

Review Article

Long non-coding RNAs in the development, diagnosis and prognosis of nasopharyngeal carcinoma

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Abstract: Long noncoding RNAs (lncRNAs), which transcripts longer than 200 nucleotides, are lack of protein coding potential. Emerging studies have shown that lncRNAs play critical roles in carcinogenesis and progression, including human nasopharyngeal carcinoma (NPC). In this article, we first provide an overview on the molecular mechanisms of lncRNAs in NPC, and then discuss the influence of lncRNAs on the diagnosis and treatment of patients with nasopharyngeal carcinoma.

Keywords: Nasopharyngeal carcinoma, long non-coding RNAs, mechanisms, diagnosis, prognosis

Introduction

Nasopharyngeal carcinoma (NPC), which arises from the nasopharyngeal epithelium, has a complex aetiology, including genetic susceptibility [1], Epstein-Barr virus (EBV) infection [2] and chemical carcinogens [3].

NPC has an extremely skewed geographic distribution. It is an uncommon disease in most parts of the world, with an age adjusted incidence less than one per 100000. However, NPC is one of the most common malignant tumors in South-eastern China, with an annual incidence rate of 20-50 per 100000 males [4]. Nowadays a majority of NPC patients are in advanced stages when diagnosed although the advances of diagnosis methods. Furthermore, the therapeutic approach for NPC patients and the molecular biomarker for prognostic prediction still limited. Therefore, identifying more accurate biomarkers is essential for the advance of diagnosis and first-rate therapy strategies for NPC.

Generally defined as transcripts longer than 200 nucleotides in length, long noncoding RNAs (lncRNAs) are lack of protein coding potential [5, 6]. According to their location and ori-

entation, lncRNAs are subdivided into intergenic and intragenic lncRNAs. In nucleus, lncRNAs modulate gene transcription and mRNA splicing; while in cytoplasm, they influence RNA stability and microRNA (miRNA) activity [7, 8]. Recently, a variety of lncRNAs have been shown to be deregulated in cancers, such as HOTAIR [9], ANRIL [10, 11], BANCR [12] and HOTTIP [13]. Emerging studies have shown that long noncoding RNAs (lncRNAs) play critical roles in carcinogenesis and progression by modulating the expression of many oncogenes or tumor suppressor genes, including in human nasopharyngeal carcinoma. In addition, the deregulated expression of these lncRNAs has been associated with prognosis or altering the sensitivity or resistance of cancer cells to various therapies.

In this review, we summarize the function and mechanism of different lncRNAs in the progression of NPC, and presented their clinical application in the diagnosis and prognosis of NPC. We also provide a report on how lncRNAs may alter the efficacy of NPC therapy and as novel therapeutic targets for overcoming chemoresistance and radiation resistance (**Table 1**). Ultimately a better understanding of the func-

LncRNAs in nasopharyngeal carcinoma

Table 1. The characteristics and functions of lncRNAs in NPC

LncRNA and References	Expression	Relevant targets or pathway	Functions	Applications
ROR [16]	↑	P53, E-cadherin, Vimentin, N-cadherin	Proliferation↑, apoptosis↓, metastasis↑, invasion↑	Dignostic and prognostic biomarker, resist-chemotherapy
XIST [19]	↑	miR-24a-5p-E2F3	Proliferation↑	NA
ANRIL [20]	↑	Glut1/LDHA	Proliferation↑	NA
EWSAT1 [22]	↑	MiR-326/330-5p-cyclin D1	Proliferation↑	Dignostic and prognostic biomarker
MEG3 [24]	↑	P53	Proliferation↓, apoptosis↑	NA
LOC553103 [25]	↑	EBV-miR-BART6-3p	Metastasis↑, invasion↑	NA
HNF1A-AS [26]	↑	EMT	Metastasis↑, invasion↑	NA
NEAT1 [27]	↑	MiR-204/ZEB1 axis	Metastasis↑, invasion↑	Dignostic and prognostic biomarker, radio-resistance
NAG7 [28]	↑	H-ras/p-c-Raf, JNK2/AP-1/MMP1	Metastasis↑, invasion↑	NA
AFAP1-AS1 [32]	↑	GTPase	Metastasis↑, invasion↑	Therapeutic target and prognostic biomarker
Hotair [37, 46]	↑	GRP78, VEGFA, Ang2	Angiogenesis↑	Therapeutic target and prognostic biomarker
LOC401317 [43]	↑	P21, P53	Apoptosis↑	Therapeutic target
LET [44]	↓	EZH2	Proliferation↑, apoptosis↓	Therapeutic target and prognostic biomarker
LINC00312 [45]	↓	EBER-1	Ppoptosis↓	Dignostic and prognostic biomarker
n375709 [47]	↓	NA	NA	Paclitaxel sensitivity
GAS5 [48]	↑	NA	NA	Prognostic biomarker
MALAT1 [49]	↑	MALAT1/miR-1/slug axis	NA	Radio-resistance

tional roles of lncRNA in NPC can translate to the development of novel strategies for the treatment or prevention of nasopharyngeal carcinoma.

LncRNAs in cancer cell growth and survival

Accumulating evidence suggests that many dysregulated lncRNAs play a vital role in tumor genesis via regulating gene transcription or post-transcriptional regulation [14, 15]. Some recent studies have elucidate the underlying mechanisms about the roles of lncRNAs in carcinogenesis and cancer progression in NPC. Li et al [16] reported that lncRNA-ROR can promote cell proliferation and reduce the apoptosis of NPC cells via suppressing the cellular p53 level after DNA damage. X-inactive specific transcript (XIST) was found overexpressed in several tumors and might act as oncogenic role, including in hepatocellular carcinoma [17], non-small cell lung cancer [18] and pancreatic Cancer [14]. Song et al [19] provided evidence that in NPC, lncRNA XIST promotes the cancer cell growth through miR-34a-5p-E2F3 axis, and specifically, lncRNA XIST expression was significantly related with tumor sizes and the stage of tumor development.

LncRNA ANRIL, which initially identified from familial melanoma patients, was higher in nasopharyngeal carcinoma than in normal tis-

sues [20]. Zou et al [20] demonstrated that ANRIL expression correlated with the clinical stage and locoregional recurrence, except age, sex, T classification, N classification or distant metastasis. LncRNA ANRIL may promote cell proliferation and transformation via stimulate the stem cell properties of NPC. Besides, in the present study, they found that there is a strong positive relationship between ANRIL and Glut 1 or LDHA, which were essential genes in glycolysis metabolism, in other words, lncRNA ANRIL can reprogram glucose metabolism via increasing glucose uptake for glycolysis to produce more ATP to promote NPC cell proliferation and transformation. They also identified that these processes may be regulated by the mTOR signal pathway. This study is the first to demonstrate that in NPC, ANRIL promotes proliferation via inducing stem-like cancer cells and reprogramming glucose metabolism. In other cancers such as cervical cancer, western blot indicated that the PI3K/Akt pathway was found to be inactivated after ANRIL inhibition, but whether this mechanism exists in NPC is unknown [21]. Therefore, future studies should investigate in lncRNA ANRIL mechanism and whether they can be targeted as part of a strategy to control NPC progression.

Another lncRNA related to NPC cell proliferation is Ewing sarcoma associated transcript 1 (LINC00277, NR_026949, EWSAT1), which is a

kind of lncRNA located on chromosome 15, has been found over-expressed and acted as an oncogenic regulator in Ewing sarcoma [22]. Marques et al [22] demonstrated that EWSAT1 also highly expressed in NPC tissues than that of in normal tissues. EWSAT1 overexpression increased nasopharyngeal carcinoma cell proliferation, while knockdown reversed it. In addition, they verified that lncRNA EWSAT1 take part in the ceRNA regulatory network and act as endogenous miRNA to regulated miR-326/330-5p. Their results revealed that miR-326/330-5p targets cyclin D1, and verified that EWSAT1's oncogenic functions are via negative regulation of miR-326/330-5p clusters partially. In summary, EWSAT1 facilitates the NPC oncogenesis and progression via the regulation of miR-326/330-5p-cyclin D1 axis. The findings verified the underlying mechanisms of EWSAT1 and imply that EWSAT1 was expected to be a therapeutic target in clinical practice. In the present study [23], EWSAT1 plays a critical role in cell progression and metastasis of osteosarcoma cells through regulation of MEG3 expression. However, the underlying mechanisms in NPC have remained unknown so far.

Unlike the above lncRNAs, Wing-Po et al [24] found that MEG3 overexpression could inhibit the proliferation and tumorigenicity of NPC cells. In the soft-agar assay, NPC cells overexpressed with MEG3 displayed fewer colonies with smaller size than those in the controls. P53 is well known to be an essential molecule in controlling apoptosis and cell cycle checkpoint, through an additional luciferase reporter assay, they also revealed the association between MEG3 activity and the p53 signaling cascade. Nevertheless, how lncRNAs participate in NPC onset remains largely unknown.

LncRNAs in invasion and metastasis

Invasion and metastasis are important biological behaviors of all cancers, making chemical therapy and other treatments useless. Because of the IMRT and CRT adoption, the result of locoregional control is satisfactory, but invasion and metastasis has been the main cause of treatment failure. Therefore explore the mechanisms of cancer invasion and metastasis is necessary to develop new diagnostic and therapeutic techniques.

Epithelial and mesenchymal transition (EMT) was a process characteristic by reprogramming of epithelial cells into a mesenchymal cells phenotype. There were numerous studies suggested that EMT played an important role in cancer cell mobility, which finally led to metastasis in cancer. Li and his colleagues [16] clarified that lncRNA-ROR was closely associated with the apoptosis and metastasis of NPC. Through using western blotting, they found that the epithelial markers E-cadherin were upregulated, whereas the mesenchymal markers N-cadherin and vimentin were down regulated in NPC. Bao et al [25] verified that through targeting and downregulating LOC553103, EBV-miR-BART6-3p could inhibit invasion and metastasis of NPC cells and change the integrity of stress fiber, leading to the upregulated expression of E-cadherin, as well as down-regulated N-cadherin, Snail, β -catenin and so on. Similar to the above lncRNAs, HNF1A-AS was also reported to be positively associated with EMT [26]. Another study [27] revealed that NEAT1 was upregulated in NPC and NEAT1 regulated radioresistance and EMT phenotype via regulating the miR-204/ZEB1 axis.

Recently, Huang et al [28] revealed that NAG7 suppresses ER α expression and stimulates NPC cell invasion through regulating the JNK2/AP-1/MMP1 and H-ras/p-c-Raf pathways in NPC cells. Through several experiments, they found that NAG7 enhanced the adhesion effect to extracellular matrix (ECM) proteins (Matrigel and fibronectin) markedly in NPC cells. In the present study, NAG7 overexpression increased the expression of H-Ras in NPC, which cause the activation of p-c-Raf, but have no influences on c-Raf, K-Ras and N-Ras [28]. These results demonstrated that the NAG7 promote the invasiveness and metastasis of NPC via regulated the H-ras/p-c-Raf pathway.

Another example is lncRNA AFAP1-AS1, which was found to be upregulated in various cancer types such as hepatocellular carcinoma (HCC) [29], gallbladder cancer [30] and esophageal squamous cell carcinoma [31]. In NPC and lung cancer cells, some reports demonstrated that NPC cells acquire metastasis and invasive via the focal adhesion change, the actin cytoskeleton reorganization and cell-cell junctions disruption [32, 33]. Present study [29] found that through the upregulation of RhoA/Rac2,

AFAP1-AS1 might promote the HCC cell progression. Other studies [30] indicated that lncRNA AFAP1-AS1 might promote gallbladder cancer cells invasion through inducing an EMT process. Nevertheless, the exact underlying mechanisms by which the lncRNA AFAP1-AS1 regulated NPC metastasis and invasion still unknown, understanding the exact molecular mechanism will be helpful for NPC treatment by targeting the lncRNA AFAP1-AS1.

In summary, lncRNAs can affect NPC invasion and metastasis through EMT, MAPK and/or GTPase pathway. However, the specific molecular mechanism of lncRNAs in NPC remains to be further studied. Based on these findings, future exploration in NPC may discover new diagnostic biomarkers or targeted therapies.

LncRNAs in angiogenesis

Angiogenesis is a universal characteristic in various human cancers and plays an essential role in cancer progression. It is described as a complex process, in which new microvessels sprout from the vasculature endothelial cells, the new microvessels proliferate, migrate and differentiate to tubular structures [34]. Therefore, anti-angiogenesis has been regarded as an attractive therapy to cancers. Among many growth factors that mediate angiogenesis, VEGF is the key regulator in the tumor angiogenesis and angiopoietin 2 (Ang2) plays a particular role in vessel maturation [35, 36]. In addition, the expression and secretion of VEGFA and Ang2 was suppressed by Hotair knockdown in NPC cells, which provides powerful evidence that silencing of Hotair acts as an anti-angiogenesis agent to NPC carcinogenesis [37].

Glucose regulated protein 78 (GRP78), which belongs to the heat shock protein 70 family, shows drug-resistant and anti-apoptotic in many tumors such as liver cancer, breast cancer, and colon cancer [38-41]. Furthermore, GRP78 silencing suppressed the angiogenesis in colon cancer and modulated tumor microenvironment during the tumor growth and metastasis [42]. Collectively, GRP78 can be a potent therapeutic target for anticancer therapy. Fu et al [37] demonstrated that GRP78 was an anti-angiogenic target of Hotair in NPC cells. The knockdown of GRP78 could achieve a similar response as siHotair treatment and Hotair

overexpression reversed the suppressive effect of siGRP78 on cell proliferation and angiogenesis. On the other hand, GRP78 overexpression rescued the siHotair-induced cell growth suppression in NPC cells. Altogether, Hotair may function as a therapeutic candidate in NPC via suppressing GRP78. These findings demonstrated that Hotair might be a promising diagnostic biomarker and therapeutic target for NPC. Therefore, disruption of the Hotair-mediated angiogenesis is highly promising for developing therapeutic strategies for NPC patients.

However, the study of lncRNAs in regulating angiogenesis in NPC is not enough, we should put more efforts on the angiogenesis mechanisms in the initiation and progression of NPC.

LncRNAs in cell apoptosis

Apoptosis is an important biological behavior of all malignancies, making chemotherapy and radiotherapy useless. Some results verified that lncRNAs play a pivotal role in NPC cell apoptosis.

Among the p53-regulated lncRNAs, Gong et al [43] found that LOC401317 overexpression may inhibit the NPC cell cycle via cyclins and p21, and may induce apoptosis via the caspase-dependent mechanism. Additionally, they revealed that LOC401317 is directly transcribed by p53 and that overexpression of LOC401317 inhibits NPC progression and inducing apoptosis. These findings verified that it is a new member in the p53 regulatory network and it may be a therapeutic target in NPC. However, the detailed mechanisms how LOC401317 functions in the p53 regulatory network remains unknown and will be the focus of future studies.

Bioinformatics analysis by Sun et al [44] revealed that lncRNA-LET was down-regulated in NPC cells and tissues. Decreased expression of lncRNA-LET is significantly correlated with tumor size, lymph node metastasis, clinical stage, and prognosis of NPC patients. Present study demonstrated that LET overexpression inhibited tumor cell proliferation and induced cell apoptosis. Moreover, the enhancer of zeste homolog 2 (EZH2) repressed LET expression through H3K27 histone methylation.

In summary, our studies demonstrated that lncRNA play a pivotal role in NPC proliferation

and apoptosis. However, there is limited knowledge about lncRNAs related to NPC apoptosis, and further investigations are needed to elucidate the molecular mechanism in NPC tumorigenesis and apoptosis.

Potential utility of LncRNAs in NPC

LncRNAs in NPC diagnosis and prognosis

Although radiotherapy have been improved in the treatment of NPC, the therapeutic outcome of advanced NPC patients remains unsatisfactory. Because of the non-specific clinical expression and the difficulty of making a clinical examination, most patients with the disease are diagnosed in advanced stage (stages III and IV), so it is urgent to search new NPC biomarkers and prognostic factors related to the outcome of NPC patients.

When validated AFAP1-AS1 expression using qRT-PCR, Bo et al [32] found that when compared with 7 non-tumor nasopharyngeal epithelium samples, lncRNA AFAP1-AS1 was highly expressed in 23 NPC samples. The data indicated that AFAP1-AS1 expression was positively correlated with distant NPC cell metastasis and had a non-significant association with advanced tumor stage. In addition, the upregulation of AFAP1-AS1 was closely related with poor prognosis, suggesting that it may be a useful biomarker for the NPC prognosis prediction, indicating that further investigation of AFAP1-AS1 may lead to the development of novel NPC diagnosis and prognosis methods. Another studies concentrating on NEAT1 had the same conclusion, NEAT1 expression was negatively associated with overall survival time but positively associated with more advanced clinical stages in NPC patients [27]. The abnormal expression of lncRNAs in NPC provides new cues for understanding the mechanism of tumorigenesis and shows a potential prognostic value in NPC.

Zhang et al [45] demonstrated the correlation between LINC00312 and the clinical pathological characteristics of nasopharyngeal carcinoma, they reveals that LINC00312 was negatively correlated with clinical stages and tumor size, while positively correlated with lymph node metastasis, and there is no relationship with age, gender, histological types, and recurrence. In addition, because of the unique fea-

ture of NPC which is strongly associated with EBV, they analyzed the relationship between LINC00312 and EBV, finding that LINC00312 was closely associated with the EBV-encoded small RNA EBER-1. In summary, LINC00312 could be a potential biomarker for progression, metastasis and prognosis in NPC.

Through using real-time PCR to quantify the expression levels of HOTAIR in NPC and non-cancer specimens, Fu et al [46] verified that the expression of HOTAIR were positively correlated with tumor size, clinical staging, lymph node tumor burden and distant metastasis. Besides, they found that the specificity and sensitivity of HOTAIR was improved in the advanced stage subgroups. These results suggest that HOTAIR be used to predict the prognosis of advanced-stage NPC patients.

In summary, these studies may provide novel diagnostic and prognostic biomarkers for NPC patients. In light of these, the more precise molecular signatures as well as underlying molecular mechanisms about NPC tumorigenesis, development and metastasis remains to be broadly illuminated.

LncRNAs in NPC therapy

More and more studies presents for further investigation into lncRNAs, leading to effective NPC therapeutic strategies. More than 60% of NPC patients are in advanced stages at diagnosis or even with metastasis. Therefore, there is still an urgent need to identify novel diagnostic biomarkers for early diagnosis as well as therapeutic targets for NPC patients. The targeted therapy will provide new insight into its pathogenesis.

Recently, there has been a renewed interest in the re-exploration of induction chemotherapy (IC) and concurrent chemotherapy in NPC since intensity-modulated radiotherapy (IMRT) are not enough to prevent distant metastasis. Chemotherapy drug resistance limits the therapeutic efficiency of cancers, therefore it is necessary to find therapeutic targets associated with Chemotherapy drug resistance. Li et al [16] demonstrated that lncRNA-ROR can promote the proliferation of NPC cells with DDP. Inhibition of lncRNA-ROR significantly reduced cells' ability to resist chemotherapeutic drugs via p53 signal pathway. Using paclitaxel cyto-

toxic assays, Ren et al [47] verified that inhibition of n375709 increased the paclitaxel sensitivity.

Distinguished by its unique clinical and pathologic characteristics, radiotherapy is the standard treatment of NPC. In the clinical therapeutics, NPC is usually resistant to radiotherapy, limiting the therapeutic efficacy and prognosis of NPC patients. When evaluate levels of lncRNA GAS5 in the treatment response in head and neck cancer patients treated with radical chemoradiotherapy (CRT), Fayda et al [48] found that patients with CR had lower GAS5 expression compared to those with PR/PD. Besides, Lu et al [27] revealed that through the regulation of EMT pathway, NEAT1 downregulation led to radiosensitivity of NPC. Moreover, Jin et al [49] found that there was reciprocal repression between miR-1 and MALAT1, and verified the important role of MALAT1/miR-1/slug axis on radioresistance in NPC.

When investigated lncRNA expression with the effects of curcumin (Cur) on the NPC cells, Wang et al [50] showed that IR-induced lncRNAs were reversed during Cur-enhanced radiosensitization in NPC cells, suggesting that lncRNAs have important functions in IR-induced radioresistance.

In terms of that most NPC patients is diagnosed at an advanced stage, the therapeutic approaches remain limited and the clinical outcome is still unsatisfactory. Therefore, it is urgently needed to develop effective diagnostic biomarkers as well as novel therapeutic targets for NPC patients.

Prospective

Nasopharyngeal carcinoma (NPC) is a prevalent tumour of the head and neck, with a complex aetiology. Because of the non-specific characteristic of the clinical manifestation, most NPC patients are diagnosed when the tumour has reached an advanced stage. Although the molecular basis of cancer has been widely studied, our knowledge of the molecular mechanisms of carcinogenesis and progression of cancer is deficient and the development of new therapeutics has been slow. Consequently, the outcomes for patients with NPC have remained dismal. It is therefore urgent to find a novel bio-

marker and therapeutic target for the diagnosis and prognostic prediction of NPC.

Here, we provide a summary on the molecular mechanisms of lncRNAs in NPC, and discuss their functions in tumor cell progression, invasion, metastasis, angiogenesis, apoptosis and clinical practice. A better understanding of the mechanisms of lncRNA in NPC can ultimately translate to the development of novel, lncRNA-based diagnostic, prognostic and therapeutic strategies for NPC. In conclusion, lncRNAs are involved in the initiation and development of NPC, further study should be conducted to verify the molecular mechanism of lncRNAs underlying NPC carcinogenesis.

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Disclosure of conflict of interest

None.

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