

The Research Progress of Long Noncoding RNAs in Nasopharyngeal Carcinoma

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Abstract

Long noncoding RNA (lncRNA) is a leader of the degree of more than 200 nucleotides, almost do not have the function of protein coding endogenous RNA molecules. Recent studies show that, lncRNA is not encoded protein, but it has a wide range of biological functions, and lncRNA in human diseases, especially in oncology, more and more attention has been paid to its role. Nasopharyngeal carcinoma (NPC) is a common malignant tumor of the head and neck in South China, which poses a serious threat to people's health and life. Studies found that lncRNA is widely involved in the invasion, metastasis and prognosis of nasopharyngeal carcinoma (NPC). In this article, we will review the research progress of lncRNA in nasopharyngeal carcinoma.

Keywords

Long Non-Coding RNA(lncRNA), Nasopharyngeal Carcinoma(NPC), Abnormal Expression, Research Progress, Regulation Mechanism

1. Introduction

Nasopharyngeal carcinoma is one of common head and neck malignant tumors in China, which is a kind of malignant tumor which occurs in the nasopharyngeal epithelium. It has obvious geographic differences, the highest rates in southern China's Guangdong area, therefore, nasopharyngeal carcinoma also known as "Guangdong carcinoma" [1]. Because of nasopharyngeal carcinoma is mainly located at the top and lateral wall of nasopharynx, relatively hidden, when the early onset of symptoms is not obvious, or lack of specificity, and is easy to be ignored by the patients. And the vast majority of poorly differentiated nasopharyngeal carcinoma, malignant degree is high, easy early cervical lymph node and distant metastases, most patients were advanced nasopharyngeal car-

cinoma on symptoms or when they see a doctor [2]. Nasopharyngeal carcinoma is generally sensitive to radiotherapy. Although with the development of medical imaging technology progress, at present the main approaches of radiotherapy for nasopharyngeal carcinoma, greatly improve the local control of nasopharyngeal carcinoma and 5 years survival rate, but frequent tumor recurrence and poor prognosis for clinical is still a great challenge [3]. The etiology of nasopharyngeal carcinoma is still unknown, and many years of research at home and abroad confirmed that nasopharyngeal carcinoma may be related to EB virus infection, environmental chemical carcinogens (such as nitrosamines) and genetic factors [4]. But what is certain is that the development of nasopharyngeal carcinoma is the development of the many factors, many steps, and multiple genes involved in the result. However, gene expression changes in which plays a vital role. Studies have shown that in recent years [5] [6] [7] [8] [9], the abnormal expression of lncRNA in many tumors is closely related to the proliferation, differentiation and migration of tumor cells. So the lncRNA differentially expressed in nasopharyngeal carcinoma and its potential regulation and control mechanism for the diagnosis, treatment and prognosis of nasopharyngeal carcinoma has extremely important clinical application value [10].

2. Biological Characteristics of lncRNA

Long non-coding RNA (lncRNA) is transcribed by RNA polymerase II, with a transcription length greater than 200 nucleotides, similar in structure to mRNA. lncRNA does not have an obvious open reading frame and does not participate in or is rarely involved in coding proteins. However, lncRNA is a class of endogenous RNA that regulates the expression of genes. It is located in the nucleus or cytoplasm, and its expression is tissue-specific and spatiotemporal [11] [12]. In comparison with other noncoding RNA, lncRNA has “more than and 3” characteristics, namely multi type, multi number and mode of action [13] [14]. lncRNA was first discovered in 2002, Okazaki *et al.* [15] found a new transcript of DNA (complementary DNA) on a large scale sequencing in mice, namely lncRNA. However, lncRNA has been regarded as the “noise” of gene transcription since it was discovered, and it is a by-product of Pol II transcription [16], and for a long time, researchers have not paid enough attention to it. Later, with the in-depth study, more and more evidence indicates that as a kind of important biological macromolecules, lncRNAs is involved in many biological processes [17]. Although lncRNA does not encode proteins, it has high tissue specificity, which can regulate gene expression from epigenetic, transcriptional and post transcriptional levels [18] [19] [20] [21] [22]. Moreover, many studies have confirmed that lncRNA is involved in various aspects of gene regulation, such as gene imprinting, epigenetic regulation, transport between nucleus and cytoplasm, mRNA splicing and translation. Through these regulation, lncRNA involved in a variety of biological processes, including: cell growth, proliferation, and apoptosis [23] [24], especially the regulation of tumor cell proliferation, apoptosis, invasion, metastasis, etc. According to their different biological func-

tions, lncRNA can be divided into four categories: 1) enhancer lncRNA; 2) as the primary miRNA transcripts of lncRNA; 3) as the primary piRNA transcripts of lncRNA; 4) the competition of endogenous lncRNA.

The production of lncRNA mainly through the following 5 ways [25]: 1) Protein coding gene disruption; 2) Chromatin rearrangement; 3) In the process of non coding gene duplication, the role of gene duplication; 4) Local replicon tandem; 5) Insertion transposable element.

Depending on the point of view, lncRNA may have a different classification. Mercer *et al.* [26] divides the lncRNAs into 5 classes according to the location and relative orientation of the genes in the genome: 1) sense lncRNAs: overlap of one or more exons of another transcription on a synonym chain; 2) antisense lncRNAs: overlapping exons of transcription on antisense strand; 3) bidirectional lncRNAs: the transcription start site of lncRNAs is very close to the transcription start site of the adjacent coding transcripts on the complementary strand lncRNAs; 4) intron lncRNAs: an intron derived entirely from another; 5) lincRNAs lncRNAs: Between the 2 coding protein genes. Laurent *et al.* [27] according to their different biological functions, lncRNA is divided into four categories: 1) lncRNA with enhancer action; 2) MiRNA as a primary transcript of lncRNA; 3) PiRNA as a primary transcript of lncRNA; 4) Competitive endogenous lncRNA. According to the different roles in the DNA sequence, lncRNA can be divided into cis regulatory lncRNA and trans regulation lncRNA [28]. According to the molecular mechanism of, it can be divided into signal molecules, decoy molecules, scaffold molecules, and molecules [29].

3. The Mode of Action and Regulation Mechanism of lncRNA

lncRNA regulates gene expression in a variety of ways and mechanisms, can be divided into the following categories:

3.1. Chromatin Remodeling

DNA replication, transcription, repair and recombination are both occurred at the chromatin level. In these processes, chromatin remodeling can lead to changes in the position and structure of nucleosomes, resulting in chromatin changes. Chromatin state, however, is a key factor in transcriptional activity, including changes in nucleosome structure and covalent modifications of histones. Some lncRNAs can regulate the expression of genes by affecting the state of chromatin, such as lncRNA HOTAIR (homeobox gene RNA antisense gene) transcription from the homeobox gene C (HOXC) sites, by raising the PRC2 complex, trans inhibition of homeobox gene D (HOXD) transcription sites. Tsai *et al.* [30] studies have shown that over expression of HOTAIR can cause the PRC2 complex to be repositioned in the whole genome, which makes some tumor suppressor genes silenced, thereby promoting the metastasis of cancer cells.

3.2. Transcriptional Regulation

Transcription regulation is by changing rate can change the level of gene expres-

sion. LncRNA can be regulated by a variety of mechanisms, including gene silencing, DNA damage activation, post transcriptional regulation and so on.

3.3. Precursor mRNA Splicing Regulation

Precursors shear refers to the process of removing unnecessary sequences of mRNA precursors in the nucleus and connecting the various parts of the shear. Studies found that long non-coding RNA-lung adenocarcinoma metastasis associated transcript 1 (MALAT1) plays a key role in the processing of mRNA precursors, and has a broad impact on human health.

4. LncRNA Related Databases

With the increasing attention to the lncRNA gene and the deepening of related research, more and more new lncRNA have been found. Databases that collect, organize and classify information about lncRNA genes are being taken seriously by researchers. In recent years, researchers have established several lncRNA related databases by combining bioinformatics techniques (Table 1) [31]-[39]. The establishment of these databases not only provides researchers with comprehensive information about lncRNA of various species, but also provides a very important platform for the study of the regulatory relationship between lncRNA and nasopharyngeal carcinoma.

5. The Research Status of lncRNA Associated with Nasopharyngeal Carcinoma

The following is the current studies have found lncRNA are closely associated with nasopharyngeal carcinoma (Table 2).

5.1. H19

H19 gene is the first tumor related lncRNA was found, which is located on human chromosome 11p15.5, length of 2 - 3 kb, a total of 5 exons and 4 introns, is one of the earliest identification of imprinted genes. It shows the characteristics

Table 1. lncRNA-related database.

Database	Website	References
Noncoding RNA database	http://biobases.ibch.Poznan.pl/ncRNA/	[31]
fRNAdb	https://www.ncrna.org/	[32]
NRED	http://jrm-research.lmb.uq.edu.au/nred/cgi-bin/ncrnadb.pl	[33]
lncRNAdb	http://www.lncrnadb.org/	[34]
ncFANs	http://www.ebiomed.org/ncFANs/	[35]
NONCODE	http://www.noncode.org/NONCODERv3/	[36]
ChIPBase	http://deepbase.sysu.edu.cn/chipbase/	[37]
LNCipedia	http://www.lncipedia.org	[38]
DIANA-LncBase	http://www.microrna.gr/LncBase	[39]

Table 2. Expression of lncRNA in NPC.

lncRNA	Tested biopsies	Biological functions	Expression in NPC	References
H19	Cell, tissue	Invasion, metastasis	Up-regulation	[40] [41]
HOTAIR	Tissue	Invasion, metastasis	Up-regulation	[41] [42] [43] [44]
LOC401317	Cell	Inhibit cancer cell proliferation	Down-regulated	[45]
MALAT1	Cell, tissue	Invasion, metastasis, radiation resistance	Up-regulation	[46] [47]
lncRNA-LET	Tissue	Inhibit cancer cell proliferation	Down-regulated	[48] [49]
lncRNA AFAP-AS1	Tissue, cell	Promote cancer cell proliferation, invasion and metastasis	Up-regulation	[50]
lncRNA-ROR	Tissue, cell	Invasion, metastasis, chemotherapy-resistant	Up-regulation	[51]

of paternally imprinted, selective expression of the maternal allele, the differentially methylated region is mainly affected by the upstream 4000 bp rich CpG island methylation regulation (DMR). H19 can regulate the growth and development of the embryo, but the expression of H19 is inhibited in the majority of tissues and organs after birth. H19 is mainly present in the cytoplasm and regulates gene expression in a regulated RNA or ribose regulator, and its first exon can encode miR-675. In recent years, studies have found that H19 in nasopharyngeal carcinoma in the presence of abnormal expression. Ng *et al.* [40], by using gene chip and Northern hybridization technology to determine the gene that is up-regulated in undifferentiated human nasopharyngeal carcinoma cell line CNE-2 is the human imprinted gene lncRNA-H19. However, H19 was down regulated in a well differentiated human nasopharyngeal carcinoma cell line HK1. The study also found that the low expression of H19 HK1 in the promoter region of H19 gene CpG locus (*i.e.* cytosine phospho guanine sites) showed a high degree of methylation, leading to transcriptional silencing, which lead to the low expression of H19 gene. And the expression of H19 was up-regulated by demethylation of HK1 cells. It is suggested that the methylation of the promoter region of the H19 gene may play an important role in the differentiation of human nasopharyngeal carcinoma cells and the transcription process of the imprinted gene. Zhang *et al.* [41] study found that the expression level of H19 in metastatic nasopharyngeal carcinoma tissues was higher than that in primary NPC tissues, the former was 1.8 - 3.0 times higher than that of the latter. Therefore, studies have shown that lncRNA H19 can promote the invasion and metastasis of nasopharyngeal carcinoma.

5.2. HOTAIR

HOTAIR, HOX transcription antisense RNA, as an important member of long-chain non-coding RNA, HOX transcription antisense RNA (HOTAIR) includes five long exons and one short exon. It is the first lncRNA to be found to regulate gene expression in antisense transcription, and is the first lncRNA found to be associated with tumorigenesis. It is highly expressed in a variety of tumors (such as breast cancer, liver cancer, etc.), mainly through chromatin remodeling, pro-

mote protein ubiquitination and as a miRNA sponge through the adsorption of miRNAs to achieve regulatory gene expression process. The homeobox gene (HOX), also known as type I homologous box gene, is a highly conserved homologous box gene of the abdominal B gene family. Its main types include HOXA, HOXB, HOXC and HOXD, its products can be combined with DNA, regulation of signal acceptance, apoptosis, differentiation, angiogenesis and other processes, in the embryonic development process plays an important role. In recent years, most studies have found that HOX gene involved in the development of a variety of human malignant tumors [42]. HOX transcript antisense RNA (HOA transcript antisense RNA, HOTAIR) is an elongation of about 2158nt, located in human chromosome 12 on the HOXC site lncRNA. HOTAIR mainly through the following ways to play its regulatory function [43]: 1) Through the interaction with histone methylase (PRC2) and demethylase (LSD1), to regulate chromatin dynamics and induce gene silencing; 2) Through competition with tumor susceptibility genes EZH2 binding PRC2; 3) Through the EZH2 phosphorylation to regulate its function; 4) Through the combination of E3 ubiquitin ligase to play its ubiquitination of protein; 5) By competing for endogenous RNA. Zhang *et al.* [41] compared the expression of lncRNA in primary nasopharyngeal carcinoma and metastatic nasopharyngeal carcinoma by using gene chip analysis. It was found that HOX transcribed antisense RNA was up-regulated in metastatic nasopharyngeal carcinoma, and increased the expression level in nasopharyngeal carcinoma tissues by 4 - 6 times. It shows that HOTAIR expression is likely to be closely related to the metastasis of nasopharyngeal carcinoma. Nie *et al.* [44] detected the expression level of HOX transcribed antisense RNA in cancer tissues and non-cancerous nasopharyngeal tissues by using real-time fluorescence quantitative PCR and in situ hybridization. The results showed that the expression level of HOX transcription antisense RNA in nasopharyngeal carcinoma was 5.2 - 48.4 times higher than that in non-cancerous nasopharyngeal tissues, and the larger the tumor volume, the more lymph node metastasis and the clinical stage of advanced nasopharyngeal carcinoma HOX The higher the expression level of transcribed antisense RNA, whereas the higher overall survival rate of patients with high expression of HOX transcribed antisense RNA was lower and the prognosis was worse. The above experimental study suggests that HOX transcribed antisense RNA plays a role in oncogenes in nasopharyngeal carcinoma and is associated with its malignancy. The study also shows that HOX transcribed antisense RNA may become a biological marker of nasopharyngeal carcinoma prognosis and survival test, and thus play an important role in the diagnosis and treatment of nasopharyngeal carcinoma.

5.3. LOC401317

P53 gene is one of the earliest tumor suppressor genes (or tumor suppressor genes), it can regulate a series of signal transduction pathways and thus widely

involved in the development of a variety of malignant tumors. A large number of studies have confirmed that p53 protein can regulate cell cycle and avoid cell carcinogenesis. Cong *et al.* [45] showed that 133 lncRNAs were up-regulated and 1057 lncRNAs were down-regulated by transgenic Pcmv-p53 vector expressing p53 gene into nasopharyngeal carcinoma cell line HNE2 by gene chip technique, while lncRNA LOC401317 significantly elevated expression. It was also found that LOC401317 was directly regulated by p53 and inhibited the growth of CNE2 cells by blocking cell cycle G1/S and induced apoptosis, suggesting that LOC401317 could play an anti-tumor effect in nasopharyngeal carcinoma.

5.4. MALAT1

MALAT1, a lung adenocarcinoma metastasis-related transcript 1, located at 11q13.1, is a long chain non-coding RNA with a transcript length of more than 8000 nucleotides. MALAT1 was first discovered by scientists in the study of genes related to the metastasis of human non-small cell lung cancer. A large number of studies have found that MALAT1 in a variety of malignant tumors (such as lung cancer, colon cancer, pancreatic cancer, etc.) and the high expression of its survival rate was significantly correlated. The study also found that MALAT1 mainly through the regulation of apoptosis, regulation of cell cycle and affect cell epithelial mesenchymal transition, thus affecting the development of malignant tumors. Xie *et al.* [46] found that MALAT1 gene was highly expressed in high metastatic nasopharyngeal carcinoma cell lines and was low in normal nasopharyngeal epithelium using Real-time PCR. The expression of E-cadherin in CNE-1 cells was significantly down-regulated by MALAT1 over-expression in CNE-1 cells after transfection of CNE-1 cells by lentiviral vector. The expression of interstitial cell markers (E-cadherin) Vimentin) expression was significantly increased, the ability to invasion and metastasis was significantly enhanced, suggesting that MALAT1 can promote the invasion and metastasis of nasopharyngeal carcinoma. Jin *et al.* [47] have shown that MALAT1 is significantly up-regulated in nasopharyngeal carcinoma, and that MALAT1 gene can make nasopharyngeal carcinoma cells more sensitive to radiotherapy. MALAT1 can also be regulated by adjusting miR-1/slug axis Tumor stem cell activity and radioactivity resistance, suggesting that MALAT1 may be a therapeutic target for patients with nasopharyngeal carcinoma.

5.5. lncRNA-LET

lncRNA-LET (lncRNA Low Expression in Tumor) is a newly identified long-chain non-coding RNA located on 15q24.1 of human chromosome. The expression of lncRNA-LET is different from that of most lncRNA in malignant tumor tissues. It has been shown to down-regulate the expression of lncRNA-LET in cancerous tissues of hepatocellular carcinoma, gallbladder carcinoma, colorectal cancer, lung squamous cell carcinoma, esophageal squamous cell carcinoma, gastric cancer and nasopharyngeal carcinoma. The degree of down-regulation

was significantly associated with progression and prognosis of malignant tumors. Yang F *et al.* [48] found that hypoxia-induced histone deacetylase 3 inhibits the expression of the lncRNA-LET gene by reducing the histone-mediated role of the lncRNA-LET promoter region, resulting in down-regulation of LET should be combined with LET after ubiquitination modified by the degradation of the nuclear factor 90 protein stable, and thus induce cancer cells to attack. Sun *et al.* [49] collected 68 nasopharyngeal carcinoma and its adjacent non-cancerous nasopharyngeal tissue by real-time quantitative PCR detection and found that nasopharyngeal carcinoma group than non-cancer nasopharyngeal LET transcript expression was significantly reduced, and LET The lower the expression level, the higher the clinical stage of nasopharyngeal carcinoma, the greater the tumor, the more lymph node metastasis, the worse the prognosis of patients. After overexpression of the LET vector into the nasopharyngeal carcinoma cell line CNE2, it was found that the proliferation of CNE2 cells was inhibited significantly, and the interference of LET with siRNA could promote the proliferation and inhibit the apoptosis of nasopharyngeal carcinoma cells. Nasopharyngeal carcinoma CNE2 cells overexpressing LET were injected subcutaneously into nude mice, and the tumor volume was decreased in nude mice. Further study also found that the expression of LET by gene (enhancer of zeste homolog 2, EZH2) inhibited EZH2 expression by histone methylation of LET promoter region and indirect inhibition of LET. LET in nasopharyngeal carcinoma play an anti-tumor effect of the specific needs of more studies confirmed that through the LET on nasopharyngeal carcinoma cell therapy has yet to be further studied.

5.6. LncRNA AFAP-AS1

BO *et al.* [50] through 12 cases of nasopharyngeal carcinoma and 4 cases of non-cancer nasopharyngeal tissue gene chip analysis, the construction of nasopharyngeal carcinoma tissue lncRNA expression profile, from which screening and validation of AFAP1-AS1 in the nose Pharyngeal carcinoma in high expression, LncRNA AFAP-AS1 (actin filament associated protein 1 antisense RNA1) was identified and selected. Followed by in situ hybridization experiments and further studies on paraffin samples of large numbers of nasopharyngeal carcinoma, the results showed that AFAP1-AS1 was up-regulated in nasopharyngeal carcinoma and correlated with distant metastasis and poor prognosis of nasopharyngeal carcinoma. The high expression of AFAP1-AS1 in patients with overall survival and disease-free survival time was shorter in patients with lower expression of AFAP1-AS1, AFAP1-AS1 and the high expression of nasopharyngeal carcinoma with clinical stage, lymph node metastasis, distant metastasis and poor prognosis are closely related. In vitro experiments also showed that knockdown of AFAP1-AS1 significantly inhibited the migration and invasion of nasopharyngeal carcinoma cells, and increased the expression of AFAP1 protein. Therefore, lncRNA AFAP1-AS1 may be a new biomarker for predicting the prognosis of patients with nasopharyngeal carcinoma, and may be a potential therapeutic

target for NPC patients.

5.7. LncRNA-ROR

LncRNA-ROR is a newly identified lncRNA. Li *et al.* [51] found that LncRNA-ROR overexpression in human nasopharyngeal carcinoma and nasopharyngeal carcinoma cell lines and found that LncRNA-ROR expression levels were detected by RT-PCR. The expression of LncRNA-ROR in nasopharyngeal carcinoma (CNE2, CNE1, 5-8F, 6-10B) was also higher than that in normal nasopharyngeal epithelium NP69 high. Study further demonstrated that LncRNA-ROR by regulating the cell cycle and promote the proliferation of nasopharyngeal carcinoma cells by affecting the epithelial mesenchymal transition and promote cell migration and invasion of nasopharyngeal carcinoma, the study discovers the LncRNA-ROR through the P53 pathway to produce chemotherapy resistance in nasopharyngeal carcinoma cells.

6. Summary and Prospect

To sum up, lncRNA, as a gene that can directly affect cell signal transduction and cell proliferation and differentiation, and can directly change the biological characteristics of cells. Research confirmed that lncRNA and nasopharyngeal carcinoma are closely related, and has been expected to become an important member of the NPC for basic research. Research and exploration of this new type of molecular marker, not only contributes to the pathogenesis of NPC further understanding, so that we understand the NPC further, but also for the early prediction of disease, early diagnosis and prognosis evaluation. But for now, we explore that the molecular mechanism of interaction between lncRNA and nasopharyngeal carcinoma are few, and the research field of lncRNA in nasopharyngeal carcinoma compared with other malignant tumors with significantly less, still needs to further expand. So far, most of the researches on lncRNA and nasopharyngeal carcinoma (NPC) are focused on nasopharyngeal carcinoma tissues and nasopharyngeal carcinoma cells, and there is still a need to explore the relationship between lncRNA and nasopharyngeal carcinoma through blood or other pathways in NPC patients. It is clear that the causal relationship and effect mechanism between lncRNA and nasopharyngeal carcinoma, and its corresponding target gene interaction in tumorigenesis and development of tumor, which is also the lncRNA need to be solved in the research of nasopharyngeal carcinoma.

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