Circular RNAs as Lung Cancer Biomarkers

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Abstract

Lung cancer is the main cause of death and morbidity from malignant neoplasms globally, and patients bear a significant burden as a result of its poor prognosis. Smoking is linked to a high percentage of lung cancer cases. A considerable number of nonsmokers develop the disease, implying an epigenetic and genetic pathway for lung cancer development. The current state of lung cancer diagnosis and treatment is dire, and effective therapeutic targets and molecular markers are desperately needed. Circular RNAs (circRNAs) are non-coding RNAs that are covalently closed and have received a lot of attention because of their biological properties like conservatism, stability, and tissue specificity. Many studies have revealed that circRNAs have a key role in the early detection, therapy, and prognosis of lung cancer by regulating it through numerous mechanisms such as microRNA adsorption. CircRNAs have been shown to play a role in the proliferation, migration, and invasion of lung cancer cells in recent years. Differentially expressed circRNAs can be exploited as non-invasive lung cancer diagnostic and prognostic indicators. This article summarizes current circRNA advances in lung cancer diagnosis, treatment, and prognosis.

Keywords: Noncoding RNAs • Circular RNAs • Lung cancer • Biology function • Biomarker

Introduction

Lung cancer is the world's most frequent malignant tumor illness, posing a major threat to human life and health. According to data, there were approximately 2.1 million new cases of lung cancer and 1.8 million deaths from lung cancer globally in 2018, with lung cancer having the highest morbidity and mortality rates of any cancer type. Lung cancer is classified into two types based on histology: small cell lung cancer and non-small cell lung cancer, with small cell lung cancer accounting for 15% and 85% of total lung cancers, respectively. Despite advances in clinical diagnosis and treatment, the 5-year survival rate for lung cancer remains dismal due to delayed diagnosis, a small beneficiary population, and other factors. Furthermore, the lack of relatively specific tumor markers complicates lung cancer diagnosis, therapy, and prognosis. As a result, it is critical to investigate the molecular mechanism of lung cancer in order to identify novel biomarkers and treatment targets [1,2].

Circular RNA (circRNA) is a type of non-coding RNA that occurs naturally in the body. CircRNA was discovered in RNA viruses as early as the 1970s [3,4]. However, because to technological limitations at the time, circRNAs were regarded as by-products of the splicing process and received little attention [5]. CircRNAs have been discovered in huge numbers in recent years, thanks to the advancement of high-through-put Sequencing technology and bioinformatics, and have increasingly become a study hotspot in the area. CircRNAs are noncoding RNA molecules that are covalently closed and found in all eukaryotic transcriptomes. According to their sources, circRNAs are classified as exonic circRNAs (ecRNAs), intronic circRNAs (ciRNAs), and exon-intron circRNAs (EIciRNAs). Exonic circRNAs are the most prevalent type. Circular RNA, unlike linear RNA, lacks a cap structure at the 5' end and a polyadenylation tail at the 3' end, which can withstand the degradation of exonuclease RNase R, making it more stable and having a longer half-life. CircRNAs have also been proven to help in species conservation, according to research. Furthermore, circRNA expression is tissue and developmental stage specific, implying that circRNAs may be involved in the regulation of many pathophysiological processes in the body.

Early and precise diagnosis is crucial for lung cancer treatment. Although many diagnostic procedures have been employed in clinical practice, there is still potential for improvement in terms of cost, accuracy, and patient acceptance. As a result, further research into lung cancer diagnostic indicators is still required. CircRNAs offer the characteristics of conservation, stability, and specificity, making them promising as new indicators of lung cancer. A meta-analysis of 8 researches on the diagnostic effectiveness of circRNAs in lung cancer tissue and blood was performed on the Chinese lung cancer population. The characteristic curve (ROC) Area under Curve (AUC) was 0.78, indicating that circRNAs have diagnostic potential in the Chinese lung cancer population.

When compared to standard biopsy, liquid biopsy has the advantages of ease of use, less invasiveness, and low cost, therefore the research potential is vast. At the moment, preliminary evidence suggests that plasma circRNAs, such as circRNA-002178, circMAN1A2, and others, have good diagnostic potential. Chen et al. identified differently expressed circRNAs in plasma exosomes from Lung Adenocarcinoma (LUAD) patients using high-throughput sequencing technology. In comparison to the control group, 105 circRNAs were expressed more, whereas 78 circRNAs were expressed less. Further investigation revealed that the expressions of hsa circ 0001492 and hsa circ 0001346 were significantly up-regulated in the early stages of LUAD but were almost undetectable in the control group's plasma, implying that hsa circ 0001492 and hsa circ 0001346 may be candidate markers for early LUAD.

The combined AUC of the two reached 0.81, implying that dual circRNAs could be employed as non-invasive indicators for LUAD diagnosis. Furthermore, blood circRNA may be linked to tumor progression, because the expression of hsa circ 0005962 in LUAD patients after surgery was much lower than before surgery. The level of hsa circ 0086414 expressions was linked to Epidermal Growth Factor Receptor (EGFR) mutation. hsa circ 0086414 was found to be substantially expressed in EFGR mutant patients when compared to wild-type patients. This work reveals the blood circRNAs' multifaceted application value. Of course, a larger sample size and more in-depth mechanism study are still required to actualize the clinical translation of blood circRNA lung cancer diagnosis [6-8].

Tumor cells can express a variety of strategies in order to avoid the immune system and generate favorable conditions for their own proliferation. The transmembrane protein programmed death protein 1 (PD-1) has been reported to be expressed on the surface of practically all types of tumor cells and participates in tumor immune escape by interacting with the PD-L1 pathway. Immune Checkpoint Inhibitors (ICIs) targeting PD-1/PD-L1 has become a potent tool in the treatment of lung cancer in recent years. Simultaneously, lung cancer cells can generate exosomal circRNA-002178 and transfer it to T cells, promoting PD-1 expression in T cells by inhibiting miR-28-5p. CircRNAs are thought to play a role in tumor

immune escape mechanisms, and the use of related pathway inhibitors in combination is expected to improve clinical efficacy and provide new ideas for tumor immunotherapy. Prognostic monitoring of lung cancer patients is an important link in evaluating the effect of clinical diagnosis and treatment, and it is crucial for changing drug regimens and enhancing patient survival time. Several studies have proven that circRNAs such as circSMARCA5, circ 11780, and circCRIM1 can be used as independent prognostic indicators of lung cancer patients and are closely associated to lung cancer patient survival. RT-qPCR detection on tumor tissues of 93 non-small cell lung cancer patients revealed that hsa circ 11780 was unusually low expressed, and patients with low expression tended to have larger tumors with distant metastases and more severe tumors according to Tumor-Lymph Node-Metastasis (TNM) staging [9].

Conclusion

The link between circRNA and lung cancer is becoming more apparent as research advances. On the one hand, circRNAs act as tumor-promoting or tumor-suppressing factors to regulate lung cancer biological behaviors such as proliferation, metastasis, apoptosis, and autophagy, as well as to regulate the sensitivity of chemotherapy or targeted drugs and the efficacy of immunotherapy, and to provide a preliminary theoretical basis for adjuvant clinical treatment. The differential expression of circRNAs in tissue or blood, on the other hand, shows a certain correlation in the early diagnosis and prognosis evaluation of lung cancer and is expected to become a potential lung cancer biomarker. However, contemporary circRNA research is still in its early stages, with most researchers focusing on the adsorption role of miRNA sponges, and many mechanisms remain unknown. Its clinical significance research is similarly restricted to a small number of samples, and its translational utility is still being debated. More breakthroughs in the field of circRNA are expected in the future, providing more ideas for lung cancer diagnosis and treatment.

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