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Research Progress on MicroRNA in Early Diagnosis of Lung Cancer

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Abstract: *Lung cancer is one of the most common and deadly types of cancer worldwide. Non-small cell lung cancer accounts for 85% of all lung cancers, and the survival rate of lung cancer patients is closely related to the time of diagnosis, with higher survival rates associated with early detection. However, early-stage lung cancer lacks specific clinical features, and most lung cancer patients do not exhibit obvious symptoms in the early stages of the disease. As a result, many patients are diagnosed in the intermediate or late stages. Pulmonary nodules are early manifestations of lung cancer, but not all nodules indicate lung cancer. With the advent of LDCT, more and more lung nodules are being detected, but distinguishing between benign and malignant nodules remains challenging. Therefore, there is an urgent need to develop blood-based biomarkers as more effective diagnostic tools for precise diagnosis of lung cancer in high-risk individuals.*

Keywords: *Lung cancer; microRNA; biomarker; early diagnosis*

1. Introduction

Lung cancer is a common and deadly cancer, and it is a major health problem worldwide. According to statistics from the World Health Organization (WHO), millions of people are diagnosed with lung cancer every year, and lung cancer is one of the leading causes of cancer-related deaths worldwide [1], as shown in Figure 1 and Figure 2. Early diagnosis plays a crucial role in the treatment and prognosis of lung cancer.The search for new biomarkers, such as miRNAs, to improve the accuracy and reliability of early diagnosis is one of the current research focuses. Future research and advancements are expected to bring better diagnostic and treatment options for lung cancer patients [2].

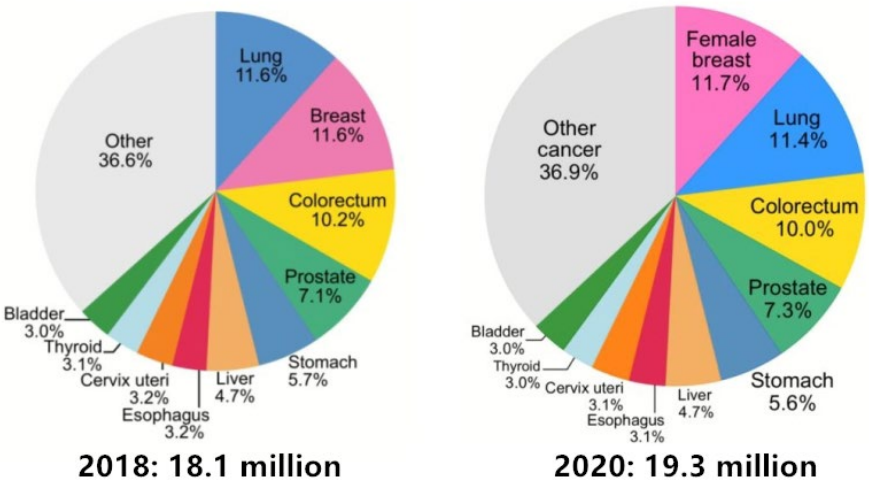

Figure 1: Incidence rate of various types of cancer

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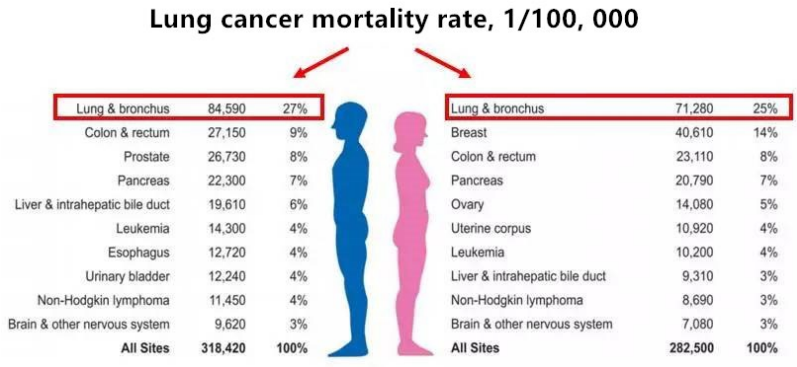

Figure 2: Lung cancer mortality rate, 1/100, 000

2. Early Diagnosis of Lung Cancer

Lung cancer, or primary bronchogenic carcinoma, is defined by the World Health Organization (WHO) as a malignant tumor originating from respiratory epithelial cells (bronchi, bronchioles, and alveoli). Clinical symptoms are often insidious, with cough, sputum production, hemoptysis, and weight loss as the main manifestations. In the early stages, lung cancer is typically confined to the lungs or local lymph nodes and has not spread to other parts of the body. Therefore, early diagnosis provides patients with the opportunity to undergo surgical resection, radiation therapy, or chemotherapy, leading to better curative effects. Additionally, early diagnosis can aid in screening high-risk populations for early interventions and preventive measures, thereby reducing the incidence and mortality rates of lung cancer [3], as shown in Figure 3.

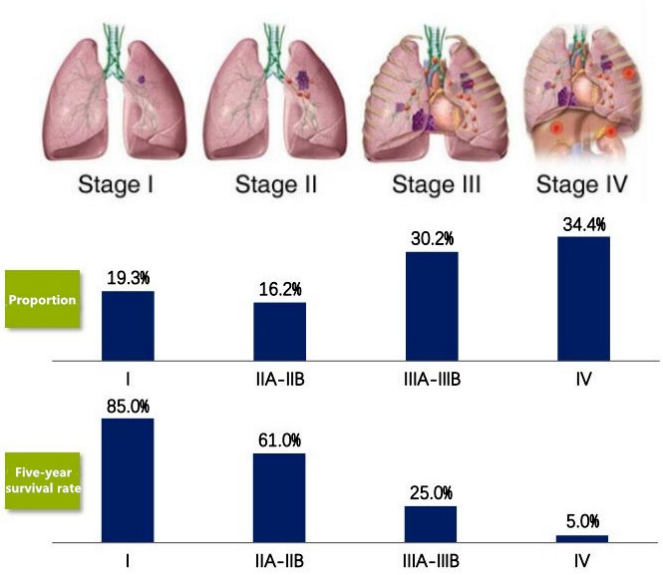

Figure 3: Proportion of lung cancer patients with clinical stage staging and 5-year survival rate

However, early diagnosis of lung cancer still faces many challenges. Firstly, lung cancer often lacks obvious symptoms or signs in the early stages, making it difficult to detect. Many patients are only diagnosed when symptoms appear or the disease has progressed to the advanced stage, significantly reducing the chances of treatment. Secondly, traditional imaging techniques (such as X-rays and CT scans) have limitations in the detection of early lung cancer, especially for small nodules. Therefore, more sensitive and specific diagnostic methods are needed to improve the detection rate of early-stage lung cancer. With advances in scientific technology, researchers are continuously striving to find new methods for the early diagnosis of lung cancer, including the detection based on biomarkers. Biomarkers are specific molecules or substances in the body that indicate the presence or development of a disease. In the early diagnosis of lung cancer, researchers have discovered many potential biomarkers, including circulating tumor DNA, protein markers, and microRNAs [4].

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3. MicroRNA and Early Diagnosis of Lung Cancer

3.1. Biological Functions of microRNAs

MicroRNAs (miRNAs) are a class of small RNA molecules approximately 20-22 nucleotides in length that function within cells by binding to the 3' untranslated region (3' UTR) of target genes. miRNAs primarily regulate target genes through two mechanisms: (1) by forming a RNA-induced silencing complex (RISC) that inhibits the translation of target mRNA, and (2) by inducing degradation of target mRNA by binding to it. The degree of complementarity between miRNAs and target genes determines the strength of their regulatory effect. Studies have shown that miRNAs can regulate cell proliferation and apoptosis processes. Some miRNAs have been identified as tumor suppressors or promoters, regulating the proliferation and apoptosis of cancer cells. They may function by inhibiting genes that promote cell proliferation or activating signaling pathways that promote cell apoptosis. Furthermore, miRNAs serve as important regulators of epigenetic modifications, such as DNA methylation and histone modification factors [5].

3.2. Association of microRNAs with Lung Cancer

There is a close association between miRNAs and the occurrence and development of lung cancer. Abnormal expression of miRNAs and changes in regulatory pathways play important roles in the occurrence, metastasis, and prognosis of lung cancer. miRNAs exhibit widespread dysregulation in lung cancer, including upregulation and downregulation. Some miRNAs have been found to be overexpressed in lung cancer tissues and are referred to as oncogenic miRNAs. Others have been found to be downregulated in lung cancer tissues and are referred to as tumor-suppressive miRNAs. Abnormal miRNA expression has been correlated with clinical features such as the occurrence, differentiation, metastasis, and prognosis of lung cancer [6]. MiRNAs play important roles in regulating lung cancer-related pathways and target genes. miRNAs can influence the development of lung cancer by modulating multiple signaling pathways, cell cycle, apoptosis, metastasis, and invasion processes. miRNAs interact with various tumor-related pathways and regulatory factors, such as the Wnt/β-catenin pathway, PI3K/AKT pathway, MAPK pathway, and transcription factors, among others [7]. Numerous studies have demonstrated the significant regulatory role of miRNAs in the occurrence and development of lung cancer. On one hand, miRNAs can function as tumor suppressors, inhibiting the proliferation, invasion, and metastasis of lung cancer cells. Downregulated miRNAs found in lung cancer have tumor-suppressive effects by inhibiting cell proliferation, metastasis, and invasion, and promoting apoptosis. Examples of typical tumor-suppressive miRNAs include the let-7 family, miR-34 family, and miR-200 family. These miRNAs exert their tumor-suppressive effects by inhibiting the expression of oncogenes or targeting the upregulation of tumor-suppressive genes. On the other hand, certain miRNAs can function as tumor promoters, facilitating the development and progression of lung cancer. Overexpressed miRNAs found in lung cancer have oncogenic effects by promoting cell proliferation, metastasis, and invasion, and inhibiting apoptosis. Examples of typical oncogenic miRNAs include miR-21, miR-155, and the miR-17-92 cluster. These miRNAs exert their oncogenic effects by inhibiting the expression of tumor-suppressive genes or targeting the downregulation of tumor-suppressive genes [8], as shown in Figure 4.

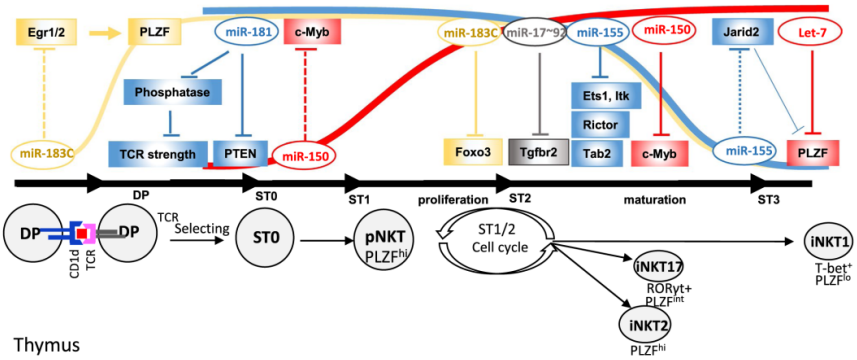

Figure 4: Dynamic expression of microRNA mediates the development of iNKT cells

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3.3. MiRNAs as Biomarkers for Early Diagnosis of Lung Cancer

3.3.1. Methods and Strategies for Early Lung Cancer Diagnosis Targeting miRNA in Existing Research

In recent years, there has been increasing attention to research on miRNAs for early lung cancer diagnosis. MiRNAs have the potential to serve as potential biomarkers for early lung cancer detection, as they can be detected in blood or other biological samples and play a crucial role in the development and progression of lung cancer [9]. Many studies have utilized high-throughput technologies, such as miRNA microarrays or gene sequencing, to analyze the differential expression profiles of miRNAs between lung cancer patients and the normal population. By comparing miRNA expression levels in different samples, researchers can identify potential biomarkers associated with lung cancer. These differentially expressed miRNAs can be considered as potential diagnostic markers for early lung cancer, helping to differentiate between patients and non-patients [10]. Circulating miRNAs refer to stable miRNAs present in body fluids such as blood, and their expression levels can reflect the presence and status of tumors. Researchers can collect blood samples from lung cancer patients, extract circulating miRNAs, and quantify their expression levels using methods such as quantitative PCR (qPCR). By comparing them with a normal control group, circulating miRNAs associated with early lung cancer can be identified, and their potential for early diagnosis can be explored [11]. Many studies have applied machine learning and bioinformatics methods to analyze miRNA data. By establishing prediction models and classifiers that correlate miRNA expression profiles with lung cancer status, early lung cancer diagnosis can be achieved. These methods can identify the most promising combinations of miRNA biomarkers for accurate prediction of early lung cancer [11]. Research targeting miRNAs for early lung cancer diagnosis has employed various methods and strategies. By analyzing miRNA expression profiles, detecting circulating miRNAs, integrating multiple biomarkers, and applying machine learning and bioinformatics approaches, researchers are continually searching for miRNA biomarkers with potential clinical utility, providing new directions and possibilities for early lung cancer diagnosis.

3.3.2. MiRNA as a Potential Biomarker for Early Lung Cancer Diagnosis

MiRNAs, as a class of small non-coding RNA molecules, have attracted considerable attention in the early diagnosis of lung cancer. Due to the abnormal expression of miRNAs and changes in regulatory pathways in lung cancer, miRNAs are considered potential biomarkers for lung cancer.MiRNAs participate in the occurrence and development of tumors by regulating gene expression and can be detected in blood or other biological samples. Studies have shown that miRNAs have potential value in the early diagnosis of lung cancer, and their abnormal expression is closely associated with the occurrence and prognosis of lung cancer [9]. Therefore, miRNAs may become promising biomarkers for the early diagnosis of lung cancer. miRNAs exhibit significant potential as biomarkers for the early diagnosis of lung cancer due to several advantages. Firstly, miRNAs are stably expressed in tumor cells and body fluids, exhibiting high detection sensitivity and specificity. Secondly, miRNA detection methods are simple, rapid, and cost-effective, allowing for detection using routine laboratory techniques or commercial assay kits. Additionally, miRNAs possess tissue-specific expression patterns, making them useful as discriminative and classificatory biomarkers for lung cancer subtypes. Lastly, combining multiple miRNA patterns can improve the diagnostic accuracy of early-stage lung cancer, enabling efficient screening through the establishment of miRNA expression profiling models [10]. However, the clinical application of miRNAs as biomarkers still faces some limitations. Firstly, miRNA expression levels are influenced by various factors, including individual variations, sample processing, and storage. Therefore, strict standardization and quality control are necessary during miRNA detection and analysis. Secondly, the functional roles and regulatory mechanisms of miRNAs are not fully understood and require further research to elucidate their relationship with the occurrence and development of lung cancer. Moreover, the specificity and sensitivity of miRNAs as biomarkers need to be further validated and compared with other diagnostic methods. Finally, the clinical application of miRNAs as biomarkers is still in the research stage and requires further large-scale clinical trials to verify their reliability and effectiveness [11].

3.4. Application of miRNA in Combination with Other Markers for Early Diagnosis of Lung Cancer

In recent years, miRNA has shown potential in the early diagnosis of lung cancer. Combining miRNA with other markers may improve the diagnostic accuracy of early-stage lung cancer, enabling earlier and more precise diagnosis [10]. The combination of miRNA with serum markers is a common strategy. For example, combined detection of miRNA with serum tumor markers such as CEA and CYFRA21-1 can

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improve the diagnostic accuracy of early-stage lung cancer. The advantages of using miRNA as serum markers lie in their stability and ease of detection [12]. The combination of miRNA with imaging examinations contributes to improved diagnostic accuracy for early-stage lung cancer. For instance, combining miRNA with CT, PET-CT, and other imaging examinations can detect smaller lesions and lymph node metastasis, enabling earlier diagnosis and treatment [13]. The combination of miRNA with clinical scoring systems can enhance the diagnostic accuracy of early-stage lung cancer. By integrating miRNA expression levels with clinical features, predictive models and scoring systems can be established for personalized early-stage lung cancer diagnosis and risk assessment [14]. The combination of miRNA with other markers can integrate information from different markers, improving the diagnostic accuracy and sensitivity of early-stage lung cancer. It facilitates earlier and more precise diagnosis and treatment. However, the application of combination approaches faces challenges such as standardization, limitations in sample size, and the need for clinical validation. Future research should focus on the combination methods and analytical approaches of different markers and conduct large-scale clinical studies to advance the development and application of early-stage lung cancer diagnosis [15], as shown in Figure 5.

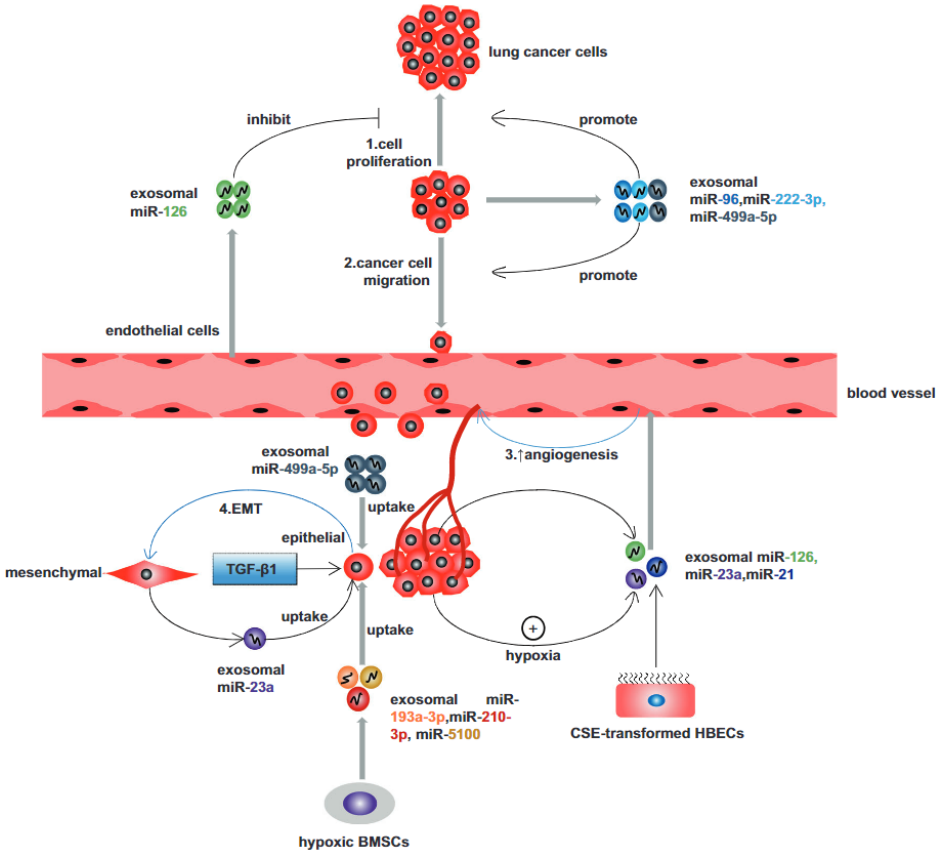

Figure 5: The roles of exosomal miRNAs and lncRNAs in lung diseases

4. Research Progress and Outlook

MiRNA has demonstrated significant potential in the early diagnosis of lung cancer. Its abnormal expression is closely associated with the occurrence and development of lung cancer, making it a promising biomarker. Through ongoing research and technological advancements, miRNA detection methods are becoming increasingly mature, providing new avenues for the early diagnosis of lung cancer. However, miRNA as a biomarker for early-stage lung cancer diagnosis still faces challenges such as standardization, sample sources, and clinical validation. Future research should further elucidate the relationship between miRNA and lung cancer, strengthen multicenter clinical trials with large sample sizes, and develop more practical miRNA detection techniques to facilitate the clinical application of miRNA in the early diagnosis of lung cancer [8].

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