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Taking Nasopharyngeal Carcinoma as an example to explore the regulatory mechanism of long non-coding RNA on Epithelial-Mesenchymal Transition

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Abstract:

Recently, more studies are actively focusing on NPC and its regulation both at home and abroad. Notably, the quantity of research projects in this field shows an upward trend. However, the specific relationship between NPC and lncRNA only has a few research about its multiple biological factors like genes and signaling pathways. Also, only a limited number of studies are dedicated to this area. This article intends to fill this research gap by systematically searching and analyzing existing research results through literature review and eventually get the whole conclusion. First, the definition of lncRNA and principles of its functioning mechanisms are divided into three patterns. Second, the details regarding oncogenic lncRNA in NPC are given. Third, two core mechanisms of lncRNA are presented with the specific objective of showing the inherent relationship. This article provides theoretical basis and guidance for the treatment of cancer. And particularly offers new insights into and innovative perspectives on the treatment of NPC and other cancers.

Keywords: lncRNA; NPC; EMT; Tumor metastasis.

1. Introduction

Today, cancer is still a serious health burden worldwide. There are many types of cancer, such as lung cancer and breast cancer, which rank first in the mortality and incidence of men and women respectively. Although there are now many treatments and diagnostic methods, human beings still cannot completely solve this problem. Taking nasopharyngeal cancer (NPC) as an example, it is one of the many familiar types of cancer. It is commonly found in Southeast Asia and the southern and southwestern regions of China, such as Guangdong. Relevant studies also revealed its age-specific pathogenesis, and the incidence is highest among people aged 55-60 [1]. The overall incidence of men is higher than that of women, and the incidence of urban men is the highest among all groups. NPC occurs in the nasopharyngeal epithelial mucosa, and the prognosis is poor due to early distant metastasis. This problem remains a major obstacle to the long-term survival of all patients. Although a new generation of drugs and targeted treatments are currently prolonging the survival of these patients. For instance, the cisplatin as a bioalkylated agent and papyruxol as a plant-based drug. However, the treatment effect is limited, and the survival period after taking the drug is short. Therefore, there is an urgent need for more effective systemic treatment.

Epithelial-stromal transformation (EMT) plays a key role in tumour metastasis and invasion. EMT affects the dynamic changes of tumour cells, thus affecting the survival rate, metastasis and prognosis of cancer patients. Therefore, it is crucial to emphasise that the regulation of EMT by lncRNA is an important target for cancer treatment.

In recent years, the important role of long non-coding RNA (lncRNA) in the regulation of EMT has been gradually recognised by more and more studies and clinically. This also provides a new perspective for the mechanism of NPC metastasis researches. lncRNA is a non-coding transcript with a length of more than 200 nucleotides (>200 nt). It cannot encode proteins due to the lack of open reading boxes. However, it can regulate the expression of different genes and have a role in the metastasis of a variety of cancers. They are involved in chromosome remodelling mechanism, transcription gene regulation and post-transcription processing. They have been proven to be associated with a variety of developmental processes and human diseases.

This article focuses on exploring and deeply studying how lncRNA regulates genes and its mechanism in the control of EMT of NPC. At the same time, the clinical transformation potential of lncRNA is specifically explained.

2. The principles of lncRNA in gene regulation

2.1 The regulatory patterns

As lncRNA plays a crucial role in eukaryotic transcriptome, it plays a diverse and important regulatory role. Regulatory patterns are divided into three types: epigenetic regulation, transcriptional regulation, and post-transcriptional regulation [2].

2.1.1 Epigenetic regulation

It can guide DNA methylation modification. DNA methylation is a key inhibitory epigenetic marker, mainly catalysed by DNA methyltransferase (DNMTs). For example, Dum and H19 can promote the whole process by binding DNMTs and guiding them to the promoter region of target gene. At the same time, it directly acts on the chromatin of the RNA-DNA trihelix complex to bind to the DNA, affecting the state of the chromatin.

2.1.2 Transcriptional regulation

lncRNAs participate in all steps of the transcription process, thus affecting the overall gene expression. Studies have shown that mutations or chromosomal slocations of the lncRNA gene itself can affect EMT. Small changes in promoter activity after lncRNA gene translocation can lead to abnormal expression and regulation of EMT related genes. For example, the mouse imprint lncRNA Airn itself cannot encode proteins, but its transcription products can cover downstream promoters through cis-action.

2.1.3 Post-transcriptional regulation

Post-transcriptional regulatory lncRNAs can directly interact with proteins and nucleic acids to exert their functions. lncRNA can lead and combine with isolated and unique RNA-Binding Proteins (RBPs). This can influence those proteins' stabilities or translation regulation functions of mRNA. For instance, HuR prevents the production of oncogenes by binding to mRNA.

Therefore, the gene regulatory network consists of those three regulatory patterns which are independent but interconnected. In addition, the intervention of lncRNA has already realized the control of multi-dimensional and full process of gene regulation.

3. Taking nasopharyngeal carcinoma as an example to explore the regulatory mechanism of lncRNA on EMT

3.1 Oncogenic lncRNAs in Nasopharyngeal Carcinoma

lncRNAs are defined as non-coding transcripts longer than 200 nucleotides (>200 nt) [3]. They lack an open reading frame and cannot encode proteins. However, they are effective in regulating the expression of different genes in various cancer metastases. As figure 1 shows that the relationship of lncRNA regulation on the genome [4].

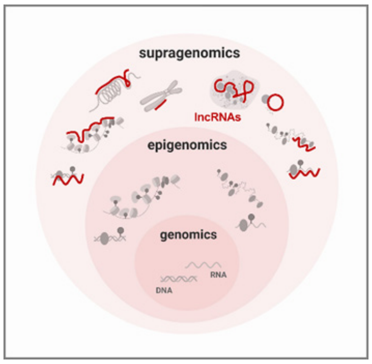

Fig. 1 The relationship of lncRNA regulation on the genome [4]

LncRNA ZFAS1 is located on chromosome 20q13.13 which is indicated by figure 2 [5]. The study found that ZFAS1 was negatively related to the survival rate. For instance, the survival rate of patients with high expression of ZFAS1 was lower than that of patients with low expression. ZFAS1 is up-regulated in the nasopharyngeal cancer cell line. And its expression level in nasopharyngeal cancer tissue is higher than that of neighbouring healthy tissues.

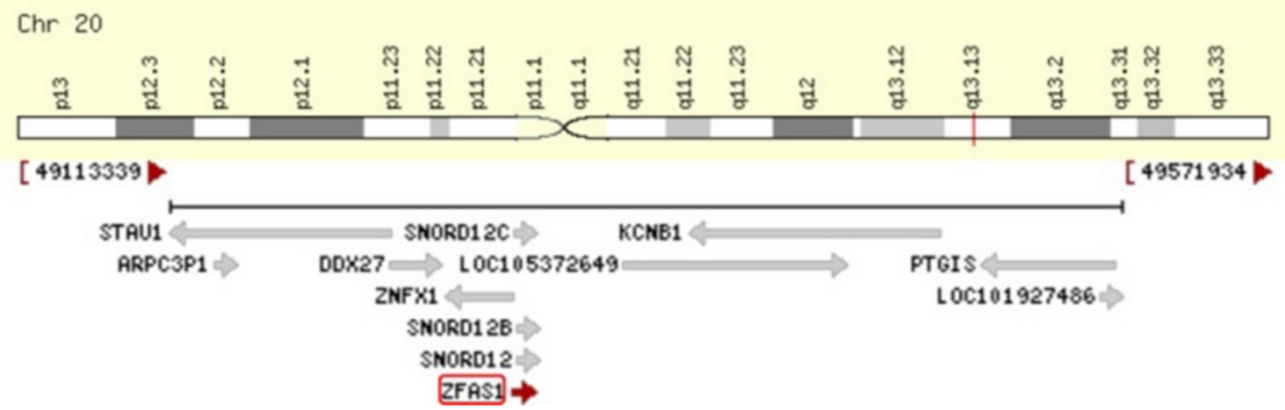

Fig. 2 The location of ZFAS1 [5]

Besides, the function of lncRNA in the cell nucleus is to regulate transcription programs through chromatin interactions and remodeling, and some scholars also temporarily localize the pathogenic gene within a 2 Mb region at 4q21 [6].

3.2 The core mechanisms of lncRNA regulates EMT

3.2.1 Competitive ceRNA mechanism regulates miRNA

Taking an example as H19, lncRNA H19, as an imprinting gene, was identified more than 2 decades ago. In recent years, it has been found to be linked to various cancers and tumor metastasis as the picture shown below. It also plays multiple roles in tumor progression through various mechanisms. It is also usually abnormally expressed in cancer cells [7].

Firstly, H19 promotes EMT by antagonistic microRNA (miRNA) activity. At the same time, as the competitive endogenous RNA of miRNA, it can regulate the expression of its downstream genes. Secondly, H19 regulates the expression of EZH2 by interacting with miRNA. So it can hinder the expression of epithelial E-cadherin and promote cell invasion [8].

The study illustrated that the expression level of H19 is negatively correlated with survival; patients with low H19 have significantly extended their length of survival. High levels of H19 are significantly associated with poor clinical outcomes as figure 3 has already shown [8]. What's more, the unnatural overexpression of H19 in NPC also predicts a poor prognosis.

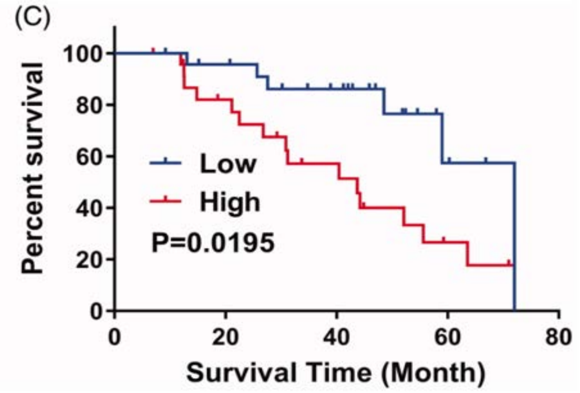

Fig. 3 Nasopharyngeal carcinoma patients with high H19 [8]

3.2.2 Other signaling pathways affect EMT

Take lncRNA small nucleon RNA host gene 1(SNHG1) as an example, which is a new type of carcinogenic lncRNA. It is also an important member of the SNHG family. It consists of a group of hosts that can be processed into small nucleated RNA and plays a biological role.

It comes in its function in cultivating tumor growth and always over express in diverse cancers. Some scholars found that it shows high levels of expression in NPC tissues and adjacent cells as figure 4 showed [9].

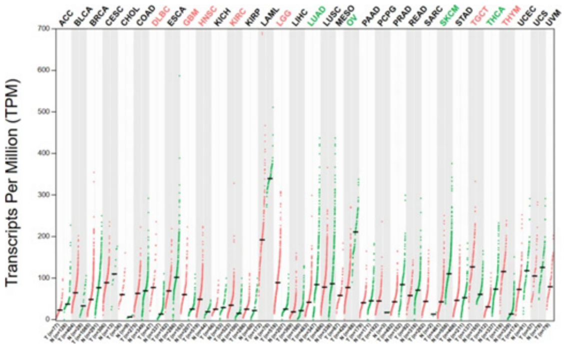

Fig. 4 Expression of SNHG1 in different cancers [9]

One study assumed that miRNA 145 acts as a target site of SNHG1. After that, subsequent luciferase experiments concluded that its expression is significantly upregulated compared to the control group. It also can be inhibited by SNHG1 in nasopharyngeal carcinoma [10].

The study found that there is a negative regulatory factor miR-154-5p in nasopharyngeal cancer. Experimental results show that NUAK1 is the target gene of miR-145-5p, so it significantly inhibits the fluorescein enzyme activity of NUAK1-UTR-WT. Thus promoting the expression of the target gene NUAK1. It works through the protein kinase B (PKB) signalling pathway and EMT. At the same time, it promotes the migration and invasion of NPC cells. And figure 5 showed that the indirect relationship between NUAk1 and EMT.

Fig. 5 The Indirect Relationship Between NUAk1 and EMT

(Picture credit: Original)

4. Clinical translational potential of lncRNA

4.1 A prognostic biomarker and targetin cancer

HOX transcript antisense intergenic RNA (HOTAIR) is a new type of lncRNA related to many diagnoses and cancers. And it is located on chromosome 12 as a specific lncRNA gene. Additionally, it is also the first gene confirmed to be capable of trans-regulation. It is abnormally expressed in various cancers. One research has proved that the HOXC Distal Enhancer (ERE) in the transcription start site of HOTAIR can control the expression of lncRNA [11].

The study of Yan Nie et al in 2013 showed that the level of HOTAIR expression in NPC tissue increased with clinical stage. And it is positively correlated with tumour size, lymph node metastasis and distant metastasis. High expression indicates that the patient's prognosis is poor. The same results have been confirmed in many subsequent studies. HOTAIR plays a role in promoting metastasis by promoting cell migration, invasion and proliferation.

Not only in NPC, previous studies have found that HOTAIR expression in esophageal squamous cell carcinoma (ESCC) tissues is higher than levels in the serum. The HOTAIR expression levels in patients with distant metastasis were significantly higher than those in patients without distant metastasis [12].

5. Conclusion

This research systematically explores the multi-dimensional mechanism of lncRNA in gene regulation. It deepens the understanding of the functional diversity of lncRNA in eukaryotic transcriptomes. Taking nasopharyngeal cancer as an example, the path of lncRNA affecting tumor progression by regulating epithelial interstitial transformation was deeply analyzed. It fills part of the gap in the action mechanism of lncRNA in the pathogenesis of NPC; At the same time, it also reveals a new mechanism that affects tumor migration and invasion through ceRNA mechanisms and signaling pathways such as Akt/PKB.

However, this article only uses a few examples such as H19 and SNHG1 to verify the core mechanisms. In the future, further researches are encouraged to discuss the details and the regulations of NPC. What's more, the study of other signaling pathways in cancer, such as kappa-B (NF-κB), also has important value.

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