studies employed siRNA/shRNA knockdown of candidate lncRNAs to validate their oncogenic functions; for example, Yan *et al.* [36] used shRNA to silence FOXP4-AS1 and confirmed that it promotes NPC cell migration, invasion, and EMT through the miR-136-5p/MAPK1 axis, suggesting that RNAi itself could serve as a potential intervention in NPC. Antisense oligonucleotides (ASOs): degrading target RNAs through an RNase H-mediated mechanism, ASOs offer the advantages of flexible design and high specificity, and several ASO drugs have already been approved for marketing. Regarding lncRNA targeting, Xia *et al.* [37] designed an oligonucleotide antagonist (ASO) targeting the lncRNA ASBEL that effectively inhibited tumor growth in a breast cancer model, providing direct evidence for ASO-based targeted therapy of lncRNAs.CRISPR-Cas13d: the CRISPR-Cas13 system can target RNA molecules to achieve post-transcriptional gene silencing with high specificity and reversibility, and is especially suitable for lncRNAs that lack effective

small-molecule binding sites. Wang *et al.* [38] used a CRISPR-Cas13d screening platform to identify KILR, a breast cancer risk-associated lncRNA, and elucidated its function in regulating DNA replication and repair; Zhang *et al.* [39] directly knocked down the bladder cancer lncRNA GACAT3 using CRISPR-Cas13, significantly inhibiting tumor cell proliferation and migration and inducing apoptosis. These studies demonstrate the reliability of Cas13d as a tool for lncRNA targeting.Small-molecule inhibitors: low-molecular-weight compounds targeting the lncRNA-protein interaction interface (e.g., the HOTAIR-PRC2/EZH2 complex) represent an emerging lncRNA-targeting strategy. Wang *et al.* [40] effectively targeted ovarian cancer stem cells and inhibited their tumorigenic capacity by dual inhibition of the lncRNA HOTAIR and the lysine methyltransferase EZH2, demonstrating the feasibility of combined blockade of the "lncRNA-epigenetic regulatory complex."

In summary, the above four strategies have demonstrated clear anti-tumor effects in various tumors, but research on lncRNA-targeted therapy specifically in NPC remains extremely limited, still mostly at the level of functional validation by siRNA/shRNA knockdown, lacking systematic exploration of ASOs, CRISPR-Cas13d, or small-molecule inhibitors in NPC. This also leaves broad space for subsequent translational research.

9.2. lncRNA-Based Combination Therapy

Combining lncRNA targeting with existing therapeutic modalities is an important direction for NPC treatment. According to the combination strategy, it can be divided into three directions: combination with radiotherapy, with chemotherapy, and with immunotherapy (**Table 4**).

9.2.1. lncRNA Targeting Combined with Radiotherapy

Radiotherapy is the preferred treatment for NPC, yet approximately 20% of NPC patients experience treatment failure due to radioresistance [22]. The core concept of combining lncRNA targeting with radiotherapy is to restore tumor cell sensitivity to radiation by knocking down lncRNAs that promote radioresistance. He *et al.* [21] found that PVT1 expression is significantly higher in NPC tissues than in normal nasopharyngeal epithelial tissues. In combination radiotherapy experiments, PVT1-knockdown NPC cells showed a significantly lower colony formation rate after irradiation than controls, indicating that PVT1 knockdown increases the radiosensitivity of NPC cells. Mechanistic studies revealed that PVT1 knockdown induces post-irradiation apoptosis by affecting the DNA damage repair pathway, manifested as prolonged persistence of gamma-H2AX foci (a DNA double-strand break marker) and reduced DNA damage repair efficiency after irradiation. Mi *et al.* [22] identified HOTAIRM1 as a key regulator of radioresistance in NPC and found that HOTAIRM1 is significantly upregulated in both radioresistant NPC cell lines and clinical tissues. High HOTAIRM1 expression is closely associated with increased NPC cell proliferation, reduced apoptosis, G2/M phase arrest, and attenuated post-irradiation DNA damage. Mechanistic studies

revealed the HOTAIRM1-FTO-YTHDC1-CD44 signaling axis: HOTAIRM1 physically interacts with the FTO protein and regulates its acetylation level and stability; as an m6A demethylase, elevated FTO activity reduces the m6A methylation level of the CD44 precursor transcript; the absence of m6A modification prevents the CD44 transcript from being recognized by the m6A reader protein YTHDC1, leading to a splicing switch of CD44 from the standard isoform (CD44S) to the variant isoform (CD44V); abundant CD44V enhances NPC radioresistance by suppressing radiotherapy-induced ferroptosis. This study was the first to link lncRNAs with RNA modification (m6A), alternative splicing, and ferroptosis, providing multi-level mechanistic support for "targeting HOTAIRM1 combined with radiotherapy" and offering multiple intervenable nodes for overcoming radioresistance in NPC.

Table 4. Strategies for lncRNA-targeted combination therapy.

Combination strategy	Targeted lncRNA	Combination approach	Expected effect	Ref No.
Combined chemotherapy	ROR	ROR knockdown + chemotherapy	Reverses chemoresistance; restores p53 pathway	[6]
Combined radiotherapy	PVT1	PVT1 knockdown + radiotherapy	Increases radiosensitivity; inhibits DNA damage repair	[21]
Combined radiotherapy	HOTAIRM1	HOTAIRM1 targeting + radiotherapy	Reverses radioresistance; promotes ferroptosis	[22]
Combined chemotherapy	DYNLRB2-AS1	Target DYNLRB2-AS1 + gemcitabine	Reverses gemcitabine resistance; inhibits DNA repair	[24]
Combined chemotherapy	H19	H19 silencing + paclitaxel	Inhibits NPC progression; enhances *in vivo* tumor suppression	[25]
Combined chemotherapy	HOTAIR	HOTAIR knockdown + cisplatin	Increases cisplatin sensitivity; promotes apoptosis	[41]
Combined chemotherapy	DLEU1	DLEU1 knockdown + cisplatin	Sensitizes to cisplatin; suppresses tumor *in vitro* and *in vivo*	[42]
Combined immunotherapy	HOXA-AS2	HOXA-AS2 knockdown (downregulates PD-L1)	Reduces PD-L1 expression; inhibits tumor progression	[43]
Combined immunotherapy	SNHG14	Nano-si-SNHG14 (downregulates PD-L1)	Downregulates PD-L1; inhibits EMT; nano-delivery	[44]

9.2.2. lncRNA Targeting Combined with Chemotherapy

Chemotherapy is an important component of comprehensive NPC treatment, with commonly used agents including cisplatin, paclitaxel, and gemcitabine. However, chemoresistance severely limits therapeutic efficacy. Multiple studies have confirmed that targeting specific lncRNAs can reverse the chemoresistant phenotype of NPC. Li *et al.* [6] found that lncRNA-ROR is significantly upregu-

lated in NPC tissues compared with normal tissues and is closely associated with NPC cell proliferation, migration and invasion, and apoptosis. In chemoresistance assays, NPC cells with high lncRNA-ROR expression showed markedly enhanced resistance to chemotherapeutic agents. Mechanistic studies showed that lncRNA-ROR mediates chemoresistance by inhibiting the p53 signaling pathway; p53 is a core transcription factor for DNA-damage-induced apoptosis, and chemotherapeutic agents kill tumor cells by activating p53-dependent apoptosis, whereas ROR-mediated inhibition of the p53 pathway enables NPC cells to evade chemotherapy-induced apoptosis. Zhu *et al.* [25] systematically explored the role of H19 in paclitaxel sensitivity in NPC. Using the NP69 (human immortalized nasopharyngeal epithelial) cell line and multiple NPC cell lines (HNE3, C666-1, SUNE1, 6-10B, and 5-8F), they detected significantly upregulated H19 in NPC cells by RT-qPCR. In functional experiments, the researchers validated its role through both overexpression and silencing of H19: silencing H19 inhibited C666-1 cell proliferation and promoted apoptosis, whereas overexpressing H19 promoted proliferation and inhibited apoptosis. In resistance assays, H19-silenced resistant cells showed significantly reduced drug resistance, while parental cells overexpressing H19 showed markedly decreased drug sensitivity. In a nude mouse xenograft model, silencing H19 inhibited tumor growth, and the H19-silencing combined with paclitaxel group showed significantly better tumor suppression than paclitaxel alone, confirming the *in vivo* efficacy of the H19-targeting strategy in reversing paclitaxel resistance.

Additional chemosensitizing lncRNA targets have been reported in NPC. DYNLRB2-AS1 mediates gemcitabine resistance by inhibiting DHX9 ubiquitination and degradation, thereby enhancing DNA repair; its knockdown reverses gemcitabine resistance and restores chemosensitivity [24]. HOTAIR confers cisplatin resistance in NPC, and HOTAIR knockdown increases cisplatin sensitivity and promotes apoptosis [41]. Similarly, DLEU1 up-regulates BIRC6 expression to support cisplatin resistance, and its knockdown sensitizes NPC cells to cisplatin and suppresses tumor growth *in vitro* and *in vivo* [42].

9.2.3. lncRNA Targeting Combined with Immunotherapy

Immune checkpoint inhibitors (ICIs) have shown significant efficacy in recurrent/metastatic NPC, yet the overall response rate remains limited. In recent years, studies on lncRNA regulation of PD-L1 expression have provided a new theoretical basis for the "lncRNA-targeted combination with immunotherapy" strategy. Wang *et al.* [43] were the first to link lncRNAs with PD-L1 regulation. They found that HOXA-AS2 is significantly upregulated in NPC tissues and cell lines and positively correlated with the expression of HIF-1alpha and PD-L1. Functional experiments showed that HOXA-AS2 overexpression enhances the proliferation, migration, and invasion of NPC cells. Mechanistic studies confirmed that HOXA-AS2 directly binds miR-519, which simultaneously targets the 3' UTRs of both HIF-1alpha and PD-L1. Thus, HOXA-AS2 acts as a sponge

for miR-519, relieving its translational repression of HIF-1alpha and PD-L1, thereby simultaneously promoting hypoxia adaptation and immune evasion. This study revealed the "HOXA-AS2/miR-519/HIF-1alpha/PD-L1" axis, suggesting that targeting HOXA-AS2 may enhance anti-tumor immune responses by reducing PD-L1 expression, providing a theoretical basis for lncRNA-targeted combination with PD-1/PD-L1 blockade therapy. Yu *et al.* [44] not only elucidated the mechanism by which SNHG14 regulates PD-L1 but also innovatively developed a nano-delivery system. They found that SNHG14 is significantly upregulated in NPC tissues and positively correlated with PD-L1 expression. Mechanistic studies confirmed that SNHG14 regulates PD-L1 through the miR-5590-3p/ZEB1 axis: SNHG14 acts as a ceRNA for miR-5590-3p, relieving its repression of ZEB1; ZEB1, as a transcription factor, directly upregulates PD-L1 transcription while promoting EMT. In a nude mouse xenograft model, SNHG14 promoted NPC EMT by regulating the PD-1/PD-L1 pathway. The innovation of this study lies in the development of nano-coated si-SNHG14 (nano-coated si-SNHG14) as an anti-tumor agent: nanoparticle-encapsulated siRNA effectively solves the problems of *in vivo* delivery and stability of nucleic-acid drugs, and *in vitro* experiments confirmed that nano-si-SNHG14 significantly downregulates PD-L1 expression and inhibits EMT. This study was the first to achieve the "nanoparticle-delivered siRNA targeting lncRNA to downregulate PD-L1" strategy in NPC, providing a technical platform for the clinical translation of lncRNA-targeted combination immunotherapy.

9.2.4. Problems and Prospects of Combination Therapy Strategies

Although lncRNA-targeted combination therapy shows great potential in NPC, it still faces several challenges. First, most current studies remain at the cellular and animal-experiment stage, and no lncRNA-targeted drug has entered clinical trials for NPC. The clinical translation of nucleic-acid drugs needs to address key issues such as *in vivo* stability, delivery efficiency, off-target effects, and immunogenicity. Second, lncRNAs often have pleiotropic functions; a single lncRNA may simultaneously regulate multiple processes such as proliferation, migration and invasion, and resistance (e.g., HOTAIR regulates both migration/invasion and cisplatin resistance), requiring comprehensive evaluation of its systemic effects. Third, nano-delivery technology provides a feasible path to solve the delivery problem of nucleic-acid drugs, but local delivery to head and neck tumors and tumor targeting still need optimization. Fourth, lncRNA-targeted combination with immunotherapy is a highly promising direction, but current evidence is limited to basic research and still needs validation in immunocompetent mouse models and clinical cohorts.

10. Summary and Perspectives

This review systematically summarizes the regulatory roles of lncRNAs in the malignant biological behavior of NPC. Studies have shown that lncRNAs exert key regulatory functions in multiple aspects of NPC, including proliferation, migra-

tion, invasion and metastasis, resistance to chemoradiotherapy, apoptosis and autophagy, and metabolic reprogramming. In terms of mechanisms, the ceRNA network is among the most frequently invoked mechanisms by which lncRNAs regulate NPC-though its apparent predominance may partly reflect reporting bias, and a proposed ceRNA axis requires supporting evidence for expression abundance, subcellular co-localization, direct miRNA binding, and target-gene rescue-in addition to signaling pathway regulation (p53, Wnt/beta-catenin, Hippo/YAP, Rho/Rac, TGF-beta, PI3K/AKT, etc.), epigenetic modifications (LSD1/EZH2-mediated histone modifications), and mRNA stability regulation (e.g., HuR/beta-catenin mRNA). Notably, several lncRNAs (including HOTAIR, AFAP1-AS1, PVT1, ILF3-AS1, and FOXD1-AS1) have been proposed as candidate diagnostic and prognostic biomarkers in NPC, although most require independent validation in large clinical cohorts before clinical use, and the finding that targeting specific lncRNAs can reverse chemoradiotherapy resistance in preclinical models provides novel insights for the development of NPC combination therapy strategies. Overall, lncRNAs have gradually evolved from early mere "functionally associated molecules" into candidate diagnostic and therapeutic targets for NPC with clear mechanistic implications and clinical translation prospects.

Although significant progress has been made in this field, several bottlenecks urgently need to be addressed. Most existing studies are *in vitro* cell experiments and a limited number of animal experiments, lacking systematic validation by large-scale multicenter clinical cohorts; the biomarker value of most lncRNAs has been evaluated in only dozens to slightly over a hundred samples, resulting in very limited statistical power. Meanwhile, mechanistic studies of lncRNAs mostly focus on isolated exploration of a single lncRNA-miRNA-mRNA axis, lacking integrated analysis of systematic ceRNA networks and lncRNA-protein interactomics, and the panoramic map of the lncRNA regulatory network in NPC has not yet been truly established. In addition, research on the role of lncRNAs in regulating the NPC immune microenvironment is scarce, yet NPC itself is characterized by abundant lymphocyte infiltration, making it an urgent direction to explore how lncRNAs regulate tumor-immune interactions; studies on lncRNA regulation of lipid and amino acid metabolism in NPC also remain a blank, and the full picture of metabolic reprogramming awaits revelation.

Based on the above analysis, future research on lncRNA regulation in NPC can be advanced synergistically at multiple levels. At the clinical level, multicenter prospective cohort studies should be conducted to systematically validate the diagnostic and prognostic value of candidate lncRNA biomarkers and to promote the clinical translation of lncRNA detection kits. At the mechanistic level, high-throughput sequencing technologies such as RNA-seq, CLIP-seq, and RIP-seq, combined with systems biology approaches, can be used to construct panoramic lncRNA-miRNA-mRNA and ceRNA networks in NPC, revealing the systematic regulatory logic of lncRNAs. At the tumor-immunology level, the regulatory roles of lncRNAs in immune cells such as tumor-associated macrophages, T cells, and

NK cells should be deeply explored, and novel strategies for lncRNA-targeted combination immunotherapy should be developed accordingly. At the metabolic level, the regulatory relationships between lncRNAs and NPC glycolysis, lipid metabolism, and amino acid metabolism need to be systematically dissected to clarify the intrinsic links between metabolic reprogramming and chemoradiotherapy resistance. At the therapeutic-translation level, lncRNA-targeted drugs based on ASOs and nucleic-acid delivery technologies should be actively developed to advance preclinical and clinical studies; meanwhile, the introduction of single-cell sequencing and spatial transcriptomics will strongly reveal the heterogeneous expression of lncRNAs in NPC tumor cell subpopulations and the microenvironment, providing a solid basis for precise targeted intervention. At the extracellular-vesicle level, the role of exosome-derived lncRNAs in intercellular communication and the formation of the pre-metastatic niche in NPC should also be explored, further expanding our understanding of the systematic regulatory network of lncRNAs.

In conclusion, as important regulatory molecules in the malignant biological behavior of NPC, lncRNAs hold promise as candidate biomarkers and therapeutic targets in the diagnosis, prognostic evaluation, and targeted therapy of NPC. With continuous advances in research technologies and ongoing preclinical and clinical translation, lncRNAs are expected to become an important component of precision medicine for NPC.

Author Contributions

He Zhiqun is responsible for literature search and review writing, while Mao Chenggang is in charge of revision and proofreading.

Conflicts of Interest

All authors declare no conflict of interest.

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