

Progress in Therapy of Lung Cancer

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Abstract. Lung cancer has become one of the most common cancers worldwide, and it is also the main cause of cancer-related deaths. It is estimated that over 22 million new cases and 1.79 million deaths are caused by lung cancer each year. The theory of "airway field of injury" has been used to explain the pathogenesis of lung cancer, but its specific molecular mechanism is not clear yet. With the completion of comprehensive genomic analysis of lung cancer, modern medicine has revealed its genetic heterogeneity and complexity, and identified many oncogenic driving genes and molecular pathogenesis of lung cancer. At present, common treatment methods for lung cancer include chemotherapy, radiotherapy, targeted therapy, immunotherapy, and gene therapy. Each treatment has a unique mechanism and targets, but also has different advantages and disadvantages. Corresponding to different lung cancer patients, it is necessary to comprehensively consider their physiological health and economic status, choosing appropriate treatment strategies.

Keywords: lung cancer; pathogenesis; therapy; treatments.

1. Introduction

Lung cancer has now become one of the most common cancer globally, which is also the main reason led to the cancer related death. It is estimated that over 22 million new patients and 1.79 million of patients die per-annum. The incidence rate, mortality and other index of lung cancer vary greatly worldwide and are closely related to smoking patterns [1]. As smoking rates rising, the lung cancer incidence rate and mortality rose in late decades, which usually first happened in men then in women, declining after the launch of comprehensive tobacco control programs. Overall, the incidence rate of lung cancer in developing countries is lower, but the mortality is higher, for whose reasons include inadequate health care, underdeveloped medical technology, pollution, and social-cultural barriers. In China, according to GLOBOCAN 2012 data, lung cancer accounts for 21% of all cancers and 27% of all cancer-related deaths [2].

Lung cancer was once considered as an incurable disease, but in the past 25 to 30 years, clinical trials conducted in the United States cooperative group system and around the world have established the standard of care and made several initial treatments possible. Nowadays, patients with lung cancer have several different treatment options, and the potential of more effective treatments is promising.

Chemotherapy is usually the preferred treatment for advanced lung cancer. However, this systemic cytotoxic therapy is only effective for certain cancers. Another common method for treating cancer is radiation therapy (RT). RT targets cancer cells through direct and indirect DNA damage, which can also regulate the immunogenicity of tumors by exposing its specific antigens [3]. RT also can stimulate the inflammatory by immunogenic cell death and other pathways. A comprehensive genomic analysis of lung cancer reveals its genetic heterogeneity and complexity, and identifies many targeted oncogenic driving changes. Works in molecular spectrum analysis enabled to develop the molecular targeted therapies. In targeted therapy, patients first determine the biomarkers that drive treatment, and then match patients with appropriate targeted drugs. The success of the clinical trial of this therapy was first confirmed in the EGFR inhibitor trial of lung cancer, and the subsequent targeted therapy trials were vigorously promoted [4]. Immunotherapy, such as the use of immune checkpoint inhibitors, greatly enhances the therapeutic efficacy of lung cancer patients. The immune system uses checkpoints to regulate immune responses and prevent overreaction. However, several targeted genetic changes have been discovered in lung cancer. With the continuous development of CRISPR

technology, gene therapy is gradually bringing new hope to lung cancer patients. CRISPR technology makes it possible to reconstruct tumor suppressive ability.

2. Pathogenesis of Lung Cancer

Modern medicine believes that the occurrence and deterioration of lung cancer is a multi-step process, during which a series of genetic changes occur. In the development of primary cancer, genetic and epigenetic abnormalities continue to accumulate, leading to the occurrence and deterioration of cancer ultimately, and continuously affecting its invasion, metastasis, and treatment processes.

2.1. Histological Type of Lung Cancer

Lung cancer is classified by histological type into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC consists of three main subtypes: lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and large-cell lung cancer (LCLC), accounting for 85% of the total lung cancer. Different types of lung cancer develop from different pathways, which is supported by different sites of onset and different origin cells. For example, LUAD originates from small bronchioles, bronchioles, or alveolar epithelial cells located in the surrounding area, unlike LUSC and SCLC, which typically originate from the main bronchus and are located in the central position [5].

2.2. Airway Field of Cancerization

The theory of lung cancer caused by smoking is known as the "airway field of injury" [6]. Research has shown that normal respiratory epithelial cells undergo changes in certain molecules after exposure to smoking, indicating the occurrence of lung cancer. These precancerous changes provide a biological basis for the lung cancer. However, the molecular mechanism of this theory is not clear yet, and we cannot sure the specific possibility of high-risk individuals developing into lung cancer patients.

2.3. Molecular Mechanism of LUAD

Clinical studies have shown that the Kirsten rat sarcoma viral oncogene (KARS) pathway and the epidermal growth factor receptor (EGFR) pathway are involved in the development of LUAD. The exon 19 framework deletion and the exon 21 mutations of EGFR are closely related to smoking status, gender, and ethnicity. The mutation of KARS is also associated with smoking. Increasing research suggests that alveolar type II (AT2) cells, expressing surface active protein C (SPC), are progenitor cells of LUAD. A study has found that EGFR mutation drivers were found in the bronchioles adjacent to LUAD associated with EGFR mutations, suggesting that LUAD may originate from the epithelium of the bronchioles and bronchioles [7].

2.4. Molecular Mechanism of LUSC

After exposing to cigarette smoke, basal cells in the respiratory tract produce differentiated and underdeveloped squamous cells, which serve as precursors for LUSC. Early studies have shown that the allelic losses of multiple 3p chromosomal sites and 9p21 (CDKN2A) in bronchial epithelial cells are considered the earliest detected changes in the development of LUSC. The changes of SOX2 are also apparent in the precancerous stage of LUSC. SOX2 has been observed to amplify and promote the growth and survival of lung tumor cells, especially squamous tissue cells [8].

Compared with normal bronchial epithelial cells, the isoforms of vascular endothelial growth factor (VEGF) and VEGF receptor (VEGF receptor) are elevated in squamous dysplasia of the bronchus, supporting the view that angiogenesis occurs in the early stages of lung cancer. In addition, vascular squamous dysplasia (ASD) exhibits vascular sprouting and increased microvascular density in subepithelial tissue, indicating a structural rearrangement of capillary micro-vessels [9]. This lesion

suggests that abnormal microvascular formation may happen in the early stages of bronchial cancer. Besides, other pathways are also shared between squamous infiltrating lesions and LUSC [10].

2.5. Molecular Mechanism of SCLC

Compared to NSCLC, clinical medicine has limited knowledge of the early molecular pathogenesis of SCLC. A study, evaluating the LOH and microsatellite instability of several chromosomal sites in normal and proliferative bronchial epithelial cells near lung cancer tissue, showed that the mutation rate of epithelial cells near SCLC was significantly higher than that of NSCLC [11]. These findings suggest that SCLC doesn't need more complicated histological changes, but directly develops from normal epithelial cells.

3. Current Treatment Methods for Lung Cancer

3.1. Chemotherapy

The treatment of lung cancer has been through several decades, and conventional chemotherapy remains the standard treatment choice for NSCLC patients, especially those in advanced stages. At present, there are four types of chemotherapy drugs commonly used in clinical treatment of NSCLC, which are: (1) alkylating agents; (2) Microtubule targeted drugs; (3) Antimetabolic drugs; (4) Topological enzyme inhibitor.

3.1.1 Alkylating agents

Cisplatin is a commonly used biological alkylating agent, which was first synthesized in 1844, but its anti-tumor effect did not receive attention until the 1960s [12]. Carboplatin is a second-generation platinum compound, and compared to cisplatin, its efficacy has decreased but its biological toxicity has greatly increased [12]. Its main mechanism of action is to induce cancer cell apoptosis by mediating the formation of platinum DNA adducts and forcing changes in DNA structure.

3.1.2 Microtubule targeted drugs

Microtubules are composed of heterodimers of microtubule proteins in dynamic equilibrium. At present, most microtubule targeted drugs in clinical practice are paclitaxel and its semi-synthetic analogues (docetaxel). They mainly disrupt microtubule dynamics by directly binding to microtubule molecules, leading to cell mitosis arrest and ultimately stimulating programmed cell death [13].

3.1.3 Antimetabolic drugs

Antimetabolic drugs induce cancer cell apoptosis by cutting off the DNA synthesis pathway of cancer cells, hindering their proliferation. Pemetrexed is an antifolate salt based on pyrrolidone [2,3-d] pyrimidine, which mainly inhibits thymidylate synthase (TYMS), thereby blocking DNA synthesis and cell proliferation [14].

3.1.3 Topological enzyme inhibitor

Etoposide is a synthetic derivative of podophyllotoxin, isolated from the roots and rhizomes of podophylloid plants. It mainly inhibits topoisomerase II and exhibits anti-tumor activity [15]. In 1983, the FDA approved the clinical application of etoposide.

3.2. Targeted Drugs

Before the emergence of targeted therapy, systemic cytotoxic chemotherapy was commonly used in clinical practice to treat cancer. However, the effectiveness of this method varies among different types of cancer, and it can also be accompanied by persistent high toxicity damage to the patient's body. With the completion of comprehensive genomic analysis of lung cancer [16], modern medicine has revealed its genetic heterogeneity and complexity, and identified many oncogenic driver genes that can be used as targets.

3.2.1 EGFR-activating genetic lesions

Research has found that EGFR is often overexpressed in several types of lung cancer, and EGFR gene mutations occur in 10-15% of lung adenocarcinoma patients, mainly in young non-smokers [17]. EGFR exon 19 deletion and EGFR L858R mutation are often observed as driving factors for oncogenic EGFR signaling in NSCLC. However, clinical trials have shown that the success of small molecule EGFR inhibitor drugs is not ideal in patients with non-selective (EGFR mutation status unknown) NSCLC.

3.2.2 ALK rearrangement

ALK encodes an anaplastic lymphoma kinase (ALK), which can rearrange with many genes. In 2007, it was found that the chromosomal inversion of the spinous microtubule associated protein 4 (EML4) gene and ALK gene (EML4-ALK) can increase the occurrence and development of lung cancer [18]. This type of gene rearrangement is a new molecular subtype discovered in recent years, accounting for about 5-7%. The partner genes involved in ALK rearrangement are diverse, with EML4-ALK being the most common, accounting for approximately 81% of all ALK rearrangements.

Shortly after the discovery of the EML4-ALK remake fusion, clotozantinib was found to be useful for targeted treatment of ALK.

3.2.3 NTRK rearrangements

The neurotrophic tyrosine kinase (NTRK) gene, encoding tropomyosin associated kinase proteins (Trk), has three subtypes: NTRK1, 2, and 3. The chromosomal aberration phenomenon of NTRK has been discovered in several types of lung cancer, and the incidence rate is about 2-3%. Entererectinib has shown significant anti-tumor effects in NSCLC patients fused with SQSTM1-NTRK1 [19].

3.2.4 KARS-activating mutations

30% of LUAD includes KRAS mutations. In previously treated advanced KRAS mutations NSCLC patients, clinical trials that compare the efficacy of using docetaxel alone with seluminib or trametinib in combination with docetaxel did not show superiority of the combination therapy [20].

3.3. Gene Therapy

YES1 regulates cell growth, apoptosis, cell adhesion and cytoskeleton remodeling. It has been found that the concentration of YES1 increases in lung cancer, making it a feasible therapeutic target. Using CRISPR/Cas9 technology to inhibit YES1 plays a key role in disrupting lung cancer progression, by downregulating the mammalian rapamycin target protein (mTOR) signal.

To date, there are 13 clinical trials documented worldwide using CRISPR/Cas9 technology for intervention in cancer therapy. Among these, only one study involved gene editing of cancer cells in vivo. The other 12 studies used CRISPR/Cas9 gene editing to modify immune cells in vitro and introduce them into the human body as interventions for cancers [21].

4. Conclusion

Lung cancer is one of the most common cancers worldwide and a major cause of cancer-related deaths. The treatment of lung cancer has a history of several decades and has developed various treatment methods, such as chemotherapy, radiotherapy, targeted therapy, immunotherapy, gene therapy, etc.

Chemotherapy is the standard method for treating lung cancer, especially advanced lung cancer. Alkylation agents, microtubule targeted drugs, anti-metabolic drugs, and topoenzyme inhibitors are commonly used in clinical practice to treat NSCLC. These four types of drugs have different targets and mechanisms, but they all inhibit the proliferation of cancer cells and the development of cancer.

However, chemotherapy has brought many side effects to patients in clinical use, due to its low efficacy, high cytotoxicity, and weak targeting. Recent studies have shown that many lung cancer patients exhibit chemotherapy resistance. Drug resistance greatly reduces the effectiveness of

chemotherapy. Analyzing the targets and causes of drug resistance is crucial for developing effective treatment strategies.

Radiation therapy, like chemotherapy, is also a widely used cancer therapy. It is often used together with chemotherapy in clinical practice. Local radiotherapy and non-invasive treatment have to some extent alleviated the systemic toxicity caused by chemotherapy. However, radiotherapy not only kills cancer tissue, but also causes damage to other organs and tissues around it, causing side effects such as radiation pneumonia, esophagitis, and cardiac dysfunction in patients. The long-term nature of radiotherapy is further exacerbating the physiological and family burden on patients.

In recent years, comprehensive genomic analysis of lung cancer has revealed its genetic heterogeneity and complexity, and identified targeted oncogenic driving changes such as EGFR, ALK, ROS1, etc. The analysis of these targeted genes has enabled the development of molecular targeted therapy. With its high specificity, efficiency, and personalization, targeted therapy can accurately interfere with the growth and spread of tumor cells, reducing damage to normal tissues. Targeted therapy is gradually replacing traditional cytotoxic chemotherapy. However, due to the mutability and complexity of cancer cells, a single targeted drug often cannot produce the best therapeutic effect. Meanwhile, if target mutations occur in cancer cells during the treatment process, it is easy to weaken or render ineffective the targeted drugs. The low applicability and high cost of targeted therapy are also common problems faced by patients and the medical community in clinical practice.

Since the 1960s, immunotherapy has been widely applied to some difficult to cure diseases, and immunotherapy for lung cancer has entered the clinical trial stage. The core of immunotherapy lies in activating the patient's own immune system, stimulating activation signals, and resisting inhibition signals, and maximizing the activation of the patient's cellular and humoral immunity. Monoclonal antibodies are commonly used immunosuppressants. However, this therapy is not applicable to all patients, as tumor cells can evade immune system attacks through various mechanisms, such as low PD-L1 expression and less immune cell infiltration. Immunotherapy may also cause immune related adverse reactions such as fatigue, rash, and liver dysfunction. In severe cases, treatment may even need to be discontinued and other intervention measures taken.

The development of epigenetics and CRISPR/Cas gene editing technology have provided possibilities for gene therapy of lung cancer. As an emerging therapy for cancer treatment, there are few clinical cases of gene therapy, and most treatment options choose to use in vitro CRISPR/Cas9 gene editing to modify immune cells and input them into the human body as an intervention for cancer. But its high specificity, long-term effectiveness, and potential for complete cure have led many scientists to engage in it. At present, there are still many issues to consider and solve for gene therapy. Selectivity is the first and most crucial issue to be addressed. Epigenetic modifications are commonly present in healthy and cancer cells, and healthy cells have adaptability to various genetic modifications. Therefore, it is important to determine the core epigenetic changes of various types of cancer. The delivery of drugs is also an urgent problem that needs to be solved. In the future, gene therapy will develop towards more targeted and safe delivery methods.

References

- [1] Thun MJ, Carter BD, Feskanich D, et al. 50-Year Trends in Smoking-Related Mortality in the United States. *New England Journal of Medicine*. 2013;368(4):351-364.
- [2] Goss PE, Strasser-Weippl K, Lee-Bychkovsky BL, et al. Challenges to effective cancer control in China, India, and Russia. *The Lancet Oncology*. 2014;15(5):489-538.
- [3] Hernandez C, Huebener P, Schwabe RF. Damage-associated molecular patterns in cancer: a double-edged sword. *Oncogene*. 2016;35(46):5931-5941.
- [4] Mayekar MK, Bivona TG. Current Landscape of Targeted Therapy in Lung Cancer. *Clinical Pharmacology & Therapeutics*. 2017;102(5):757-764.
- [5] Wistuba II, Gazdar AF. LUNG CANCER PRENEOPLASIA. *Annual Review of Pathology: Mechanisms of Disease*. 2006;1(1):331-348.

- [6] Kadara H, Wistuba II. Field Cancerization in Non–Small Cell Lung Cancer: Implications in Disease Pathogenesis. *Proceedings of the American Thoracic Society*. 2012;9(2):38-42.
- [7] Tang X, Shigematsu H, Bekele BN, et al. EGFR Tyrosine Kinase Domain Mutations Are Detected in Histologically Normal Respiratory Epithelium in Lung Cancer Patients. *Cancer Research*. 2005;65(17):7568-7572.
- [8] Bass AJ, Watanabe H, Mermel CH, et al. SOX2 is an amplified lineage-survival oncogene in lung and esophageal squamous cell carcinomas. *Nature Genetics*. 2009;41(11):1238-1242.
- [9] Buchheidt D, Skladny H, Baust C, Hehlmann R. Systemic Infections with *Candida* sp. and *Aspergillus* sp. in Immunocompromised Patients with Hematological Malignancies: Current Serological and Molecular Diagnostic Methods. *Chemotherapy*. 2000;46(3):219-228.
- [10] Khuri FR, Cohen V. Molecularly Targeted Approaches to the Chemoprevention of Lung Cancer. *Clinical Cancer Research*. 2004;10(12):4249s-4253s.
- [11] Karthaus M, Doellmann T, Klimasch T, et al. Intensive Intravenous Amphotericin B for Prophylaxis of Systemic Fungal Infections. *Chemotherapy*. 2000;46(4):293-302.
- [12] Dasari S, Bernard Tchounwou P. Cisplatin in cancer therapy: Molecular mechanisms of action. *European Journal of Pharmacology*. 2014; 740:364-378.
- [13] Olaussen KA, Postel-Vinay S. Predictors of chemotherapy efficacy in non-small-cell lung cancer: a challenging landscape. *Annals of Oncology*. 2016;27(11):2004-2016.
- [14] Hanauske AR, Chen V, Paoletti P, Niyikiza C. Pemetrexed Disodium: A Novel Antifolate Clinically Active Against Multiple Solid Tumors. *The Oncologist*. 2001;6(4):363-373.
- [15] Hande KR. Etoposide: four decades of development of a topoisomerase II inhibitor. *European Journal of Cancer*. 1998;34(10):1514-1521.
- [16] Clinical validation of a comprehensive cancer genomics analysis for lung cancer patients. | *Journal of Clinical Oncology*.
- [17] The Cancer Genome Atlas Research Network. Author Correction: Comprehensive molecular profiling of lung adenocarcinoma. *Nature*. 2018;559(7715): E12-E12.
- [18] Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4–ALK fusion gene in non-small-cell lung cancer. *Nature*. 2007;448(7153):561-566.
- [19] Farago AF, Le LP, Zheng Z, et al. Durable Clinical Response to Entrectinib in NTRK1-Rearranged Non-Small Cell Lung Cancer. *Journal of Thoracic Oncology*. 2015;10(12):1670-1674.
- [20] Jänne PA, Van Den Heuvel MM, Barlesi F, et al. Selumetinib Plus Docetaxel Compared with Docetaxel Alone and Progression-Free Survival in Patients with KRAS -Mutant Advanced Non–Small Cell Lung Cancer: The SELECT-1 Randomized Clinical Trial. *JAMA*. 2017;317(18):1844.
- [21] Nair J, Nair A, Veerappan S, Sen D. Translatable gene therapy for lung cancer using Crispr CAS9—an exploratory review. *Cancer Gene Therapy*. 2020;27(3-4):116-124.