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Research Progress on the Role of Long Non-coding RNA in Cervical Cancer

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Abstract: Cervical cancer is one of the most common malignant tumors in women, and its morbidity and mortality remain at a high level. In recent years, with the deepening of research, the role of long non-coding RNA (lncRNA) in cervical cancer has gradually become a focus. Studies have shown that lncRNA is involved in the occurrence, development, metastasis and drug resistance of cervical cancer through various mechanisms, and is regarded as a potential diagnostic marker and therapeutic target. In this review, the abnormal expression of lncRNA in cervical cancer, molecular regulatory mechanisms and possible clinical applications are reviewed, aiming to provide new insights and directions for early detection and personalized treatment of cervical cancer.

Keywords: Cervical Cancer; Long Non-coding RNA; Molecular Mechanism; Clinical Application.

1. Introduction

Cervical cancer is a very common malignant tumor in the female reproductive system, and its incidence ranks fourth among female cancers in the world [1]. Although widespread vaccination of HPV vaccine and advances in cervical cancer screening technology have significantly reduced the morbidity and mortality of this disease, cervical cancer is still a major threat to women's health [2]. The development process of cervical cancer is complex and diverse, with multiple factors acting together and going through multiple stages, among which abnormal regulation of gene expression plays a crucial rolein its pathogenesis [3]. In recent years, lncRNA has become increasingly important in the field of oncology, and its function in cervical cancer has gradually been revealed.

Long non-coding RNA (lncRNA) are a class of transcription products with a length of more than 200 nucleotides and are synthesized mainly by RNA polymerase II. In the past, these molecules were not thought to have protein-coding functions [4]. However, recent studies have shown that lncrnas play a key role in a number of biological processes, including chromatin modification, transcriptional regulation, and translational regulation [5]. In a variety of malignant tumors, the abnormal expression of lncRNA can not only promote the development of cancer, but also play a role in tumor inhibition [6]. Especially in cervical cancer, the abnormal expression of multiple lncrRNA is closely related to the occurrence, development, invasion and metastasis of tumors [6].

In addition, lncRNA also show great potential as diagnostic and prognostic biomarkers [7]. The study found that the expression levels of various lncRNA changed significantly at different stages of cervical lesion progression and before and after cervical cancer treatment.

Therefore, in-depth exploration of lncRNA functions and molecular mechanisms in cervical cancer will not only help to reveal the occurrence and development mechanism of cervical cancer, but also provide a theoretical basis for the development of new diagnostic methods and treatment strategies.

2. Basic Characteristics of lncRNA

2.1. The Structural Characteristics of lncRNA

Long non-coding RNA (lncRNA) refer to those RNA molecules that are more than 200 nucleotides long and are mostly transcribed by RNA polymerase II [4]. lncRNA's secondary structure, splicing mode and localization within the cell are relatively stable, which is crucial for the realization of their functions [8]. lncRNA can be classified into five types, including sense, antisense, bidirectional, intronic and intergenic, according to the relative positions of lncRNA and protein-coding genes on the genome [6]. Understanding these position relationships will help us to better predict the specific functions of lncRNA.

2.2. Functional Mechanisms of lncRNA

Although lncRNA do not have the ability to encode proteins, they play important roles in regulating gene expression, chromatin remodeling and cell cycle control [9]. LncRNA affect the expression of protein-coding genes at multiple levels, including epigenetic regulation, transcriptional regulation and post-transcriptional regulation [5]. Specifically, the functional mechanism of lncRNA mainly includes the following aspects:

2.2.1. Epigenetic Regulation

Some specific lncRNA can recruit chromatin remodeling and modification complexes to specific locations, and then adjust the degree of DNA/RNA methylation, chromatin configuration and modification state, thereby affecting the expression of related genes [10]. For example, lncRNA HOTAIR can direct the PRC2 chromatin modification complex to the HOXD gene cluster and inhibit HOXD gene expression by altering the chromatin modification status in this region [11].

2.2.2. Transcriptional Regulation

Some lncRNA are able to bind to transcription factors to form complexes to regulate the transcription level of genes [12]. For example, lncRNA Dlx6os1 from a highly conserved

region can not only influence the expression of Dlx6 through antisense regulation, but also regulate the expression of Dlx5 and Gad1 genes by recruiting proteins such as Dlx2 or MECP2 [13].

2.2.3. Post-transcriptional Regulation

lncRNA is also involved in post-transcriptional modification of mRNA, involving alternative splicing, RNA editing, protein synthesis and RNA transport, which is of great significance for enhancing the diversity of gene function [12]. Antisense lncRNA play a key role in the post-transcriptional regulation of mRNA. By binding to complementary sequences on mRNA, these lncRNA interfere with the recognition of specific splicing sites, thereby regulating mRNA splicing process [14]. In addition, they can also affect the RNA editing (A-to-I) process [15].

2.2.4. Regulating miRNA

In addition to directly affecting mRNA, lncRNA can also indirectly affect the expression of target genes by regulating miRNA expression [16] . In specific types of tumor cells and tissues, some lncRNA contain "seed sequences" with specific miRNA, which enable them to absorb miRNA like a sponge and prevent miRNA from binding to its target mRNA, thereby affecting gene expression [17].

3. Abnormal Expression of lncRNA in Cervical Cancer

With the deepening of research, it has been found that the expression levels of multiple lncRNA in cervical cancer tissues and cells are significantly different from those in normal tissues, and these differentially expressed lncRNA play an important role in the development of cervical cancer.

3.1. Highly Expressed lncRNA

Studies on highly expressed lncRNA indicate that MALAT1, which is widely present in cervical cancer cell lines, is almost undetectable in normal cervical tissues, suggesting that MALAT1 may be activated during the development of cervical cancer and has important functions [18]. In addition, the overexpression of HOTAIR in cervical cancer can promote the growth of tumor cells, indicating that HOTAIR plays a role in promoting the development of cervical cancer. HOTAIR regulates the expression of B lymphoblastoma 2 gene (Bcl-2) through competitive binding with miR-143-3p, thus promoting the proliferation of cervical cancer cells and inhibiting cell apoptosis[19] .

3.2. Lowly Expressed lncRNA

Hu et al. found through controlled experiments that the expression level of ZNF667-AS1 in cervical cancer tissues was significantly lower than that in paracancer tissues and normal cervical tissues, indicating that ZNF667-AS1 may have a tumor suppressive effect. Further analysis showed that low expression of ZNF667-AS1 was closely related to higher FIGO stage, lower differentiation degree and lymph node metastasis, suggesting that ZNF667-AS1 may be a potential indicator of poor prognosis [20].

4. Molecular Regulatory Mechanisms of Lncrnas in Cervical Cancer

4.1. LncRNA Act as ceRNA to Regulate miRNA

lncRNA can regulate the function of miRNA indirectly through competitive binding with miRNA, and then affect the expression of target genes. This process is called competitive endogenous RNA (ceRNA) mechanism [21, 22] . In the study of cervical cancer, it has been found that multiple lncRNA use ceRNA mechanism to regulate miRNA, which has an impact on the behavior of cervical cancer cells.

4.1.1. HOTAIR:

For example, HOTAIR regulates the expression of the B lymphoblastoma 2 gene (Bcl-2) through competitive binding to miR-143-3p, thereby promoting the proliferation of cervical cancer cells and inhibiting apoptosis [23]. In addition, HOTAIR can further enhance the proliferation, migration and invasion of cervical cancer cells by regulating the miR-23b/MAPK1 signaling pathway [24].

4.1.2. EBIC:

Studies have shown that EBIC regulates the expression level of ZEB1 through competitive binding with miR-200c, thus enhancing the migration and invasion ability of cervical cancer cells [25].

4.2. The Interaction of lncRNA with Signaling Pathways

lncRNA can also affect the proliferation, migration and invasion of cervical cancer cells by participating in a variety of signal transduction pathways.

4.2.1. Wnt/β- - Catenin Signaling Pathway:

For example, HOTAIR has a positive regulatory effect on Wnt signaling pathway in cervical cancer HeLa cells. When HOTAIR level is reduced, the Wnt signaling pathway can be inhibited to reduce the autophagy, proliferation and epithelial mesenchymal transformation (EMT) of cervical cancer cells [26]. In addition, MALAT1 has been found to promote tumor epithelial-stromal transformation and angiogenesis by activating the Wnt/β-catenin signaling pathway [27].

4.2.2. MAPK Signaling Pathway:

CARMN exerts anti-tumor effects by inhibiting MAPK13 transcription and further inhibiting the MAPK cascade[28]. HOTAIR promotes the growth and invasion of high-risk HPV-positive cancer cells through the MALAT1-miR124-RBG2 axis[29].

4.2.3. PI3K/Akt Signaling Pathway:

Studies have shown that CARMN can inhibit the normal process of autophagy flow by down-regulating the Akt/mTOR signaling pathway, and thus exert significant anti-tumor effects [28] .

4.3. Effects of lncRNA on the Behavior of Cervical Cancer Cells

lncRNA regulates the proliferation, apoptosis, migration and invasion of cervical cancer cells through various molecular mechanisms.

4.3.1. Cell Proliferation and Apoptosis:

Studies have shown that HOTAIR regulates the expression of Bcl-2 through competitive binding with miR-143-3p, thus promoting the proliferation of cervical cancer cells and inhibiting their apoptosis[30] . In addition, CARMN

effectively inhibited the proliferation and migration of cervical cancer cells by inhibiting Akt/mTOR and MAPK signaling pathways [28].

4.3.2. Cell Migration and Invasion:

EBIC regulates the expression of ZEB1 through competitive binding with miR-200c, promoting the migration and invasion ability of cervical cancer cells [25]. On the other hand, MALAT1 promotes tumor epithelial-mesenchymal transformation (EMT) and angiogenesis by activating the Wnt/β-catenin signaling pathway, further enhancing tumor invasiveness and metastasis potential [27] .

4.3.3. Cell Cycle Regulation:

It has also been found that CARMN inhibits the proliferation of cervical cancer cells by inhibiting the Akt/mTOR signaling pathway, which impedes the normal process of autophagy flow [28]. This mechanism not only affects cell growth, but also plays an important role in the regulation of cell cycle.

5. Conclusion and Prospect

With the deepening of biomedical research, the key role of long non-coding RNA (lncRNA) in the occurrence, development, invasion and metastasis of cervical cancer has been gradually revealed. Recent studies have not only confirmed the abnormal expression patterns of multiple lncRNA in cervical cancer tissues and cells, but also revealed their profound effects on the behavior of cervical cancer cells by participating in complex molecular mechanisms such as gene regulatory networks and affecting signal transduction pathways. These findings provide a new perspective for understanding the pathophysiological processes of cervical cancer and open up new ways to search for early diagnostic markers and potential therapeutic targets. Specifically, changes in the expression levels of certain specific lncRNA have been shown to be closely related to the prognosis of patients with cervical cancer, suggesting that they may serve as effective biomarkers to evaluate patients' disease progression and treatment response. In addition, given that lncRNA can specifically regulate gene expression, they show great potential for the development of personalized treatment strategies. For example, lncRNA-based targeted therapies may inhibit tumor growth by precisely intervening in disease-related molecular pathways, thereby improving therapeutic efficacy and reducing side effects. Despite the remarkable achievements in lncRNA research, the field still faces many challenges. For example, how to accurately identify and verify clinically significant lncRNA and how to analyze their mechanism of action in depth need to be solved. Future studies need to adopt a multidisciplinary approach and combine advanced technical means such as high-throughput sequencing and CRISPR gene editing technology to further explore the function of lncRNA and its role in cancer biology. Promoting the transformation of basic research results into clinical applications is one of the important directions of future research. This means not only accelerating the exploration and validation of novel lncRNA targets, but also establishing an effective translational research platform to facilitate the rapid transition from the laboratory to the bedside. By strengthening the cooperation between basic scientists and clinicians, theoretical knowledge can be more effectively translated into practical diagnosis and treatment plans, and ultimately achieve the goal of improving the quality of life of cervical cancer patients.

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