Journal of Biosciences and Medicines, 2024, 12, 130-137
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

# The Investigation into Intrinsic Elements Influencing the Onset of Lung Cancer

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**How to cite this paper:** Chen, S., Lin, W.L. and Lu, F. (2024) The Investigation into Intrinsic Elements Influencing the Onset of Lung Cancer. *Journal of Biosciences and Medicines*, **12**, 130-137.
https://doi.org/10.4236/jbm.2024.123011

**Received:** February 20, 2024
**Accepted:** March 15, 2024
**Published:** March 18, 2024



## Abstract

Lung cancer is a highly heterogeneous malignancy with a complex pathogenesis, involving a series of endogenous alterations such as genetic mutations, epigenetic modifications, and oxidative stress. Recent advancements in lung cancer research, especially at the genomic and molecular biology levels, have continuously provided new potential targets and perspectives for the diagnosis and treatment of lung cancer. Therefore, this article summarizes the recent progress in the study of endogenous factors related to the pathogenesis of lung cancer, aiming to enhance the understanding of intrinsic factors in lung cancer and to organize ideas for subsequent related research.

## Keywords

Lung Cancer, Pathogenesis, HRR Gene Mutation, Epigenetic Modification, Oxidative Stress

## 1. Introduction

Lung cancer, originating from the epithelium of the trachea, bronchi, or glands, is categorized into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). According to the World Health Organization's 2019 report, lung cancer ranks as the sixth leading cause of death globally [1] and is the primary cause of cancer mortality [2]. Smoking is the principal exogenous factor leading to lung cancer, whereas endogenous factors include genetics, gene mutations, and the abnormal accumulation or imbalance of physiological metabolites. With increasing emphasis on smoking cessation, the incidence of lung cancer attributa-

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ble to exogenous factors is trending downward, whereas the proportion attributed to endogenous factors is rising [3]. Thus, exploring the endogenous factors of lung cancer could facilitate better solutions to the dilemmas of diagnosis and treatment. Based on this, the article provides a comprehensive review of the mechanisms of disease associated with endogenous factors identified in lung cancer.

## 2. HRR Gene Mutation

Homologous recombination repair (HRR) is the body's most precise DNA damage repair mechanism, involving genes known as HRR genes [4]. The impairment of HRR leads to the accumulation of DNA damage and the disruption of normal cell growth regulatory mechanisms, thereby inducing cancer.

### 2.1. The Association between HRR Gene Mutations and Lung Cancer

In China, 35.3% of SCLC patients exhibit mutations leading to disruptions in DNA repair mechanisms [5], while 33.29% of NSCLC patients are affected [6]. In both types of lung cancer, mutations related to HRR genes occur most frequently in the ATM gene. ATM gene mutations are highly associated with female lung adenocarcinoma, even among non-smokers [7], and research suggests that mutations in ATM may increase the risk of familial lung cancer [8]. Additionally, the NBN and BRCA2 genes also have a significant mutation frequency among lung cancer patients [9]. The p.I171V heterozygous mutation in NBN, a protein encoded by the NBN gene and a component of the MRN complex, is considered a risk factor for lung cancer development [10]. Although BRCA2 is primarily associated with breast cancer, studies have found that 2.5% of all tumor patients with BRCA1/2 mutations are diagnosed with SCLC [11]. However, a Meta-analysis has challenged the association among these genes and lung cancer [12], thus the relationship between BRCA2 and lung cancer remains a topic for further discussion.

### 2.2. The Association between HRR Gene Mutation and Germline Mutation

Germline mutations refer to genetic alterations occurring in reproductive cells [13], affecting not only the individuals but also their direct descendants, thus having profound implications. In lung cancer patients, the presence of HRR gene mutations entails a 61.3% likelihood of germline mutations, particularly with mutations in the BRCA2 and CHEK2 genes. Consequently, studies recommend screening all lung cancer patients for germline genetic mutations to mitigate the impact on future generations [14].

## 3. Epigenetic Modification

Epigenetic modifications refer to alterations in the gene expression without chang-

ing the DNA sequence itself, through the regulation of gene activity. These modifications play a crucial role in the cancer regulation and are considered potential tumor biomarkers [15]. Currently, epigenetic modifications are primarily categorized into three types: DNA methylation, histone modification, and non-coding RNA (cnDNA).

### 3.1. The Association between DNA Methylation and Lung Cancer

DNA methylation, a process of gene silencing through the addition of methyl groups, is considered a primary epigenetic modification in the human genome [16]. Abnormal DNA methylation leads to genome-wide demethylation or localized hypermethylation of certain non-coding regions, disrupting the balance between oncogenes and tumor suppressor genes, thereby initiating cellular transformation into cancer.

In early-stage lung cancer, abnormalities in DNA methylation can be detected [17], suggesting its pivotal role at the onset of lung cancer, such as methylation of the MGMT promoter, which is highly associated with lung cancer [18]. The methylation of the RASSF1A gene can activate the RAS oncogene related to lung cancer [19]. In the recurrence of lung cancer, DNA methylation levels remain aberrant, and a recurrence model for early-stage lung cancer constructed from this can achieve 100% sensitivity and an area under the curve of 0.95 for specificity [20]. This further indicates its close association with the development of lung cancer.

Different types of lung cancer exhibit distinct DNA methylation patterns, especially in the case of SCLC [21], a highly malignant type of lung cancer. Utilizing the unique DNA methylation patterns of SCLC to construct detection models with high sensitivity and specificity could advance diagnosis and treatment, potentially improving survival rates for patients with SCLC. Professor Carl M. Gay's team has even leveraged DNA methylation for further subtyping of SCLC, delineating four new subtypes each with unique cellular and molecular characteristics and therapeutic vulnerabilities [22]. This could lead to more refined and personalized treatment approaches, significantly enhancing treatment efficacy for SCLC patients.

### 3.2. The Association between Histone Modification and Lung Cancer

Human chromosomal DNA is coiled around four different histones, forming nucleosome the specific combination of histone modifications allows for the reading of certain DNA information to produce specific biological outcomes [23]. Since this process does not involve changes in the DNA sequence, it is considered one of the regulatory mechanisms of epigenetic modifications [24].

Oncogenes are typically in a state of silence or low expression. However, when histones are modified in a specific way that exposes oncogenes, a series of downstream molecules and proteins are translated and expressed, leading to cancer. For instance, SENP1 can promote the progression of lung adenocarcinoma by

activating the AAT gene [25], and SETDB1 can upregulate methylation at K64, leading to the overactivation of Akt [26], thereby promoting lung cancer progression and predicting poor outcomes.

The fundamental cause of epigenetic modifications resulting from histone modifications is the aberrant expression of specific DNA, involving both gene activation and silencing. Experimentally silencing the histone acetyltransferase HOB1 in NSCLC patients can activate anti-NSCLC cell activity [27], and knocking down the histone acetyltransferase KMT9 can trigger non-apoptotic death in the lung cancer A549 model [28].

### 3.3. The Association between ncRNA and Lung Cancer

The ncRNA represents a category of RNA molecules that function at the RNA level without being translated into proteins. With the deepening understanding of ncRNA functions, it has been found to play a significant role in the development and progression of tumors.

It has been documented that a multitude of different ncRNAs are differentially expressed in various tissues and bodily fluids of lung cancer patients, influencing nearly every aspect of lung cancer, including its initiation, invasion, metastasis, progression, and resistance to chemotherapy drugs [29]. Different ncRNAs play significant roles in the development and progression of lung cancer through various pathways, such as miR-125a-5p, which induces apoptosis in lung cancer cells by increasing the expression of the tumor suppressor gene p53 mRNA and protein [30]. Similarly, miR-301b-3p [31] and miR-376a-3p [32] has been shown to promote the proliferation and metastasis of lung cancer cells. However, many studies to date have focused on the expression levels of ncRNAs, with the specific mechanisms of their functions not yet fully elucidated.

## 4. Oxidative Stress

Reactive oxygen species (ROS) encompass a variety of metabolic byproducts related to oxygen, including oxygen-containing free radicals and peroxides prone to forming free radicals, generated during biological metabolic processes [33]. When the levels of ROS surge dramatically, they inflict damage upon cellular structures and DNA, altering their normal physiological functions and fostering inflammatory responses, a process known as oxidative stress [34].

In the progression of lung cancer, ROS plays a pivotal role. At a precancerous stage, ROS promotes the onset of cancer by inducing mutations in oncogenes and tumor suppressor genes through oxidative stress. In the later stages of tumor progression, they assist in cancer cell invasion and metastasis by activating the NF-$\kappa$B and MAPK pathways [35]. Oxidative stress contributes to lung cancer not only by damaging DNA, altering its coding, and triggering certain inflammatory pathways but also by increasing the risk of mutations and malignant tumors through attacks on lipids and proteins. Lipid peroxidation can damage cell membranes, affecting normal cell functions, while protein peroxidation may lead

to an accumulation of DNA damage by inhibiting enzymes involved in DNA damage repair processes [36].

## 5. Summary and Prospect

Endogenous factors related to lung cancer primarily encompass mutations in HRR genes, epigenetic modifications, and oxidative stress, which may induce cancer by altering original genetic information or directly impacting the gene expression. Mutations in HRR genes lead to lung cancer by accumulating DNA damage due to impaired DNA repair mechanisms. Among the principal modes of epigenetic modification, DNA methylation is highly associated with lung cancer, currently serving mainly as a biomarker for diagnosis. Histone modifications express specific biological outcomes by activating or silencing certain genes, while the role of non-coding RNA, though not fully elucidated, is confirmed to be aberrantly expressed in lung cancer. Oxidative stress, a result of abnormal ROS, can be considered a cumulative effect of damage leading to the onset of lung cancer. Distinct therapeutic strategies should be employed for lung cancer contingent upon the underlying pathogenic mechanisms. For instance, in cases attributable to HRR gene mutations leading to the incapacitation of DNA damage repair mechanisms, the focus should shift towards the restoration of these mechanisms rather than the erroneously spliced genetic information. Conversely, in lung cancers precipitated by alterations in epigenetic modifications, identifying genes that have been aberrantly activated or silenced becomes paramount.

The pathogenesis of lung cancer related to endogenous factors has been extensively studied; however, the mechanisms are dispersed, and it is unclear whether many molecules and genes serve as "drivers" or "concomitant changes". Furthermore, many studies focus only on detecting expression levels without delving into the pathogenic mechanisms of pathways. Future research could benefit from focusing more on the relationships between molecules to explicit the mechanisms of lung cancer pathogenesis. Additionally, many studies suffer from small sample sizes, limiting the reliability of detected molecular and gene level changes. It is recommended that further researches involve multicenter studies to increase sample sizes and enhance persuasiveness. Understanding the role of endogenous factors in the development and progression of lung cancer can provide better insights and evidence for diagnosis and treatment, aiming to improve patient survival rates and quality of life.

## Fund

Science and Technology Development Project of Chinese Rehabilitation Medical Association (Project No. KFKT-2022-024) "Study on the influence of Taijiquan on cardiopulmonary function and negative emotion in patients with pulmonary nodules".

Fujian University of Traditional Chinese Medicine Major Scientific and Tech-

nological Innovation "Jie Bang Gua Shuai" special project (Project number: XJB2022002) "Construction of lung nodule risk stratified multidimensional markers and evaluation of exercise rehabilitation Program".

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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