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Genetics and Environmental Causes of Lung Cancer: Insights into KRAS, ALK, EGFR Mutations and the influence of Tobacco Smoking

Jiarui Hu*

Western Christian High School, Upland, CA, USA

* Corresponding Author Email: Jiarui.Hu@mywcs.com

Abstract. As a critical worldwide health issue, Lung cancer represents one of the leading causes of cancer-related mortality worldwide. Grasping the root causes of lung cancer is essential for creating and utilizing effective treatment strategies. This paper will explore four primary causes in-depth: tobacco smoking, KRAS mutation, ALK mutation, and EGFR mutation. Tobacco smoking, the most prevalent cause, introduces carcinogens that damage lung tissue, leading to cellular mutations. The KRAS mutation, found in about 25% of lung adenocarcinomas, results in uncontrolled cell growth and division by activating oncogenic pathways. The ALK mutation, present in approximately 5% of non-small cell lung cancers (NSCLC), involves a genetic rearrangement, creating a fusion gene that drives malignant cell proliferation. The GFR mutation, found in 10-15% of NSCLC cases, leads to uncontrollable and continuous Epidermal growth receptor activation, promoting uncontrolled cell division. Understanding these causes allows for specific therapies that target each cause to be formed, underpinning the development of diagnostic and therapeutic approaches, which offers hope for more personalized and effective treatments. This paper will also briefly discuss the current treatments for lung cancer, including targeted therapies for each cause of lung cancer and ongoing research aimed at improving patient outcomes.

Keywords: lung cancer; tobacco smoking; KRAS; EGFR; ALK.

1. Introduction

Cancer refers to a collection of diseases marked by uncontrollable cell growth and can invade or metastasize to other parts of the body. While benign tumors are non-cancerous and typically localized, malignant tumors, or cancers, possess the ability to metastasize, making them particularly dangerous and challenging to treat. The cell cycle, which regulates cell growth, division, and death, is critical for maintaining healthy tissue function. Disruptions in this orderly process can lead to the formation of tumors, with malignant neoplasms capable of invading nearby tissues and spreading throughout the body. The development of cancer is a complex, multi-step process that involves genetic mutations and alterations in cell signaling pathways. These changes can be triggered by various factors, including environmental exposures, lifestyle choices, and inherited genetic predispositions. For instance, exposure to carcinogens such as tobacco smoke, ultraviolet radiation, and certain chemicals can cause DNA damage, leading to mutations that promote cancer development [1]. Lung cancer, a type of malignant neoplasm, occurs when cells in the lungs grow uncontrollably and metastasize to other parts of the body. It is one of the most common and deadliest forms of cancer worldwide, accounting for a significant proportion of cancer-related deaths. According to the World Health Organization (WHO), lung cancer is responsible for approximately 1.8 million deaths annually, making it the leading cause of cancer mortality globally [2]. The high mortality rate is attributed to the often-late detection of the disease and its aggressive nature. There are two main types of lung cancer: NSCLC and SCLC. Of the two, NSCLC is the most common; according to scientists, it accounts for about 85% of all lung cancer cases, while the rest are SCLC. [3]. Each type has distinct biological behaviors, clinical presentations, and treatment approaches. Clinically, lung cancer symptoms often do not appear until the disease is advanced, contributing to its high mortality rate. Some common symptoms are -- persistent coughing, dull chest pain, shortness or lack of breath, and

sudden weight loss. In some cases, patients may experience hoarseness, recurrent respiratory infections, and coughing up blood. Frequently mistaken for other respiratory diseases that are way less severe, these specific symptoms can significantly delay the process of diagnosis and treatment. The etiology of lung cancer is multifactorial, with both genetic and environmental factors playing crucial roles. Cigarette smoking, the primary environmental cause, is linked to as many as 85% of lung cancer cases [3]. There are hundreds of carcinogens in tobacco smoke, including those capable of inducing genetic alterations leading to cancer. Other risk factors include radon gas exposure, asbestos, air pollution, and a history of first-degree relatives with lung cancer. Occupational exposure to other carcinogens, such as arsenic and diesel motor exhaust, also increases the risk of developing lung cancer.

Genetic mutations also play a significant role in lung cancer development. Among these, KRAS mutations are prevalent within non-small cell lung cancer patient's genomes, occurring in approximately 25-30% of cases [4]. Nowadays, these mutations have been identified as the cause of resistance to certain therapies, making them a critical area of study for developing targeted treatments. Another significant genetic factor in lung cancer is the presence of ALK mutations, found in about 5% of NSCLC patients. These mutations result from chromosomal rearrangements and lead to the generation of dysfunctional proteins, which drive uncontrolled cell proliferation and, finally, tumor growth. Similarly, epidermal growth factor receptor (EGFR) gene mutations are also implicated in the pathogenesis of lung cancer, accounting for anywhere between 10-15% of NSCLC cases, particularly among non-smokers and individuals of Asian descent. All these mutations result in the abnormal amplification of signal transduction in the down-stream pathway, which promotes persistent cell division and survival.

2. Key Causes of Lung Cancer

2.1. Tobacco Smoking

Tobacco smoking, the primary cause of lung cancer, is responsible for approximately 85% of all diagnosed cases. Which is recognized as the major factor of lung cancer development. The carcinogens in tobacco smoke cause direct damage to the DNA in lung cells, leading to mutations that can initiate and promote cancer growth. Smoking is strongly correlated with both SCLC and NSCLC, the two primary types of lung cancer.

The carcinogenic properties of tobacco smoke are well-documented. Tobacco smoke contains over 70 known carcinogens, including polycyclic aromatic hydrocarbons (PAHs) and nitrosamines, which cause genetic mutations. These carcinogens induce mutations in critical genes involved in cell cycle regulation and DNA repair, leading to uncontrolled cell proliferation and tumor development [5]. Moreover, smoking is associated with chronic inflammation in the lung tissue, further contributing to carcinogenesis. Chronic inflammation due to smoking results in a continuous cycle of injury and repair, which can create a microenvironment conducive to tumor development and progression.

Epidemiological studies have consistently shown that tobacco smoking causes lung cancer in a dose-dependent manner, as the occurrence is positively related to the number of cigarettes smoked per day and the duration of smoking. For instance, long-term smokers are at significantly higher risk of developing lung cancer compared to non-smokers or those who quit smoking [6]. The cessation of smoking reduces the risk of lung cancer, but former smokers still carry a higher risk compared to never-smokers due to the irreversible genetic damage caused by prolonged exposure to tobacco carcinogens. The latency period between smoking initiation and lung cancer diagnosis can span several decades, making early intervention and smoking cessation crucial in reducing lung cancer incidence.

2.2. KRAS Mutations

KRAS, also known as Kirsten rat sarcoma viral oncogene homolog, is one of the most prevalent genetic alterations in non-small cell lung cancer, occurring in approximately 25-30% of cases [7]. As a critical component of the RAS/MAPK signaling pathway, KRAS regulates differentiation, proliferation, and survival, which are all essential cellular processes. KRAS gene mutation also leads to the near-permanent activation of the KRAS protein, driving uncontrolled cell growth and cancer development.

The mechanism by which KRAS mutations contribute to lung cancer involves the continuous activation of the RAS/MAPK pathway. Normally, this pathway is activated only when the signals transmitting from outside the cell to the nucleus. While in mutated KRAS, the protein remains in a permanently active state, disrupting the balance of cell signaling and promoting unchecked cell proliferation.

Compared to EGFR mutations and ALK rearrangements in lung cancer, KRAS mutation is harder to treat, as it shows significant resistance to corresponding targeted therapies. This resistance arises from the intricate nature of the RAS signaling pathway and the lack of effective inhibitors that specifically target KRAS mutations [8]. Recent advancements in molecular biology have, however, led to the development of KRAS-specific inhibitors such as the KRAS(G12C) inhibitor, which shows promising results in clinical trials.

KRAS mutations are more frequently found in smokers than in non-smokers, indicating a significant association between smoking and KRAS-mutant lung cancer. Tobacco smoke carcinogens are known to induce mutations in the KRAS gene, contributing to the initiation and progression of lung cancer in smokers. This correlation underscores the necessity for personalized treatment approaches that account for both genetic predispositions and environmental exposures in lung cancer patients. Ongoing research continues to explore the molecular mechanisms underlying KRAS-mutant lung cancer, aiming to uncover novel therapeutic targets that can enhance treatment outcomes for this specific subtype of the disease.

2.3. ALK Mutations

Anaplastic lymphoma kinase (ALK) mutations are identified in about 5% of non-small cell lung cancer cases, primarily affecting younger patients and non-smokers [11]. These mutations arise from chromosomal rearrangements that lead to the production of abnormal fusion proteins, such as EML4-ALK, which is involved in driving uncontrolled cell proliferation and tumor growth. The fusion typically involves the ALK gene and another partner gene, most commonly EML4 (echinoderm microtubule-associated protein-like 4), resulting in the formation of a hybrid gene that encodes an oncogenic fusion protein.

The oncogenic potential of the EML4-ALK fusion protein stems from its constitutive tyrosine kinase activity, which perpetually activates downstream signaling pathways crucial for cell growth and survival, notably the PI3K/AKT and RAS/MAPK pathways. These pathways are instrumental in regulating cell cycle progression and inhibiting apoptosis, thereby promoting tumor initiation and progression. The continuous activation of these pathways by the ALK fusion protein facilitates unchecked cellular proliferation and impedes programmed cell death, characteristic features of cancer development.

The identification of ALK rearrangements in lung cancer has spurred the development of targeted therapies specifically designed to inhibit the activity of these fusion proteins. ALK inhibitors, exemplified by crizotinib, have demonstrated substantial efficacy in treating patients with lung cancer caused by ALK rearrangements, resulting in notable improvements in both survival outcomes and quality of life. Crizotinib functions by binding to the ATP-binding site within the ALK tyrosine kinase domain, thereby preventing its activation and subsequent signaling. This inhibition disrupts the

proliferative and survival signals, prompting tumor cells to undergo apoptosis and effectively curbing tumor growth.

Despite the initial success of ALK inhibitors, resistance to these therapies remains a significant clinical challenge. Resistance mechanisms can emerge over time, often involving secondary mutations within the ALK gene that alter the binding affinity of the inhibitor and diminish its effectiveness. Additionally, tumor cells may employ alternative signaling pathways or undergo histological transformations to evade the inhibitory effects of ALK inhibitors.

In response to emerging resistance, second-generation ALK inhibitors such as ceritinib and alectinib have been developed to address these challenges. These inhibitors exhibit enhanced potency against a broader spectrum of ALK mutations and possess the ability to penetrate the blood-brain barrier, offering improved therapeutic outcomes for patients with brain metastases. Further advancements in treatment include third-generation inhibitors like lorlatinib, which are engineered to overcome resistance mechanisms encountered with earlier generations and effectively target a wide array of ALK mutations.

ALK-positive lung cancer represents a distinct molecular subtype of NSCLC characterized by unique clinical and pathological features. Patients harboring ALK rearrangements generally experience a more favorable prognosis compared to those with KRAS mutations or other genetic alterations, particularly when treated with targeted therapies tailored to their specific genetic profiles. Effective management of ALK-positive lung cancer necessitates ongoing surveillance for resistance mechanisms and the timely adaptation of therapeutic strategies based on molecular testing results. This proactive approach enables clinicians to detect secondary mutations and alternative pathway activations, facilitating the informed selection of subsequent treatment modalities [9].

2.4. EGFR Mutations

Epidermal growth factor receptor (EGFR) mutations occur in approximately 10-15% of non-small cell lung cancer cases, predominantly among non-smokers and individuals of Asian descent. EGFR functions as a transmembrane receptor tyrosine kinase pivotal in regulating cell proliferation, survival, and differentiation. In normal conditions, activation of the EGFR signaling pathway is initiated by epidermal growth factor (EGF) binding to the receptor's extracellular domain. This interaction induces receptor dimerization and subsequent autophosphorylation of tyrosine residues within the intracellular domain, triggering downstream signaling pathways, including PI3K/AKT and RAS/MAPK, essential for maintaining cellular homeostasis [10].

Mutations in the EGFR gene result in the constitutive activation of its pathway, independent of ligand binding. Typically occurring within the tyrosine kinase domain, these mutations lead to persistent receptor dimerization and autophosphorylation, perpetuating signaling through PI3K/AKT and RAS/MAPK pathways（Shown in Figure 1). This sustained activation promotes uncontrolled cell proliferation and survival, hallmark features of cancer progression. Common EGFR mutations in NSCLC include deletions in exon 19 and the L858R point mutation in exon 21, which enhance EGFR kinase activity and drive oncogenic processes.

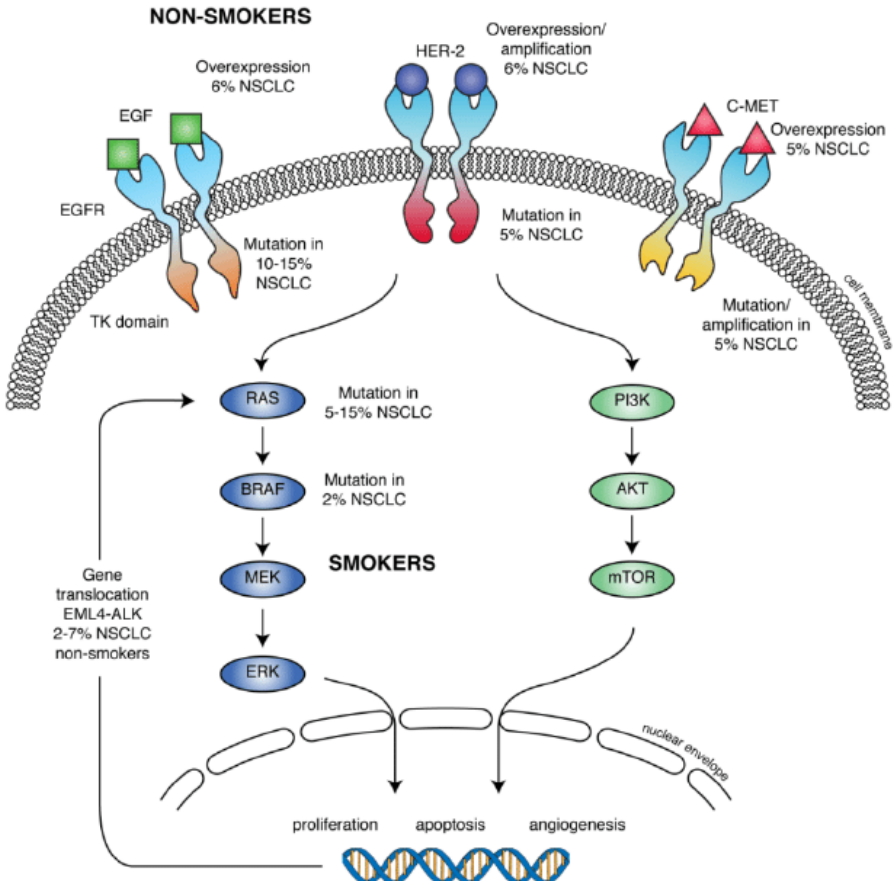

Figure 1. EGFR Pathway in Non-Small Cell Lung Cancer [11]

The discovery of EGFR mutations has revolutionized NSCLC treatment, particularly through the development of targeted therapies like tyrosine kinase inhibitors (TKIs). TKIs such as gefitinib and erlotinib selectively block the activity of mutant EGFR by binding to its ATP-binding site, thereby inhibiting downstream signaling and inducing apoptosis in cancer cells. These targeted interventions have achieved great success in EGFR-mutant lung cancer patients.

Despite initial successes, acquired resistance to EGFR TKIs poses a significant clinical challenge. Resistance mechanisms often involve secondary mutations within the EGFR gene, such as the T790M mutation, which alters the binding affinity of TKIs and diminishes their efficacy. Additionally, cancer cells may activate alternative signaling pathways, such as MET or HER2, to sustain growth and survival despite EGFR inhibition.

To address resistance, second- and third-generation EGFR TKIs such as Osimertinib have been developed. These inhibitors are designed to target specific resistance-associated mutations, including T790M, thereby prolonging disease control in patients who have progressed on earlier therapies. As the mechanism of resistance varies, the key to improve the efficiency of inhibitors is exploring them thoroughly and designing a universal drug that could be applied in broad-spectrum of lung cancer categories.

3. Conclusion

Lung cancer remains a significant global health concern, driven by various causes including tobacco smoking, KRAS mutations, ALK mutations, and EGFR mutations. Tobacco smoking introduces carcinogens that damage lung tissue, leading to gene mutations and cancer development. KRAS mutations result in continuous activation of the RAS/MAPK signaling pathway, driving uncontrolled cell growth. ALK mutations, caused by chromosomal rearrangements, produce fusion proteins that lead to unchecked cellular proliferation. EGFR mutations cause constant activation of the receptor tyrosine kinase, promoting abnormal cell division and survival.

Understanding these causes is crucial for developing targeted treatment strategies. For lung cancer caused by tobacco smoking, prevention through smoking cessation is essential, alongside conventional treatments like chemotherapy and radiotherapy to address the resulting tumors. For KRAS-mutant lung cancer, the development of KRAS-specific inhibitors shows promise, although challenges remain due to the complexity of the RAS signaling pathway. Additionally, new approaches like CRISPR gene editing are being explored to directly target and correct the KRAS mutations at the genetic level.

ALK-positive lung cancer can be effectively managed with ALK inhibitors, which target the fusion proteins responsible for tumor growth. Second- and third-generation ALK inhibitors have been developed to overcome resistance and provide sustained clinical benefit. Similarly, EGFR-mutant lung cancer benefits from tyrosine kinase inhibitors that specifically inhibit the aberrant EGFR activity. Newer generation TKIs, such as Osimertinib, are designed to overcome resistance mechanisms and provide longer-lasting control of the disease.

Personalized treatment approaches, based on the specific genetic alterations driving the cancer, offer the potential for improved outcomes and prolonged survival. Ongoing research into the molecular mechanisms of lung cancer will continue to enhance our ability to develop effective therapies. Advances in targeted therapies, gene editing technologies like CRISPR, and immunotherapy hold promise for significantly reducing the global burden of this devastating disease, providing hope for better management and cure of lung cancer.

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