Molecules Associated with the Development of Lung Cancer

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A thesis submitted to the **Department of Mathematics and Natural Sciences** in partial fulfillment of the requirements for the degree of

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Declaration

It is hereby declared that-

1. The thesis submitted is our original work while completing the bachelor degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material that has been accepted or submitted, for any other degree or diploma at a university or other institution.
4. We have acknowledged all the main sources of help.

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1. Abstract

Molecular association with lung cancer is one of the most important and a very primary queries to understand the molecular basis of lung cancer and its development mechanism. There are different factors involved with the development of lung carcinoma. Smoking, environmental hazards, and occupational hazards are the main risk factors. Different molecules are involved differently in the development, progression, and spread of lung cancer. Similarly, some molecular associations are also found in the diagnosis and treatment of this disease. Epigenetic alterations have been reported widely in the sector of lung cancer which plays a major role in the genesis of lung cancer. Here in this review, we try to provide an overview of different molecular associations with lung cancer in different steps including- risk factors, disease induction, disease catalyzation, disease sustenance, epigenetic factors, biomarker appearance, and therapeutic purposes. We give more emphasis on different mutational changes which induce, accelerate and animate this deadliest disease. Our focus is also on different therapeutic aspects of lung cancer.

2. Introduction

Molecular understanding is the most essential part of any disease to find solutions for it. A similar norm goes for lung cancer. Lung cancer has a diverse and complex molecular origin. There is a lot of genetic variation in lung tumors, but only a small number of recurrent mutations occur often. The diagnosis, prognosis, and management of lung cancer could all be affected by advances in our knowledge of molecular changes at several levels, including genetic, epigenetic, and protein expression, and their functional relevance. Multiple genetic and epigenetic changes, most notably the activation of growth-promoting pathways and the suppression of tumor suppressor pathways, play a role in the multi-step process by which lung malignancies arise (Cooper et al., 2013). Despite substantial improvements in both diagnostic and treatment methods, lung cancer continues to be the primary cause of cancer-related death globally with a 5-year survival rate of fewer than 15%. Due to different disease patterns and therapeutic approaches, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) have long been considered the two primary forms of lung cancer. NSCLC accounts for the bulk of cases (85%), with adenocarcinomas (AC) accounting for 40%, squamous cell carcinomas (SCC) for 25%–30%, and large cell carcinomas (LCC) for 10%–15% (Wood et al., 2015).

The stage of the disease at presentation affects prognosis, with radical radiotherapy and surgical resection of early-stage disease giving patients a higher chance of recovery. Unfortunately, the majority of patients are diagnosed with advanced disease, which has a negative impact on their prognosis. One of the main objectives of cancer research is to comprehend the distinctive genetic alterations that underlie lung cancer, as well as the changed expression of the biomolecules that either cause or result from lung cancer. As a result, strategies for treating, classifying patients, and monitoring patients can be developed, leading to outcomes including the ability to detect disease recurrence after prior therapy (Wood et al., 2015).

3. Overview of Cancer

In a simplest word, cancer is one kind of cell state where cells don't have the ability to follow body's natural control mechanism. Our body contains billions of cells with multiple types of functions. These are very complex process which have incredibly phenomenal control capacity. If these controls are disturbed due to some malfunctions of the normal cellular control processes and if those malfunctioned cells keep growing that's call cancer. As those cells grow and divide, they turn into a mass or they clump together, that's what termed as tumor. This tumor can get smart and spread other places, that's what is known as metastasis.

As there are cells everywhere in the body so, cancer can actually occur in any part of the body. In women, one of the most common cancers is breast cancer. In men, prostate cancer and in both men and women lung cancer and colon cancer are common cancers. Every person has cancer of unique characteristics due to genetic changes of different combinations.

Amongst all type of cancers, lung cancer leads more cancerous death worldwide. According to WHO, lung cancer is a leading cause of death worldwide, accounting for nearly 1.80 million deaths in 2020 (Organization, 2022). Lung cancer is a highly complicated group of various but related neoplasms from a histopathological and biological perspective, and it likely has many preneoplastic pathways (Kadara & Wistuba, 2014). Numerous studies have suggested that lung cancer is largely influenced by epigenetic changes, such as DNA methylation, histone modifications, and non-coding RNA expression (Langevin, Kratzke, & Kelsey, 2015). Lung cancer consists of several histological types, including small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC) with types of squamous cell carcinoma, adenocarcinoma

(including the noninvasive type of bronchioloalveolar carcinoma, BAC), and large cell carcinoma. Lung cancers may arise from the major bronchi (central tumors) or small bronchi, bronchioles, or alveoli (peripheral tumors) of the distant airway of the lung. Squamous cell carcinomas and SCLCs usually arise centrally, whereas adenocarcinomas and large cell carcinomas usually arise peripherally (Kadara & Wistuba, 2014).

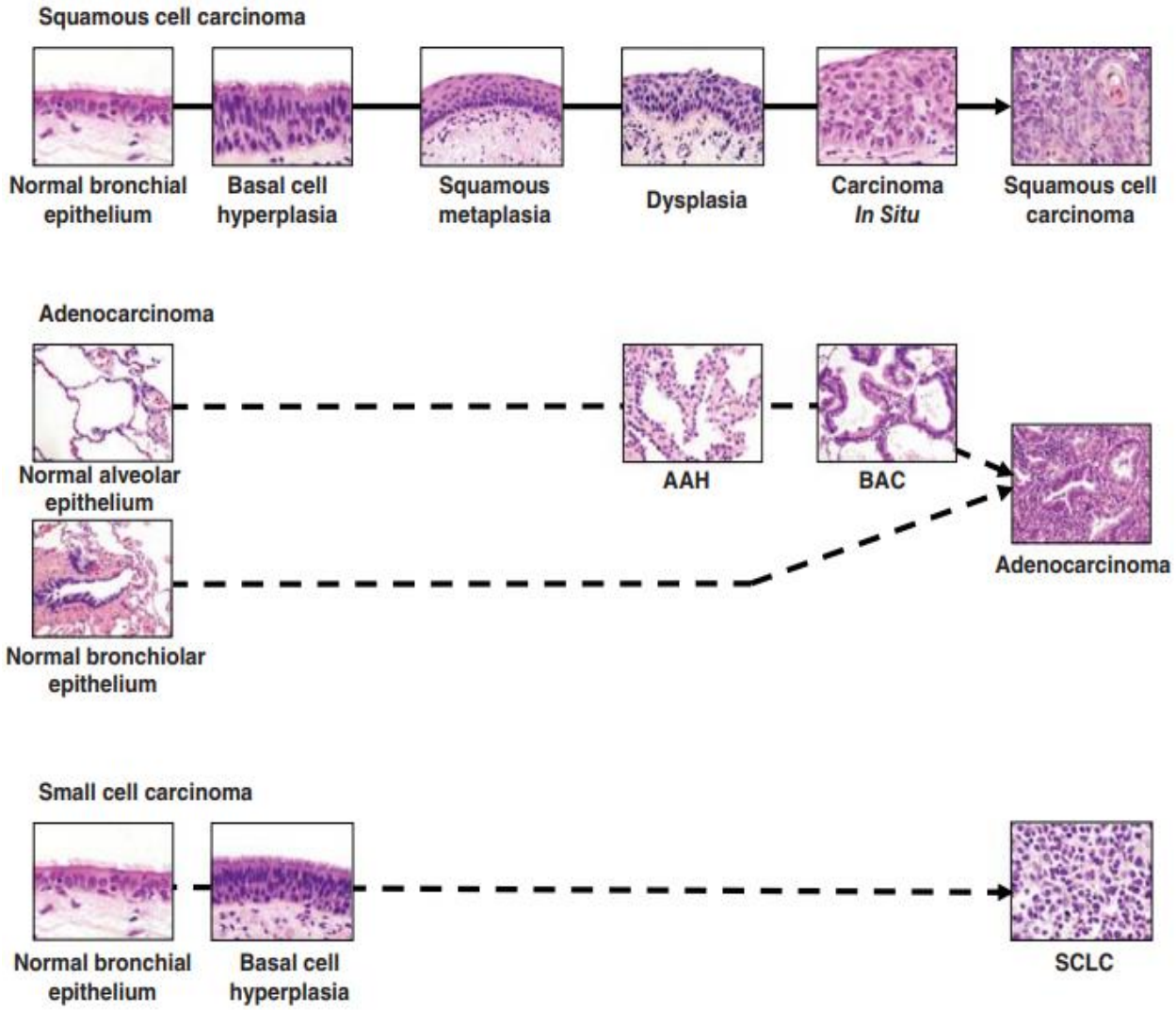

Figure 1: Summary of histopathologic changes involved in the pathogenesis of lung cancer. The sequence of preneoplastic lesions involved in the development of squamous cell carcinoma of the lung has been elucidated. For adenocarcinoma histology, the only known preneoplastic lesion is AAH (Atypical Adenomatous Hyperplasia), which seems to be the precursor for a subset of lung adenocarcinomas. No preneoplastic lesion has been recognized for SCLC (microphotographs of histological tissue sections stained with hematoxylin and eosin) (Kadara & Wistuba, 2014).

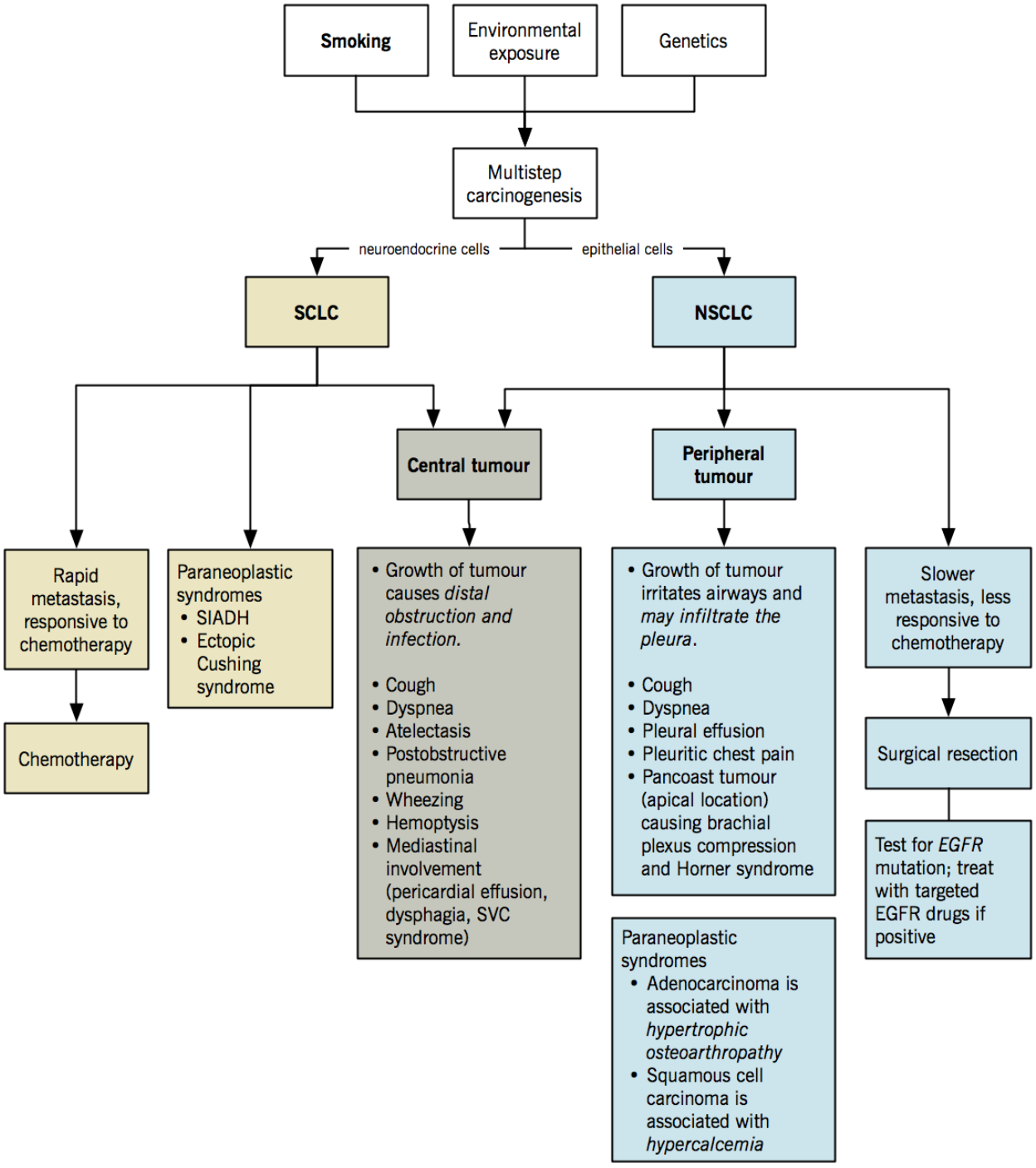

Figure 2: Overview of lung cancer pathophysiology (Wu, Wong, & Chaudhry, 2012).

Exposure to carcinogens is the cause of lung cancer. Cigarette smoke, which is responsible for 85% of cases of lung cancer, is the main cause. Toxic substances like asbestos and tar as well as metals like arsenic and chromium pose additional dangers. In people who acquire lung cancer, hereditary vulnerability is frequently increased by environmental exposure. Both small-cell lung

cancer (SCLC) and non-small-cell lung cancer (NSCLC) develop from distinct cell types and have unique clinical characteristics. While NSCLC can arise from both central and peripheral malignancies, SCLC only arises from central tumors. SCLC spreads quickly, yet treatment frequently has good results. Surgical excision is the first line of treatment for NSCLC because it is less likely to spread and is less sensitive to chemotherapy. Paraneoplastic syndromes can occur in both SCLC and NSCLC; SCLC is related to SIADH and ectopic Cushing syndrome (Wu, Wong, & Chaudhry, 2012).

4. States of Lung Cancer

Lung cancer is identified as the most prevalent type of cancer in the world. Every day in every minute someone in this earth diagnosed with lung cancer and, it takes precious lives of our loved ones. States and statistics of this fatal disease is differed from country to country and region to region in worldwide. Two different perspectives are shown below-

4.1. Global Perspective

With an estimation of 2 million diagnoses and 1.8 million deaths, lung cancer is considered as the main cause of cancer incidence and mortality globally. After prostate and breast cancer, respectively, lung neoplasms are the second most frequent cancer diagnoses in both men and women where 70 years old is the average age of diagnosis (Thandra, Barsouk, Saginala, Aluru, & Barsouk, 2021). With existing risk levels and age-specific rates, according to statistical prediction, there would be 3.2 million lung cancer-related deaths worldwide in 2050, with 3.8 million new diagnoses of the disease (Sharma, 2022). In recent days, with an expected 2.3 million new cases (11.7 percent), female breast cancer has overtaken lung cancer as the most frequently diagnosed cancer (11.4 percent) (Sung et al., 2021).

4.2. Bangladesh Perspective

Lung cancer, the most prevalent and main cause of cancer-related death worldwide, is becoming more frequent in Bangladesh. One-third of all malignancies in men occur in this group, and they typically manifest in advanced stages (Parveen et al., 2018). In the western region, numerous studies have been conducted on the epidemiology of lung cancer, where the issue has grown significantly in recent decades. Upper digestive system cancers like oral, pharyngeal, and esophageal cancers have garnered significant attention in epidemiological studies in South Asian

regions like Bangladesh (Elahi et al., 2020). The majority of lung cancer patients admitted in their late stages with no operable condition show poor performance status. One-year survival for lung cancer was 27% following supportive, symptomatic, and anticancer treatments like chemotherapy and radiation. Patients who were female and under 40 years old had a considerably better rate of survival than patients who were male and older, more than 40 years old (Parveen et al., 2018).

5. Risk Factors Associated with Lung Cancer

Lung cancer risk can be increased by a variety of factors. A higher chance of developing lung cancer is associated with these factors. Some of these might not be relevant for small cell lung cancer (SCLC). Causative and putative lung cancer risk factors that are discussed below are summarized in Table 1.

Established and putative lung cancer risk	
Risk Factor	**Magnitude of association**
Tobacco smoking	20-fold increased risk vs. never smoker
Secondhand smoke	25% to 28% increased risk vs. never smoker
Electronic cigarettes	Presently unknown
Other tobacco use (cigars, pipes, water pipes)	1.9- to 4.6-fold increased risk
Smoked cannabis	Presently no known risk
Radon	14% to 29% increased risk
Asbestos	12% to 24% increased risk
History of COPD, emphysema, or chronic bronchitis	2- to 3-fold increased risk
History of asthma	28% to 44% increased risk
History of pneumonia	30% to 57% increased risk
History of Chlamydia pnuemoniae	1.2- to 2.4-fold increased risk
History of tuberculosis	48% to 76% increased risk
HIV	2-fold increased risk

Abbreviation: COPD, chronic obstructive pulmonary disease.

Table 1: Lung cancer risk factors (Schabath et al., 2019)

5.1. Tobacco Smoking

The use of tobacco products is without a doubt the single most significant and widespread risk factor for lung cancer. Lung cancer was one of the earliest diseases to be connected to tobacco use; it was a relatively rare disease before the turn of the 20th century (Thun et al., 2010). Epidemiological studies dating back to the 1950s and the mid-1960s respectively showed that tobacco smoking causes cancer of the lungs, and this was acknowledged by public health and regulatory authorities since the mid-1960s (Wynder et al., 1997). People who smoke regularly are 20-50 times more likely to develop cancer than people who have never smoked (Doll et al., 2004). The length of time a smoker has been a smoker is the single most important factor in determining their chance of developing lung cancer. Smoking newer, lower-yield cigarettes has changed the location of lung cancer from the trachea and bronchi to the periphery of the lungs, and hence the histology of lung cancer from mostly squamous cell to adenocarcinoma (US dept, 2014). Comparing them to traditional, higher-tar cigarettes, their effect on the incidence of lung cancer remains unclear. Former smokers had a lower relative risk, and there is a substantial benefit to quitting at any age. However, even long-term abstainers likely continue to face a lifetime of added danger (IARC, 2004). Tobacco smoking may operate as a strong confounder or modifier, making it more difficult to investigate potential alternative causes of lung cancer given its central role in the disease's etiology.

Tobacco use is also a leading cause of pancreatic cancer, bladder cancer, cancer of the renal pelvis, and vascular disorders, as well as malignancies of the esophagus, mouth, throat, and larynx (Pope et al., 2011). Approximately 1010 particles/m L and 4,800 chemicals, many of which are poly aromatic hydrocarbons, make up the aerosol that is exhaled from the mouthpiece of a cigarette (Hecht et al., 1999). Cigarettes include many carcinogens, including polycyclic aromatic hydrocarbons (PAHs), nitrosamines found only in tobacco, such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 1,3-butadiene, ethyl carbamate, ethylene oxide, nickel, chromium, cadmium, polonium-210, arsenic, and hydra (Hecht et al., 1999).

5.2. Secondhand Smoke

Indirect exposure to the carcinogens in tobacco smoke, known as secondhand smoke or side-stream smoke, can have serious health consequences. Tobacco control initiatives and smoke-free legislation and policies in workplaces and public places led to a dramatic decrease in the prevalence of secondhand smoke exposure among never smokers in the United States, from 87.5% to 25.2% between 1988 and 2014. (Tsai et al., 2018). Secondhand smoke exposure increases the risk of lung cancer in nonsmokers by 20-30% in a married couple where both partners smoke (IARC, 2004), according to epidemiological evidence and biological plausibility (hackshaw et al., 1997; Boffetta et al., 2002). Both passive smoking in the home, most commonly from a spouse or coworker, and active smoking in the workplace (Stayner et al., 2007; Boffetta et al., 2000), and possibly passive smoking as a child, appear to have an influence (Bofetta et al., 2000). The chance of developing lung cancer is increased by 25% in people who are exposed to secondhand smoking, according to a meta-analysis of 12 research published in 2018. (Kim et al., 2018). A separate meta-analysis looked at the risk of lung cancer in non-smokers in Japan, and they found it to be 28% higher when exposure to secondhand smoke was considered (Hori et al., 2016).

5.3. Electronic Cigarettes

Nicotine can be delivered to the lung epithelium using an electronic device, such as those known as electronic nicotine delivery systems (ENDS), electronic cigarettes (e-cigs), and vaporizers. There are now more than 460 brands of electronic cigarettes available in the United States, along with more than 7,700 flavors (Villanti et al., 2014). The estimated prevalence of e-cigarette use among adults is between 2.6% and 4.5%. (Mirbolouk et al., 2018). Electronic cigarettes, although come in a wide variety of designs, all have the same basic components: a mouthpiece connected to a battery-powered heating element that warms a fluid contained in a disposable cartridge or reservoir that often contains liquid nicotine, artificial flavors, and other chemicals (Unger et al., 2018). It has been proven that the vapors from the solvents used in e-cigarettes, primarily propyleneglycol and vegetable glycerin, contain hazardous and carcinogenic carbonyl chemicals such as formaldehyde, acetaldehyde, acetone, and acrolein (Dautzenberg et al., 2017). Increased oxidative stress appears to mediate the negative effects of e-cigarette usage, according to studies. Human bronchial and pulmonary epithelial cells exposed to e-cigarettes undergo oxidative stress,

which can lead to inflammation, cytotoxicity, and an increase in endothelial cell permeability (Scheffler et al., 2015).

5.4. Other Tobacco Uses

Other tobacco products, such as pipes, cigars, and water pipes (such as hookah), are still common and have been connected with an increased risk of lung cancer as well as a higher mortality rate from the disease. Christensen et al. (2018) linked data from the National Longitudinal Mortality Study and the Tobacco Use Supplement of the Current Population Survey to identify 357,420 individuals who had never, were current, or were previous users of cigars, pipes, and cigarettes. The risk of dying from lung cancer was highest among daily cigarette smokers (12.7-fold increased risk), followed by daily cigar smokers (4.2-fold increased risk), and finally by daily pipe smokers. These results were reached after excluding nearly 49,000 people who reported using multiple tobacco products (1.7-fold increased risk). Pipe smoking alone was related with a 3.3-fold increased risk of lung cancer, while cigar smoking alone was associated with a 2.95-fold greater risk, according to a meta-analysis (Lee et al., 2012) of 287 epidemiological studies of lung cancer. An increased risk of lung cancer of 2.7-fold for cigar usage solely and 1.9-fold for pipe use only was identified in a recent pooled analysis (Malhotra et al., 2017) of five prospective cohort studies from the U.S. National Cancer Institute (NCI) Cohort Consortium that had collected data on cigar and pipe smoking. In a study of 13 case-control studies, Waziry et al. (2017) found that people who got their water from pipes had a 4.6-fold higher risk of developing lung cancer. Even if these products' users have a lower chance of developing lung cancer and dying from the disease than smokers, it's important to remember that this is because their use is associated with a reduced level of smoking intensity and maybe a reduced level of inhalation.

5.5. Occupational Hazards

It is believed that occupational exposure to carcinogens is responsible for between five and ten percent of cases of lung cancer (Zhang et al., 2012). Of these cases, asbestos exposure has traditionally been the most common. Asbestos is a trade name for several different types of silicate minerals found in nature; they include amphiboles (crocidolite, amosite, tremolite, anthophyllite, and actinolite) and chrysotile (the lone serpentine strand). It has been mined commercially since

the 19th century and is being utilized in some nations today for a variety of purposes, including insulating material, clothing, construction, and roofing (Albin et al., 1999). Direct and indirect cellular and molecular effects likely contribute to the etiology of lung cancer. These effects include oxidative stress, chronic inflammation, genetic and epigenetic abnormalities, as well as cellular toxicity and fibrosis. Although the underlying mechanisms in asbestos-associated diseases are complicated and the molecular pathways involved are not fully understood, asbestos-associated disorders have been linked to lung cancer (Huang et al., 2011). Exposure to asbestos was related with a 24% increased risk in males and a 12% increased risk in women for developing lung cancer, according to a meta-analysis of 14 case-control studies that included 17,705 cases and 21,813 controls and was done in Europe and Canada (Olson et al., 2017).

5.6. Radon

Radon is a radioactive gas that is found naturally in soil and rocks; it is odorless, tasteless, and invisible to the naked eye. Originally a byproduct of uranium-238 decay, radon-222 is a gas that can be found in nature and eventually disintegrates into short-lived radioactive alpha and beta particles (Ruano-Ravina et al., 2009). Radon exposure (whether in mines or homes) has been linked to lung damage and, in extreme cases, lung cancer (Zhang et al., 2012). Radon was labeled a Class 1 human carcinogen in 1988, and it is now documented that prolonged exposure through inhalation can lead to lung cancer (Brauner et al., 2012). Home exposure to radon and its decay products is now more concerning than exposure in the workplace for causing lung cancer. Based on data from 13 European case-control studies, researchers found that for every 100 Bqm3 rise in indoor radon levels, the relative risk was 1.084 (95% CI 1.030-1.158). (Darby et al., 2005). After accounting for variance introduced by measurement errors, the relative risk was 1.16 (95% CI 1.05-1.31). There was no indication of a threshold in the exposure-response relationship, suggesting instead a linear relationship. The same outcome was achieved by analyzing studies conducted in North America (Kreweski et al., 2006). According to the Environmental Protection Agency, it's the nation's number two source of lung cancer deaths.

5.7. Other Risk Factors

Oestrogen and progesterone receptors are expressed in the normal lung and in lung cancer cell lines, and oestradiol has a proliferative effect on the latter type of cells (Thomas et al., 2005). A small increased risk of lung cancer has been reported in early studies, while a decreased risk was detected in the more recent studies (Lipson et al., 2012). No effect was observed in the only randomised trial (Rossouw et al., 2002). While the different results might be explained by changes in the formulations used for replacement therapy, the lack of an effect in the only study with an experimental design argues towards residual confounding by smoking and hence against an effect of this type of exposure on lung cancer. There is some evidence that a reduced body mass index is associated with an increased risk of lung cancer. However, this inverse association can be explained, at least in part, by negative confounding by smoking and tobacco-related lung disease (Henley et al., 2002), and no clear association has been demonstrated among never-smokers. Subsequent studies supported this conclusion (Calle et al., 2003).

6. Molecular Association with Lung Cancer

Lung cancer has a complex and diverse molecular origin. Molecular alteration of certain genes like proto-oncogenes or tumor suppressor genes is considered as the basic molecular reason for cancer. Understanding molecular anomalies are necessary to combat lung cancer. Molecular association with lung cancer can be classified into three types-

6.1. Inducer

These molecules are considered as the initiator for lung neoplasms or lung cancer. Tobacco consumption is considered one of the major health issues throughout the globe. Death rallies are increasing day by day due to tobacco-related cancer each year. Despite the fact that many tobacco chemicals contribute to the growth of malignancies, the powerful effects of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone or NNK and N'-nitrosonornicotine or NNN are exceptional. Through the formation of DNA adducts, metabolically active NNK and NNN cause undesirable alterations in oncogenes and tumor suppressor genes, which might be viewed as the beginning of a tumor (Xue et al., 2014). It seems that the genetic processes that lead to cancer are

different in smokers and non-smokers. Individuals exposed to tobacco develop cancer as a result of these two distinctive NNK and NNN characteristics working together.

Radiation can be a potent inducer for developing lung cancer. One use of radiation is to treat lung cancer by radiation therapy where high-energy X-rays are used to kill cancer. Radiation, however, can potentially corrupt healthy cells' DNA over time, leading to cancerous cells (*Lung Cancer After Radiation: What to Know*, n.d.). It's like a boomerang mechanism where radiation is used to treat lung cancer but later on radiation itself becomes an inducer as a lung cancer initiator. Due to physiological position, radiation can also induce breast cancer in females. Environmental radiation in regions with high natural radioactivity also has an impact on the Incidence of Lung Cancer. A statistically significant positive correlation between radiation exposure and the incidence of lung cancer was discovered by combining radiometric data with information from regional health statistics on non-infectious diseases. According to data from international organizations like the International Atomic Energy Agency (IAEA), the International Commission on Radiological Protection (ICRP), and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), people from high background radiation areas (HBRAs) may experience a variety of radiation-induced health effects. Radiation-induced genetic, genomic, and chromosomal abnormalities may be responsible for these side effects, which may lead to an increase in lung cancer. The World Health Organization (WHO) recently stated that chronic inhalation of Rn gas is the second leading cause of lung cancer in the world's population, behind cigarette smoke, and is responsible for 3–14% of all lung malignancies. This finding is supported by a large body of research (Zlobina et al., 2022).

The link between air pollution and lung cancer is one of the discussed issues related to lung cancer for a long time. Climate change-related particles also encourage malignant alterations in the cells that line the airways. In experiments performed in the lab, researchers from the Francis Crick Institute demonstrated that the same pollutants (PM2.5) accelerated the transition of airway cells with EGFR and KRAS mutations into a condition resembling cancer stem cell. Most of the particles in the air that inducing lung cancer are derive from the combustion of fossil fuels (*Scientists Discover How Air Pollution May Trigger Lung Cancer*, n.d.). Different environmental chemicals whether forming naturally or through pollution induce lung cancer. Over the past few years, a great deal of research has been done on how the environment affects the lungs and it is now known that long-

term exposure to chemicals causes genetic and epigenetic changes, which influence critical signaling pathways and may even alter the bacterial community makeup in the lung, which aids in the growth of cancer. For instance, exposure to arsenic results in significant cellular alterations that could be the cause of the surge in lung cancer cases in some geographical areas (Soza-Ried et al., 2019). In reality, a number of studies indicate that arsenic contamination during pregnancy or at an early age can induce bladder and lung cancer at later ages (Steinmaus et al., 2013). By altering genomic integrity, interfering with DNA repair processes, and influencing the expression of several crucial molecular pathway genes, arsenic can cause the development of tumors (Soza-Ried et al., 2019). Glutathione, an antioxidant, reduces arsenic from arsenate (As^{V}) to arsenite (As^{III}) when it is absorbed in the gastrointestinal system (Soza-Ried et al., 2019). Different biochemical pathways are disrupted in cells by As^{V}'s interference with phosphorylation processes and As^{III}'s reactivity with sulfhydryl groups of proteins which leads to lung cancer induction (Hubaux et al., 2012a). Inhibition of the mitochondrial complexes I and III by a by-product of the oxidative methylation of arsenite named MMA^{III} causing electron leakage from the electron transport chain. This process results in the production of reactive oxygen, reactive nitrogen, and other free radical species. The expression of genes linked to the nucleotide excision mechanism (NER) and base-exchange repair systems are disrupted by these factors, which also impact genomic integrity and result in DNA mutations. DNA amplifications at the 19q13.31 and 19q13.33 loci and deletions at the 1q21 chromosomal locus are two examples of arsenic influence on genomic stability. Usually, these alterations are found in lung cancers from non-smokers who have endured prolonged arsenic exposure (Hubaux et al., 2012).

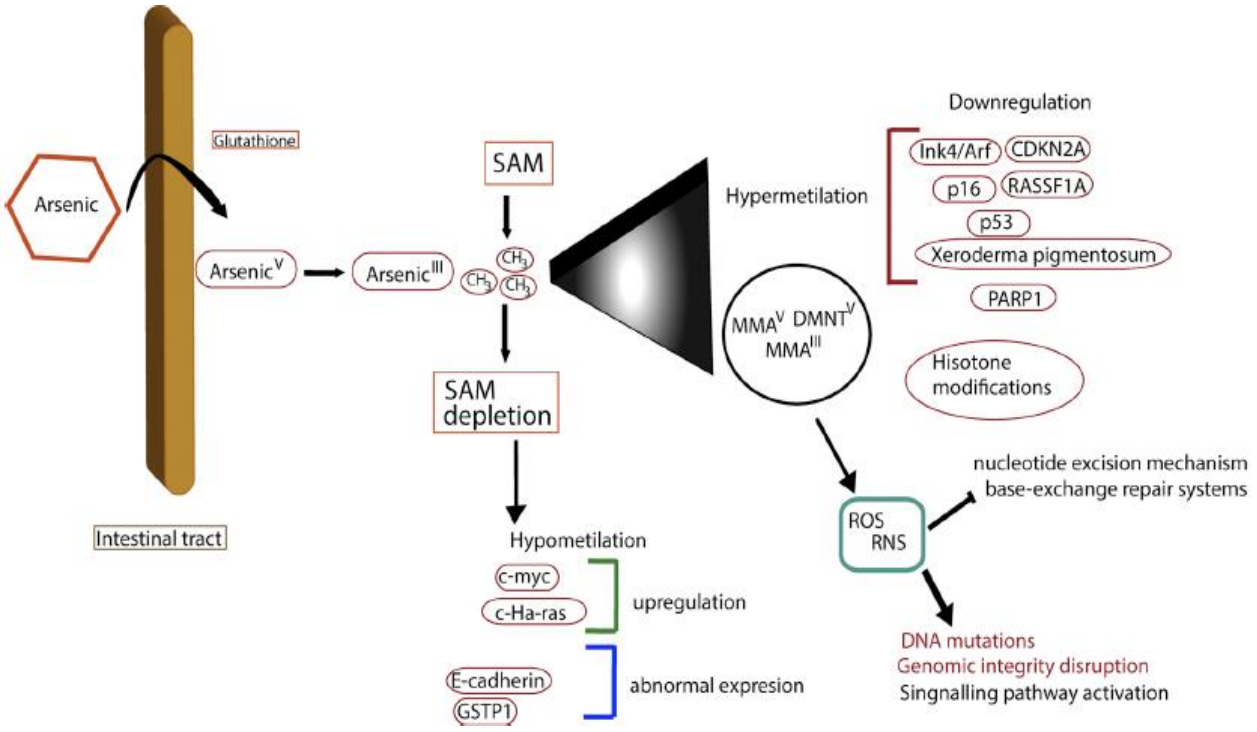

Figure 3: **Arsenic is absorbed in the intestinal tract and transformed into several arsenic derivatives.** Arsenic is reduced from arsenate (As^{V}) to arsenite (As^{III}) by the action of the antioxidant glutathione. In the cells SAM is use to methylate As^{III} and as a consequence MNA^{V}, MNA^{III} and $DMNT^{V}$ is produced. These by-products induce the production of ROS and RNS, leading to DNA genomic mutations and disrupting cell signaling pathways. Along this process, the expression of several genes (including tumor suppressor genes) is downregulated due to the hypermethylation of their promoter regions. SAM depletion, on the other hand, leads to hypomethilation of several proto-oncogenes (Soza-Ried et al., 2019).

Arsenic also induces lung cancer through epigenetic modifications by tumor production. Chromatin remodeling can be caused by epigenetic changes at the DNA and protein levels that affect gene expression (Soza-Ried et al., 2019). Ectopic expression of WNT family genes is induced by abnormal epigenetic changes of histone proteins, which aids in the action of malignant transformation (Hubaux et al., 2012a). These findings, in essence, point to two distinct situations following exposure to arsenic: hypermethylation at the gene-specific level and hypomethylation at the genome-wide level (Rozek et al., 2014). Arsenic biotransformation results in the disruption of several significant cellular processes (Soza-Ried et al., 2019). Acute exposure to As^{III}, for instance, induces AKT through JNK/STAT3 signaling, activating the PI3K/AKT signaling pathway (Jensen et al., 2009). AKT activation by As^{III} promotes the expression of Vascular Endothelial Growth Factor (VEGF), which is essential for angiogenesis and tumor growth, according to studies utilizing Human Bronchial Epithelial Cells (HBEC) (Hubaux et al., 2012).

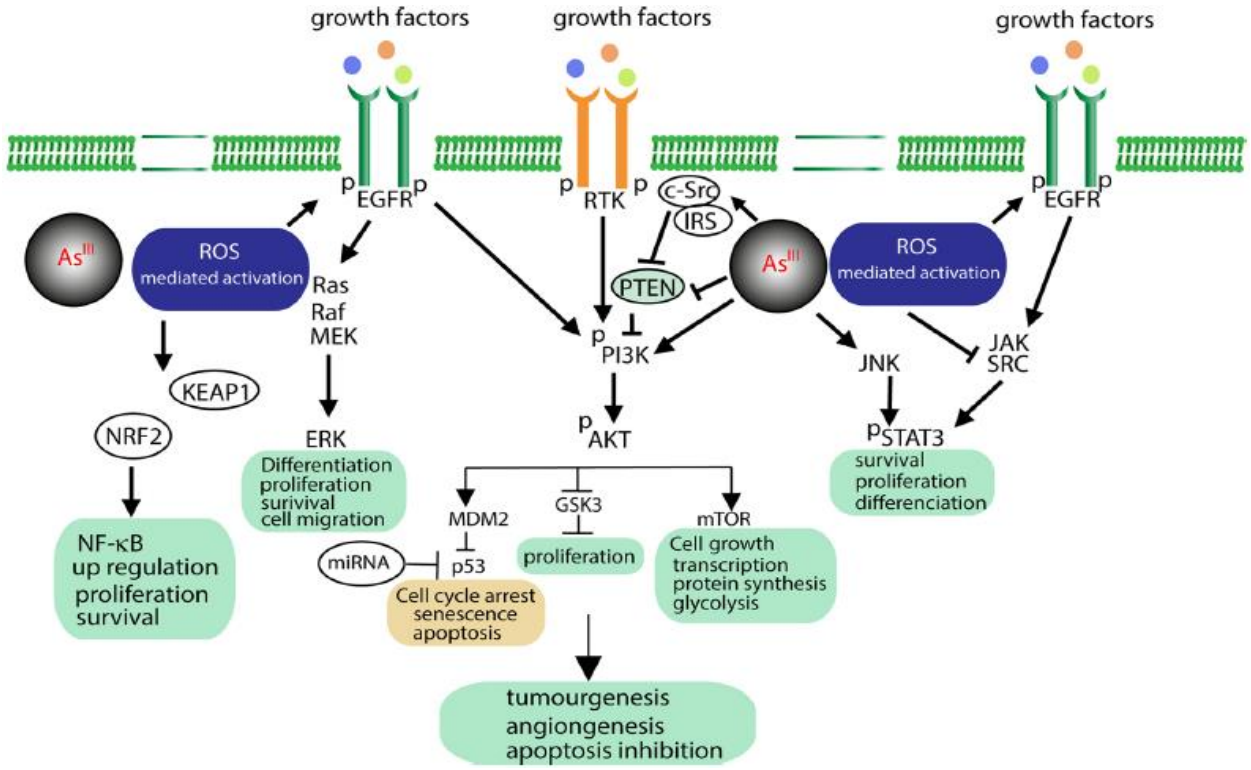

Figure 4: **Chronic arsenic exposure disrupts several signaling pathways leading to tumorigenesis**. As^{V} is reduced to As^{III}, which is subject to oxidative methylation. As byproducts of this process reactive oxygen species (ROS), RNS and others free radical species are produced. Thus, increased concentration of As^{III} disrupts the EGFG, RTK/AKT and Nrf2-KEAP1 signaling pathways. The constitutive activation of the EGFR leads to the activation of Ras/Raf/MEK/ERK signaling inducing cell proliferation, migration and survival. Likewise, EFGR signaling pathway activates PI3K, which is reinforced by the RTK/AKT pathway and the block of PTEN, both by the action As^{III}. The activation of these pathway leads to inhibition of p53, and different process that contribute to tumorigenesis, such as cell proliferation, inhibition of apoptosis, angiogenesis, protein synthesis and gene transcription. miRNA such as miR200b and up regulation of MDM2 block the expression of the tumor suppressor p53. Others miRNA are also involved in the constitutive activation of AKT and its target proteins. Exposure to As^{III} induces the expression of STAT3 through JNK inducing cell survival, proliferation and differentiation. The permanent activation of the Nrf2-KEAP1 signaling pathway induces the up regulation of NF-κB contributing further to cell proliferation and survival. All these events contribute to events that facilitates tumor formation, survival and angiogenesis. Phosphorylation is indicated as "p"(Hubaux et al., 2012).

Asbestos is another term in lung cancer which is a group of minerals including actinolite, amosite, anthophyllite, chrysotile and tremolite are employed in some industries and are found naturally as fibers. One of the most significant occupational carcinogens, asbestos is responsible for nearly half of all fatal occupational cancer cases (Singh & Kathiresan, 2014). Inhaling the particles can cause them to settle in the lungs, harming cells and induce the risk of lung cancer (Dodič Fikfak et al., 2007). The molecular mechanisms by which asbestosis and cancers are caused are not entirely known but the assumptions are mitochondrial DNA (mtDNA)-damage and oxidative DNA damage (Liu et al., 2013). Redox-active iron accumulates on the surface of asbestos fibers that have been

inhaled; this iron alternates between reduced and oxidized states and can lead to oxidative DNA damage in neighboring cells. According to the available data, asbestos fibers are mutagenic carcinogens, which are characterized as substances that cause cancer in living things by inducing mutations (S. X. L. Huang et al., 2011).

Certain types of respiratory diseases such as TB (Tuberculosis), COPD (Chronic Obstructive Pulmonary Disease), Chronic Bronchitis, Emphysema, Pneumonia, Asthma, COVID, etc. can induce lung cancer by DNA damage, and inhibition of DNA repair (Qi et al., 2022; Singh & Kathiresan, 2014). It has been suggested that Tb-induced chronic lung inflammation may activate the clastogenic pathway in the DNA of the bronchial epithelium. Another option is lateral gene transfer; because *Mycobacterium Tuberculosis* (MTb) is an intracellular organism, bacterial DNA may combine with bronchial epithelial cells, causing neoplastic transformation (Molina-Romero et al., 2019). Numerous studies have established a link between the etiology of lung cancer and COPD, suggesting that they may both contribute to or even directly cause one another. Numerous elements of COPD may contribute to the process of lung cancer induction, including gene expression, hereditary predisposition, epigenetics, epithelial-to-mesenchymal transition (EMT), chronic inflammation, and oxidative stress injury (Qi et al., 2022). All of these are somehow linked to the side effects of smoking.

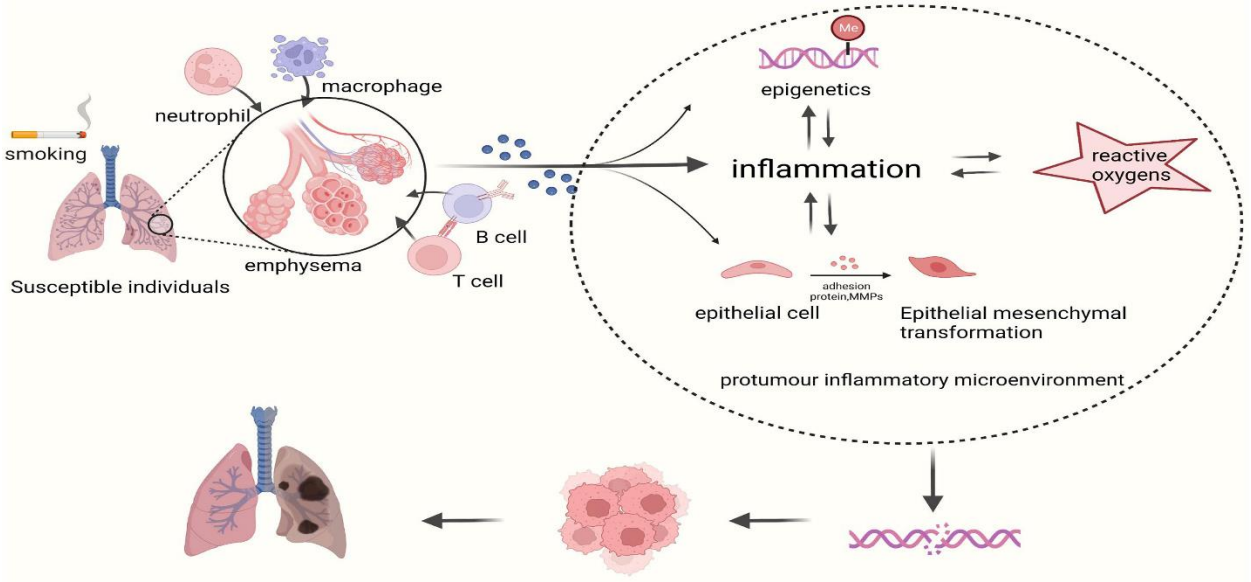

Figure 5: Graphical representation of lung cancer and COPD linkage (Qi et al., 2022).

COPD count as an independent inducer for lung cancer. The possibility of high incidence of lung cancer in COPD patients due to the shared processes in both diseases including premature aging in the lungs, genetic predispositions to either disease or common pathogenic factors, such as growth factors, activation of intracellular pathways, or epigenetics (Durham & Adcock, 2015). By increasing oxidative stress and the consequent DNA damage, chronic exposure to pro-inflammatory cytokines, inhibition of the DNA repair systems, and enhanced cellular proliferation, COPD may be a contributing factor in lung cancer. Oxidative stress caused by RNOS (Reactive Nitrogen and Oxygen Species) in COPD can induce lung cancer by damaging DNA. This DNA damage can be introduced by several processes like- point mutations, single-strand breaks (SSBs), double-strand breaks (DSBs), and DNA cross-linking, which ultimately lead to mutation (Durham & Adcock, 2015).

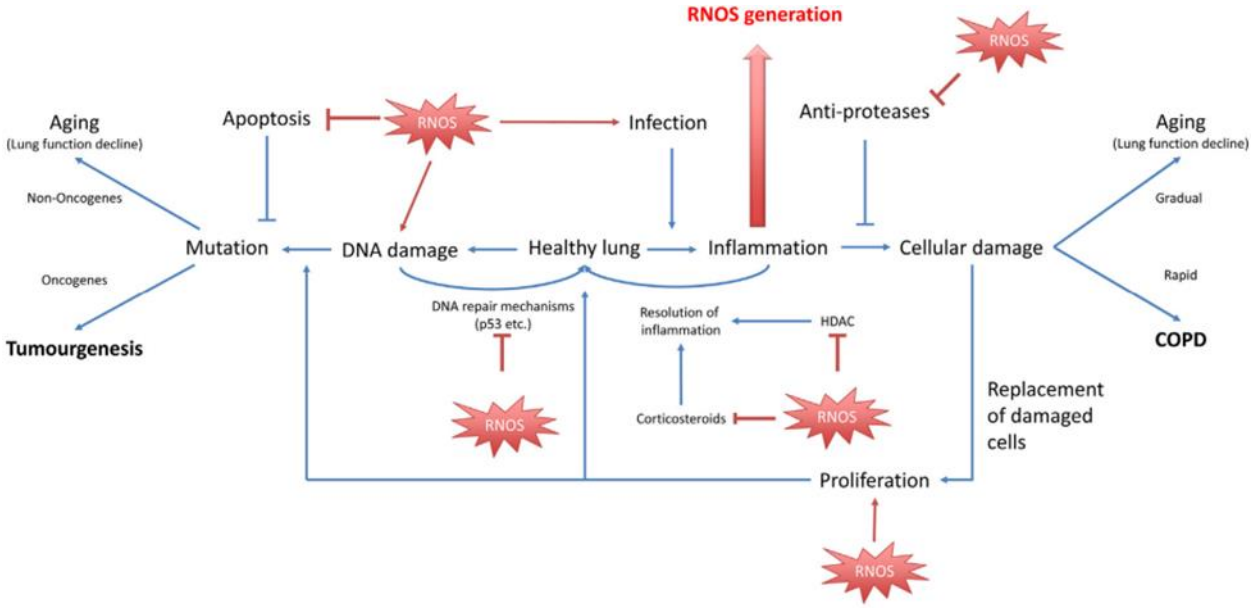

Figure 6: Many of the processes in both COPD and lung cancer are driven by reactive oxygen and nitrogen species (RNOS), which can originate from both external and internal sources. Interaction between RNOS and DNA causes DNA damage, mutations can be the result if DNA damage is not properly solved. RNOS may increase the risk of infection and fuel lung inflammation. Additional cellular and DNA damage may result from increased production of RNOS during inflammation as well as from the actions of cytokines and proteases. RNOS has the power to block defense mechanisms like anti-proteases. Cellular proliferation is one of the mechanisms used to repair lung damage, and this process can also encourage the growth of tumors (Durham & Adcock, 2015).

The prevalent chronic lung condition known as asthma is characterized by reversible airway obstruction, increased bronchial responsiveness, and chronic inflammation. According to certain theories, lung oxidative damage brought on by asthmatic patients' prolonged lung inflammation

may eventually result in the development of lung cancer. An elevated induction of lung cancer was linked to asthma that was only partially under control (Jiang et al., 2021).

COVID also have an impact on lung cancer induction especially recent pandemic of COVID-19. It can induce lung cancer by the activation of different pathways like- the anti-inflammatory and carcinogenic properties of 2019-nCoV-2 can be attributed to its ability to activate the PI3K/Akt and ERK signaling pathways. Furthermore, the development of hypoxemia may lead to an increase in HIF-1 expression, which can contribute to the incidence, angiogenesis, invasion, and metastasis of lung cancer. In cases where 2019-nCoV-2 infection is present, the immune system may also be inhibited, leading to tumor immune evasion (Tao et al., 2020).

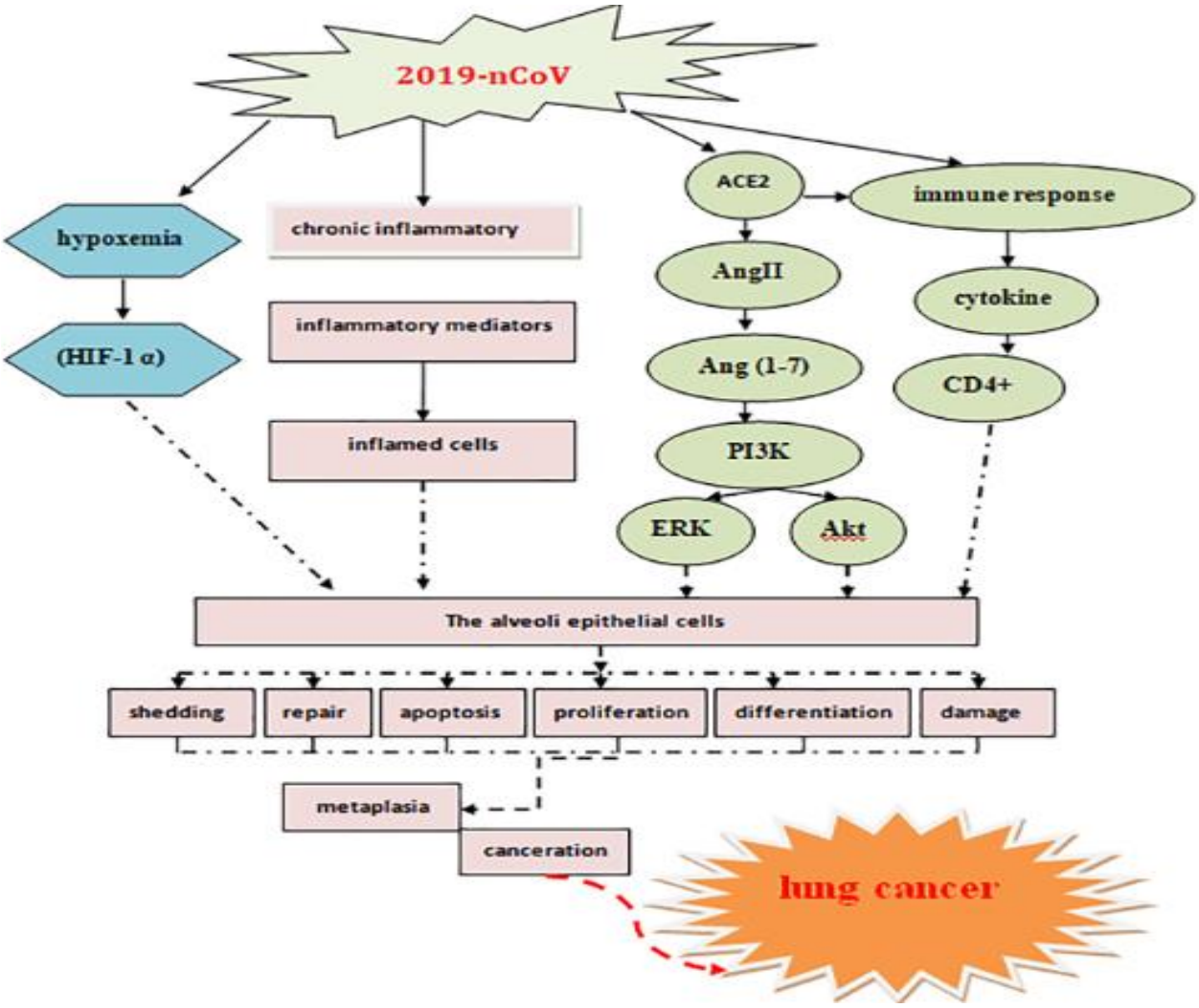

Figure 7: Suggested mechanism of lung cancer induction by COVID-19 (Tao et al., 2020).

In addition, the persistent inflammation brought on by COVID-19 can stimulate and harm alveolar epithelial tissues, causing pulmonary fibrosis, which may ultimately bring on lung cancer (Faner et al., 2012).

6.2. Accelerators

The rapid development of lung tumors is favored by a plethora of factors. In cases of lung cancer, the development of metastases is the primary factor that ultimately results in patients' deaths. Although lung cancer can be detected at an early stage with the help of chest x-rays and the Lung Screening Trial (low dose helical computed tomography, LDCT), the prognosis for metastatic lung cancer remains bleak despite the use of surgery, radiation, chemotherapy, immunotherapy, and gene-targeted medication therapy.

6.2.1. Antioxidants Play a Role in the Acceleration of Lung Cancer

Antioxidants have long been recognized as helpful in the fight against cancer and as a means of defense against harmed cells. However, the outcomes of big randomized clinical trials have been inconsistent, and some research suggests that antioxidants may actually raise cancer risk. In addition, new genomic investigations of lung malignancies have revealed a high prevalence of mutations in genes that activate an endogenous antioxidant program, indicating that reducing ROS concentrations encourages tumor growth. Experiments corroborate this idea, demonstrating that oncogenes like K-RAS and B-RAF enhance tumor growth by increasing NRF2-mediated transcription of endogenous antioxidant genes. According to a study that tracked the development of lung cancer in mice (Sayin, 2014), antioxidants sped up tumor growth. Tumor growth was accelerated by NAC and vitamin E in mice with K-RAS G12D and B-RAF V600E-induced lung cancer, as seen in the picture below.

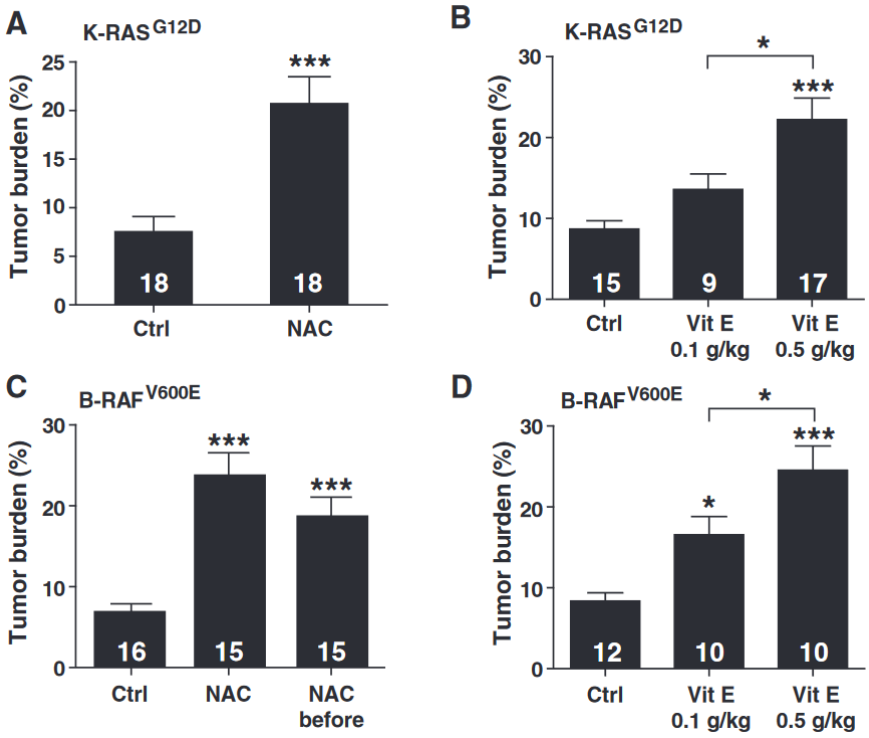

Figure 8: A and B in Figure Lung cancer incidence (as measured by the ratio of tumor area per total lung area) in NAC-treated (A), vitamin E (Vit E)-treated (B), and control K-RASG12D mice, the effects of inhalational of Cre adenovirus on after 10 weeks (Sayin et al., 2014).

Gene expression related to the body's natural defenses against reactive oxygen species (ROS) was suppressed by the antioxidants. This finding agrees with the decreased levels of reactive oxygen species (ROS) and oxidative DNA damage as well as the enhanced GSH/GSSG ratio. The most apparent interpretation for this finding is that when the levels of reactive oxygen species (ROS) are reduced by NAC or vitamin E, a feedback mechanism in lung cells down-regulates the endogenous ROS defense system. Numerous lines of evidence point to decreased p53 levels as the mediator of the antioxidant-induced increase in tumor development. To begin, NAC and vitamin E decreased p53 in tumors and cultured mice and human tumor cells. Furthermore, antioxidants promoted growth only in human lung cancer cells with wild-type p53, not in those with a mutated form of the gene. Third, when p53 was inactivated or inhibited by shRNAs, antioxidants lost their capacity to increase tumor cell growth. Antioxidants may have played a role in the decrease of p53 by removing powerful triggers for p53 activation and stabilization, such as oxidative DNA

damage, gamma-H2AX, and phospho-ATM. However, additional research are needed to rule out the potential of other factors being involved.

6.2.2. Linc00426 Accelerates Lung Adenocarcinoma Progression

LncRNAs, or long non-coding RNAs, are a subclass of non-protein coding RNAs that are longer than 200 nucleotides and can regulate gene expression both during transcription and after post-transcription. By regulating the expression of protein-coding genes and taking part in cellular proliferation, development, invasion, migration, and apoptosis, LncRNAs serve as oncogenes or tumor suppressors. Multiple tumor forms, including lung cancer, often display aberrant regulation of their expression. Epigenetic deletion of p27 by a novel LncRNA of LUADT1, for instance, enhances LUAD growth. Increased ZXF1 LncRNA expression promotes LUAD invasion and metastasis. In addition, another inadequately expressed LncRNA, RPLP0P2, is linked to a poor prognosis and can inhibit LUAD cells' capacity for proliferation and adhesion. Long non-coding RNAs (lncRNAs) are transcripts that range in length from 200 nucleotides (nt) to 100 kilobases (kb) and are found all over the genome. Rather than encoding proteins, lncRNAs regulate the expression of coding genes and other non-coding RNAs. Long noncoding RNAs (LncRNAs) were once thought of as useless by-products. In the present day, they are thought to have critical regulatory roles, adding another degree of complexity to our knowledge of genomic modulation. Different LncRNAs are thought to have different spatiotemporal relationships with processes such cell proliferation, cell death, transcription, and translation. RNA polymerase II is responsible for their transcription, and some of them are further controlled by splicing at their 5′ and 3′ ends before being exported to the cytoplasm. For myoblast proliferation, Lnc-31 is necessary because it regulates post-transcriptional gene expression and speeds up protein synthesis of Rho-associated c, oiled-coil containing protein kinase 1 (ROCK1) by stabilizing its translational activator, Y-box binding protein 1. (YB-1). In order to regulate the expression of zinc finger E-box binding homeo-box 1 (ZEB1), which in turn affects NSCLC proliferation, migration, invasion, and EMT, Linc00673 acts as a miR-150- 5p sponge.

6.2.3. SH2B1 as an Accelerator

The role of SH2B1 in cancer was first investigated in 2012 by Zhang H, who found that SH2B1 was significantly more highly expressed in non-small cell lung cancer (NSCLC) tissue compared to adjacent noncancer tissues, and that this high expression was significantly correlated with tumor grade, TNM stage, and recurrence. In cell tests, SH2B1 mRNA expression was observed to be greater in NSCLC cell lines compared to normal HBE cell lines. The results of the study back up the hypothesis that SH2B1 expression in lung cancer is regulated in a pre-transcriptional stage. Further mechanistic studies have now shown that SH2B1 promotes the epithelial-mesenchymal transition (EMT) through the IRS1/-catenin signaling axis in lung adenocarcinoma and that the SH2B1/Akt/mTOR/PTEN axis is necessary for regulating NSCLC cell proliferation. MicroRNA-361-3p reduces tumor cell proliferation and metastasis by directly targeting SH2B1 in NSCLC. The most recent studies suggest that accurate survival predictions and treatment decisions may be made for patients with early-stage NSCLC by combining the 8-gene (including SH2B1) signature with the stage.

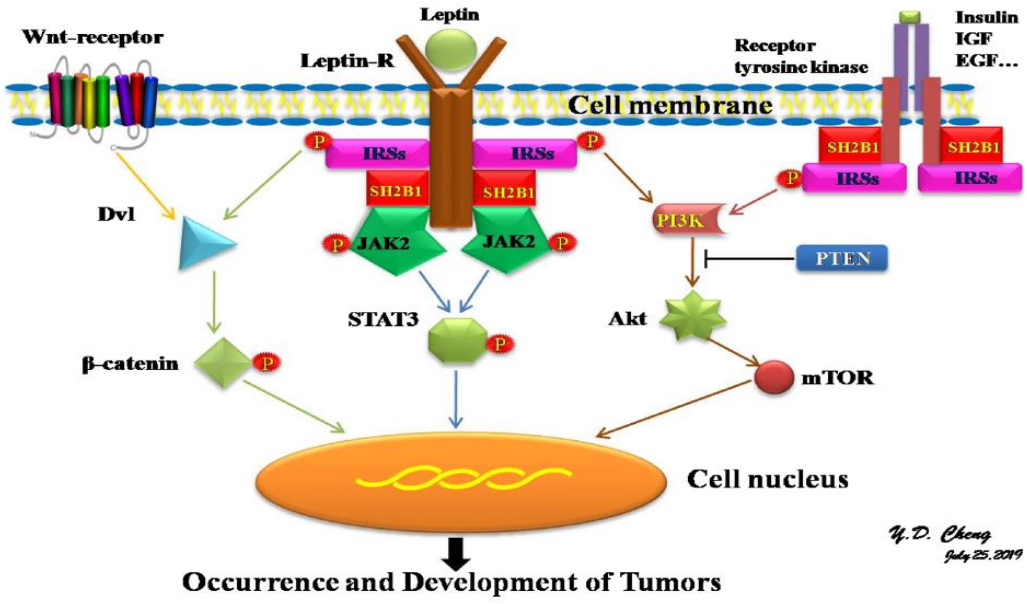

Figure 9: The potential signaling pathways by which SH2B1 is involved in the development of cancers (Liu et al., 2022).

SH2B1 is a type of adaptor protein that helps to construct signaling complexes, couples upstream activators to downstream effectors, and can even boost the catalytic activity of tyrosine kinases that it binds to. Several members of the Janus kinase (JAK) family of tyrosine kinases, as well as those of the receptor tyrosine kinase family, have been linked to SH2B1's involvement in signal transduction. Due to the binding of SH2B1 to JAK2, JAK2 kinase activity is increased, promoting the traditional JAK2/STAT3 signaling that is a known driver of cancer growth. SH2B1 has the ability to bind to IRS1/2, and this connection makes it possible for JAK2 to phosphorylate the IRS proteins, which in turn activates the PI 3-kinase pathway. STAT3 and the PI3-kinase pathway are both involved in tumorigenesis. The connection between SH2B1 and IRS1/2 inhibits the autophagic degradation of Dvl2, which promotes Wnt-mediated EMT and cell proliferation.

6.2.4. SCRIB Cooperates with KRAS Hyperactivation To Accelerate Lung Cancer Progression

In Drosophila melanogaster, Scribble (Scrib) was first recognized as a neoplastic tumor suppressor, with its loss of activity causing a breakdown in apicobasal polarity, junctional integrity, and the uncontrolled growth of tissues. Leucine Rich Repeats and PDZ (LRR, Leucine Rich Repeats, and PDZ, PSD95/DLG/ZO-1) and LRR and PDZ domains are both present in the membrane-associated LAP protein known as Scrib. Scrib expression level changes are seen in many different kinds of tumors, like those of the breast, cervical, and prostate. Multiple biological functions, such as cell division, differentiation, death, stem cell maintenance, cell migration, and vesicle trafficking, have been linked to Scrib. Research in Drosophila has shown that the loss of Scrib works in concert with activated Ras to promote tumor growth and metastasis. Loss of Scrib cooperates with activated RAS to increase invasion in the non-transformed human breast cell line MCF10A and to accelerate carcinogenesis in the prostate of mice, demonstrating that this cooperative connection is retained in mammals. Mice with scrib heterozygosity are more susceptible to developing lung tumors, and the loss of both scrib copies works in tandem with oncogenic KRAS to spur the development of tumors that are both numerous and aggressive.

6.3. Animator

After the complete development of lung cancer, different mechanisms help to sustain the cancerous cells. In this case, some mechanisms help to provide energy, some help to indefinite cell proliferation, some help to skip cell death, etc. As opposed to normal cells, which age and die, cancer cells can reproduce indefinitely, leading to the description of them as immortal (*Biologists Unravel Pathway for Cancer Cells to Become Immortal | Iowa Now*, n.d.). Through asymmetric cell divisions, which result in daughter cells with varying potentials for self-renewal and differentiation, normal tissue homeostasis is preserved. The ability of some tumor cell subfractions to self-renew and replenish the heterogeneous tumor bulk raises the possibility of asymmetric cell division. However, another theory that is equally believable is that the offspring cells of a symmetric division go on to adopt various cell fates. In human lung cancer cell lines and actual tumor cell cultures, it is found that a tiny number of cells asymmetrically partitioned their template DNA, which could be seen in individual cells and in real time. Contact between cells improves template DNA co-segregation. Additionally, it has also been discovered that isolated CD133+ lung cancer cells have the capacity to repopulate tumors(Pine et al., 2010). DNA damage can be repaired more effectively by stem cells and cancerous cells than by differentiated progeny, and deficiencies in DNA repair in stem cells are linked to a number of cancer syndromes. An unregulated leftover that cancer cells may adopt to defend themselves against fatal DNA mutations is symmetric DNA partitioning. Asymmetric segregation of the template strands in cancer cells would only shield the genome from replication errors since oxidative DNA damage would harm both DNA strands (Pine et al., 2010).

Proteins, other macromolecules, and organelles are assumed to be degraded by autophagy, which also recycles them. Autophagy inhibits the buildup of damaged mitochondria and encourages malignancy in genetically modified mice (GEMMs) for *Kras*-driven lung cancer. Therefore, a major obstacle for starving *Kras*-driven tumor cells is the maintenance of nucleotide pools. Autophagy supports nucleotide stocks and, thus, famine survival by supplying bioenergetic and biosynthetic substrates (Guo et al., 2016).

There is growing evidence that telomeres, telomerase, cellular aging, and cancer are all related in a significant way. By adopting systems that may preserve telomere lengths, such as producing telomerase, cancer cells have gained the ability to avoid senescence and continue to divide indefinitely (Shay & Wright, 2011).

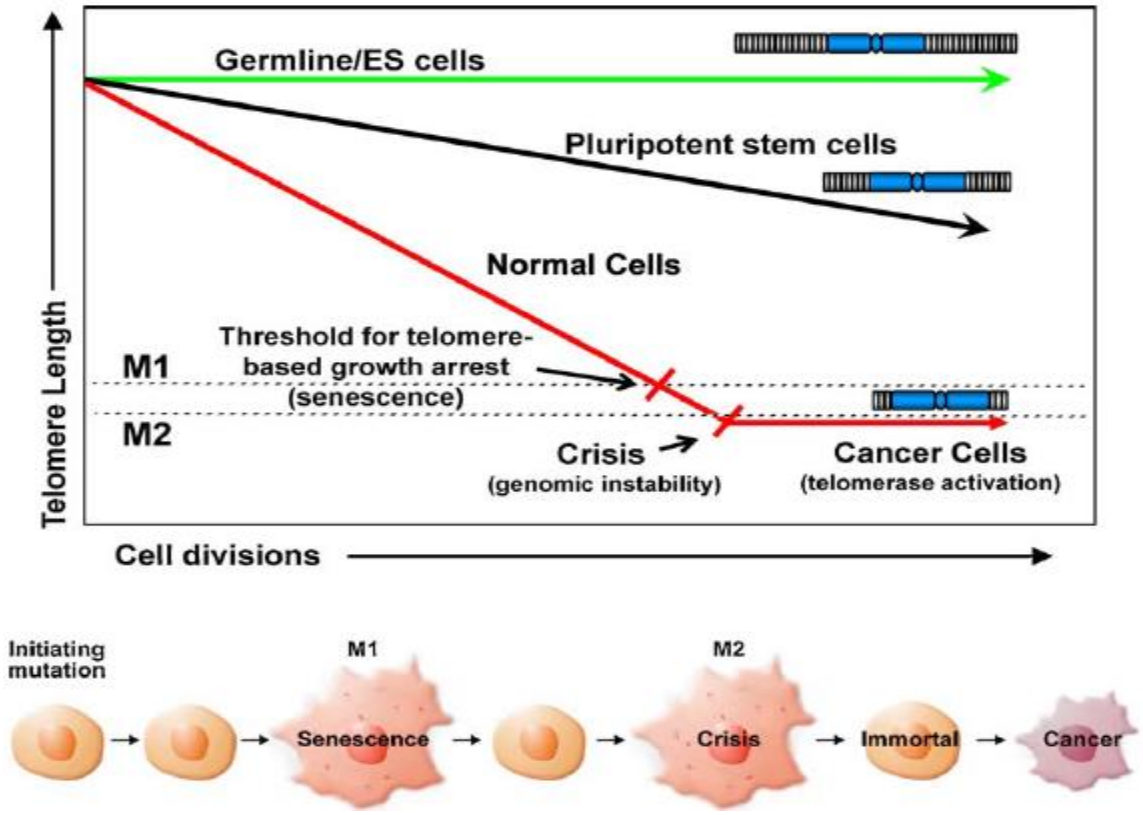

Figure 10: Certain male reproductive cells and embryonic stem cells retain full or almost full telomere length due to the expression of telomerase activity. Pluripotent stem cells have regulated telomerase activity and thus they lose telomeres throughout life but at a reduced rate. Most somatic cells do not express telomerase activity and thus lose telomere length with each division at a faster rate until the cells uncap a few of their telomeres and undergo a growth arrest called replicative senescence. In the absence of cell cycle checkpoints like p53/pRB pathway, cells bypass senescence until they reach crisis. In crisis, telomeres are so short that chromosome end fusions occur and there is increased genomic instability (probably due to chromosomal, breakage, fusion, bridge cycles). A rare cell that escapes crisis almost universally do so by reactivating telomerase and this cell can now become a cancer cell with limitless potential to divide. Almost all cancer cells have short telomeres (Shay & Wright, 2011).

A roadblock to the growth of tumors is the progressive shortening of telomeres caused by cell division or replicative aging. However, a persistent cell proliferation is one of the characteristics of advanced malignancies, and this is nearly always correlated with the reactivation of telomerase. The cellular enzyme telomerase, also known as a molecular motor, adds new DNA to the telomeres at the ends of chromosomes. The majority of the time cellular senescence and DNA damage signaling pathways are bypassed by human tumor cells originating from carcinomas. By deleting

key cell cycle checkpoint genes including TP53, $p16^{INK4a}$, and pRb in human cell culture models, senescence bypass can be achieved. This causes pre-malignant cells to grow more slowly than normal, eventually resulting in crisis. Crisis is an equilibrium point of cell proliferation and death. Chromosome end fusions cause chromosome breakage-fusion-bridge events, which result in genomic instability, chromosome rearrangements, and finally telomerase activation. Approximately 90% of all malignant tumors have telomerase present in them (Shay & Wright, 2011). Similar to many other cancer forms, lung cancer cells express telomerase to prevent telomere shortening. Early investigations found telomerase activity in the majority of primary lung cancer samples using a polymerase chain reaction-based telomeric repeat amplification technique test. TERT (telomerase reverse transcriptase) mRNA and TERT protein are overexpressed in lung cancer biopsies compared to normal lung tissues, according to numerous research employing animal models and human non-small cell lung cancer (NSCLC) tissues. TERT is one of the active subunits of the active telomerase RNP, which is a part of telomerase. Human bronchial epithelial cells that overexpressed cyclin-dependent kinase 4 and hTERT gave rise to immortal cell lines, demonstrating the need to avoid senescence before cell immortalization with telomerase. There have also been reports of changes in the expression of other telomere-associated proteins in lung cancer sustenance (Fernandez-Garcia et al., 2008).

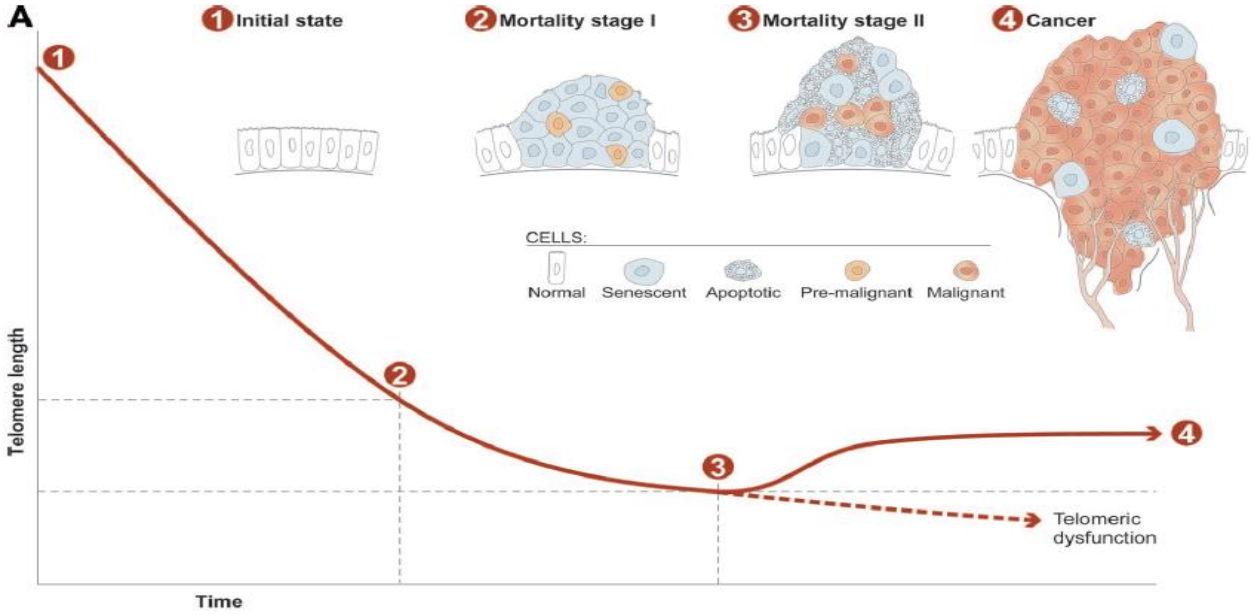

Figure 11: A model explaining how telomere length and the development of cancer are related. Preneoplastic lesions' continually reproducing cells have chronic telomere shortening, which causes senescence (mortality stage I). By changing their DDR, some cells are able to avoid senescence and continue to grow. These cells live longer until their telomeres malfunction and they undergo apoptosis (mortality stage II). A tiny portion of cells with genetic defects avoids both stages of mortality and develops into cancer (Fernandez-Garcia et al., 2008).

Lung cancer stem cells (LCSCs) is another term in lung cancer sustenance. Recent research has focused a lot of attention on lung cancer stem cells (LCSCs), which play a significant role in the development of lung cancer. The primary source of LCSCs is the de-differentiation of normal cancer cells or normal tissue stem cells (Wang et al., 2018). Current research and clinical data indicate that lung cancer stem cells are responsible for maintaining the malignant phenotype in this disease (CSCs). They may act as putative stem cells to start the development of lung cancer and are distributed throughout the airways. Long lifespan, enhanced proliferation and differentiation, as well as resistance to chemotherapy and radiation therapy, are all shared traits of these cells (Hardavella et al., 2016). Studies on patients with suboptimal clinical outcomes have shown that the CSC-specific complex tumor microenvironment plays a role in the promotion of tumor metastasis, medication resistance, and radiation resistance. Compared to normal cancer cells, CSC colonies develop more quickly, and they overexpress particular mRNAs and proteins that are linked to cancer stem cells, such as octamer-binding transcription factor 4 (OCT4), homeobox protein NANOG, and sex-determining region Y HMG-box 2 (SOX2). LCSCs may also arise from typical cancer cells that have regained the ability to self-renew after de-differentiation to a progenitor-like state, according to some reports (Wang et al., 2018).

7. Epigenetic Factors of Lung Cancer

The development of lung cancer is associated with a sequence of genetic and epigenetic modifications in the respiratory epithelium (Dumitrescu et al., 2012). Despite the widespread awareness of the involvement of somatic genetic aberrations such mutations and copy number variations in oncogenesis, epigenetic alterations are more common than somatic mutations in lung cancer (Brzezianska et al., 2013). Both smoking and nonsmoking-related malignant transformations have been linked to epigenome dysregulation, which plays a crucial role in the development of cancer hallmarks like uncontrolled cell growth, resistance to apoptosis, angiogenesis, and metastasis (Lin et al., 2007). Several large-scale projects, like the Cancer Genome Atlas (TCGA), the Human Epigenome Project, and the Human Epigenome Atlas, have annotated the epigenome, thereby considerably enhancing the knowledge of the epigenetic landscape in lung cancer.

Class of epigenetic regulators	Example of key targets
DNA methyltransferases	DNMT1, DNMT3, DNMT3a, DNMT3b
Histone Lysine methyltransferases (KMTs)	EZH1/2, SETD2, SMYD3
Histone lysine demethylases (KDMs)	LSD1, KDM2, KDM3A
Histone arginine methyltransferases	PRMT!, PRMT4, PRMT6
Histone arginine demethylases	JMJD6
Histone acetyltransferases (HATs)	CREBBP/EP300,CBP,CAT6B
Histone deacetylases (HDACs)	HDAC1, HDAC3, HDAC6, HDAC7
Histone readers	BRD2/3/4, YEATS2
MicroRNA (miRNA)	Let-7, miR-200
Long noncoding RNA (IncRNA)	MALAT1, HOTAIR
Circular RNA (circRNA)	CDR1as, circ-FOXO3
Small nucleolar RNA (snoRNA)	SNORA42. SNORA78

Table 2: Summary of mechanism of epigenetic regulation and examples of key targets within each class (Yvonne et al., 2021).

Epigenetic dysregulation in lung cancer influences not just cancer hallmarks but also multiple critical signaling pathways, including the ERK family, the NF-kB signaling pathway, and the Hedgehog signaling pathway (Shi et al., 2017). Insight into the identification of potential cancer biomarkers for use in diagnosis, follow-up care, prognosis, risk assessment, and oncotherapy can be gained through studying epigenetic processes (Figure 11).

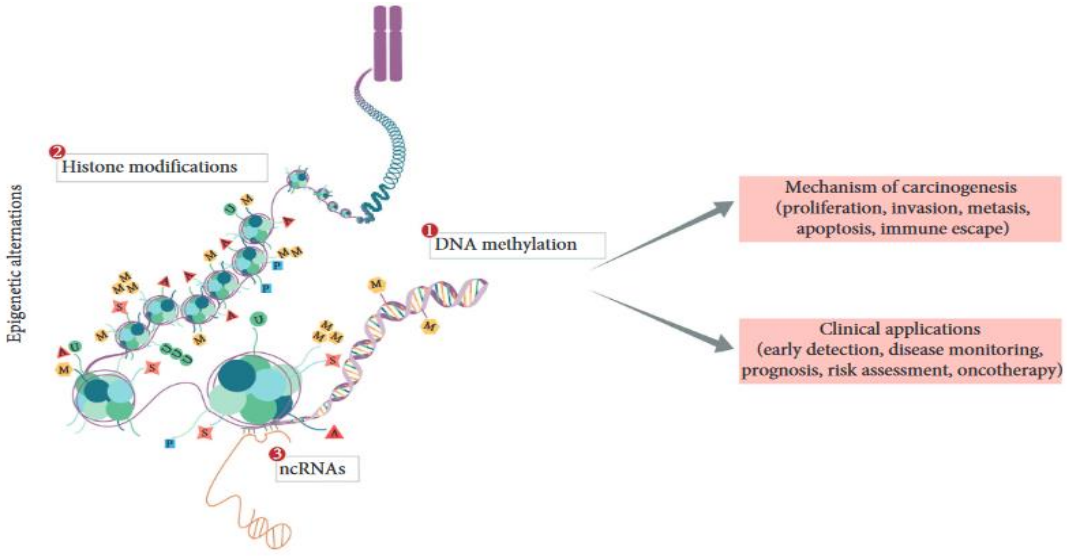

Figure 12: Current landscapes of epigenetics mechanism and application in lung cancer (Shi et al., 2019).

7.1. DNA Methylation

CpG sequences, which are the sites of DNA methylation, are dispersed irregularly throughout the genome and tend to cluster in promoter areas known as "CpG islands" (Ahuja et al. 2016). The process of DNA methylation is carried out by three different DNA methyltransferases (DNMTs). The most common DNMT1 is responsible for maintaining preexisting methylation, while DNMT3A and -3B generate de novo methylation. Tobacco smoke causes lung cancer through increasing the expression of DNMT1, which has a direct role in the silencing of tumor suppressors during the development of lung cancer (Belinsky et al., 2004). The amount of methylation that is added to genomic DNA is generally quite high; but, in cases of lung cancer, there is pervasive aberrant DNA methylation that includes both hypo- and hypermethylation. Modifications in global DNA methylation patterns result from the dysregulated expression of many master epigenetic regulators (Yang et al. 2015). Loss of imprinting, microsatellite instability, and the activation of oncogenes are all consequences of global DNA hypomethylation (Brzeziaska et al., 2013). In contrast, an early step in the development of lung cancer is the hypermethylation of normally unmethylated CpG islands, which silences tumor-suppressor genes (Belinsky et al., 2004). Various research studies conducted on the LUSC cells showed that the lung tumors are caused due to the extreme DNA hypomethylation including some gene specific hypermethylation (Raunch et al., 2008).

7.1.1. Methylation of Tumor Suppressors and Oncogenes

Inactivation of two important tumor suppressor genes, RB1 and TP53, is one of the defining characteristics of SCLC. Although certain mutations have been documented, promoter hypermethylation is the main source of deactivation for these tumor suppressor genes (Massion et al., 2015). SCLC aggressiveness is caused by the promoter methylation of tumor suppressors and the hypermethylation of other genes during tumor formation (Zhai et al., 2020). Tumor suppressor genes frequently have their promoters methylated in combination with deletion or mutation events (Licchesi et al., 2008), indicating that inactivation may occur at numerous points for each allele. Some research indicates that inactivating both copies of an allele may not be important to affect the cellular activity that results in carcinogenesis. In these situations, clonal selection occurs when the promoter of even a single allele is methylated (C.A. Lareau et al., 2020).

EZH2, a chromatin modifier and the main enzymatic component of polycomb repressive complex (PRC), is highly expressed in the majority of SCLC cells and is the essential regulator of significant promoter hypermethylation. In particular, as a component of the histone methyltransferase complex, its overexpression is linked to trimethylation of histone H3 at lysine 27, which creates abnormal DNA methylation in the majority of malignancies, including SCLC (Zhai et al., 2020). Elongation factor E2F controls the production of EZH2, and as RB1 encodes the repressor for E2F, its elevated activation in SCLC can be attributed to loss of function mutations of RB1.

7.1.2. Methylation of DNA Repair Pathway Genes

One of the pathways commonly compromised in SCLC is the DNA repair pathway. According to research, methylation regulates genes involved in the DNA repair process in the vast majority of SCLC cases (promoter methylation or gene methylation). The O6-methylguanine DNA methyltransferase (MGMT) gene, which encodes for an enzyme that controls DNA repair by removing alkyl groups from guanine (at the O^6 position) (Toyooka et al., 2001), is one of the most prominent signatures in this group. In around 90% of SCLC cell lines, MGMT promoter hypermethylation was detected, while in only about 20%-30% of SCLC tissues, MGMT gene methylation was discovered (Hiddinga et al., 2017). The fragile histidine triad (FHIT) is another member of this group; it is a tumor suppressor gene that controls cell-cycle progression and apoptosis independently of p53 and protects against lung cancer caused by chemical exposure (R. Zandi et al., 2011). Most SCLC tissue samples and cell lines showed FHIT promoter methylation, leading to inactivation or downregulation of FHIT.

7.1.3. Methylation of Metastasis

Methylation patterns have a major effect on genes involved in cell adhesion and metastasis, which help to preserve tissue integrity and slow the evolution of SCLC. Some of these are the genes for cadherins, such as cadherin 1 (CDH1 or E-cadherin), cadherin 13 (CDH13 or H-cadherin), tissue inhibitor of metalloproteinase 3 (TIMP3), matrix metalloproteinases (MMPs), and snail (S. Toyooka et al., 2001). It has been found that the CDH1 promoter is frequently hypermethylated in SCLC (Roncarati et. al, 2020). The expression of CDH1 is epigenetically repressed by a number of genes and pathways, including snail2 and NFIB (Y. Hu et al., 2019). The other cadherin family

member whose expression is regulated by methylation is CDH13, and it has been linked to SCLC metastasis (Hiddinga et al, 2017). Methylation of CDH13 is related to cisplatin resistance in various kinds of lung cancer (Wang et al, 2018). CDH13 methylation is regulated by DNA polymerase β (Pol β), an enzyme essential for genomic integrity and repair of DNA base excision damage. Specifically, it acts as a demethylase to reduce methylation in the CDH13 promoter (M. Wang et al., 2020). Increased migration and angiogenesis occur in SCLC when CDH13 is downregulated. The potential of these epigenetic alterations towards the establishment of early-stage lung cancer diagnosis was recently demonstrated by the study of circulating cell-free DNA from patients with early-stage lung cancer (Z. Yang et al., 2019).

7.2. Chromatin Remodeling

Epigenetic regulation occurs on many different levels, with DNA methylation having downstream effects on histone modifications, nucleosome architecture, and chromatin conformation (Gilbert et al. 2007). Unmethylated DNA has a more open conformation, but methylated DNA causes genomic DNA to spiral tightly around histone proteins H2A, H2B, H3, and H4, producing a nucleosome. Remodeling of chromatin or changes in its structure determine whether transcription is actively repressed or actively promoted. DNA packing and unloading into chromatin is a process facilitated by chromatin remodeling complexes. Both non-small cell lung cancer and small cell lung cancer have been linked to mutations in the SWI/SNF chromatin remodeling complex (Wilson et al., 2011). Among the most frequently altered genes in lung ADC, chromatin regulators SMARCA4/BRG1 and ARID1A play a role in lung carcinogenesis (Orvis et al. 2014). The loss of BRG1/SMARCA4 causes broad alterations in nucleosome placement and chromatin remodeling, which in turn reduces the expression of downstream tumor-suppressor genes (Orvis et al. 2014). In most situations, SMARCA4 functions as an oncogene rather than a tumor suppressor. Patients with non-small cell lung cancer (NSCLC) who have mutations in both SMARCA4 and another chromatin remodeler have a poorer prognosis because their disease is more resistant to chemotherapy (Reisman et al. 2003). Recent in vitro and in vivo research suggests that tumors lacking SMARCA4 may respond differently to therapies that target other pathways. SMARCA4-deficient NSCLC cells were inhibited in their proliferation by bromodomain and extra terminal motif protein (BET) inhibitors, which targeted BRD4 and HER3. Similarly, a lack of SMARCA4

in NSCLC cells results in a lack of cyclin D1, making the cells more vulnerable to CDK4/6 inhibitors (Shorstova et al. 2019).

7.3. Histone Modifications

In addition to changes in chromatin conformation, histones can also be modified post-translationally, which can affect gene expression. Depending on the chemical group and its location within the histone, a modification can either be repressive or activating (Schiffmann et al. 2016). Writer and eraser enzymes add and remove alterations to histones, respectively, to control histone modifications. Histone methylation and demethylation play critical roles in regulating gene expression, mediated by methyltransferases and demethylases. High levels of global histone H3 and H4 methylation as well as high expression of histone methyltransferases are associated with a poor prognosis in lung cancer (Song et al. 2012). DNA replication, DNA damage response, cell-cycle progression, and transcriptional control are just a few of the numerous physiological activities that histone lysine methyltransferases (KMTs) play essential roles in and are frequently dysregulated in cancer. Both gene activation and repression can result from aberrant histone modifications, depending on factors such as the surrounding chromatin structure, the kind of cell in which the alteration occurred, and the presence or absence of other mutations. Among the KMTs, EZH2 has received the greatest attention since it is overexpressed in both NSCLC and SCLC (Coe et al. 2013). Polycomb repressive complex 2 (PRC2) inhibits transcription by blocking histone methylation via the enzyme element EZH2. Enhanced EZH2 expression is sufficient for malignant transition to lungADC and is associated with resistance to chemotherapy and poor survival (Xu et al. 2014; Zhang et al. 2016). Overexpression of EZH2 promotes lung cancer growth via multiple signaling pathways, including VEGF-A, AKT, E2F/Rb, and TGF- (Coe et al. 2013; Riquelme et al. 2014; Xu et al. 2014; Geng et al. 2015; Murai et al. 2015; Serresi et al. 2016). In contrast, a KRAS G12D mouse model of lung ADC shows that deletion of the KMT, SETD2, hastens tumor growth in both early and late stages (Walter et al. 2017). Tumorigenesis can also be controlled by KMTs through the lysine methylation of non-histone proteins. SMYD3, for instance, is overexpressed in Ras-driven malignancies and, through promoting MAP3K2 methylation, promotes Ras/Raf/MEK/ERK signaling (Mazur et al. 2014).

Histone acetyltransferases (HATs) function as "writers" by adding acetyl groups to lysines in histone tails. This results in DNA being accessible to transcription factors, leading to active transcription due to the open conformation of chromatin. Mutations in the HATs belonging to the CREBBP/EP300 family are frequently seen in SCLC, although their role in carcinogenesis is poorly known (Kim et al. 2018). Silencing P300 results in suppression of Snail and activation of E-cadherin expression in lung ADC cells, suggesting regulation of EMT as a potential mechanism (Chang et al. 2017). Similar to EP300 in structure and function, mutations in CBP have been found in 10% of lung cancer cell lines and 5% of lung cancer patients' surgical specimens (Kishimoto et al. 2005). Similarly, mutations in KAT6B, another HAT, are seen in some SCLC cell lines and patients. Tumorigenesis is boosted in both the laboratory and in living animals when KAT6B is knocked down in nonmutated SCLC cells (Simó-Riudalbas et al., 2015).

By contrast, histone deacetylases (HDACs) act as "erasers" that eliminate acetyl marks from histones. These enzymes acetylate and deacetylate a wide variety of proteins, not just histones; in this case, the acetyl groups on these proteins serve as docking sites for the assembly of protein complexes at promoters. Many members of the histone deacetylase adenosine diphosphatase (HDAC) family have been linked to malignant transformation, metastasis, and other hallmarks of cancer, and HDACs are frequently overexpressed in NSCLC (Osada et al. 2004; Adeegbe et al. 2017).

8. Biomarkers and Lung Cancer

According to the National Cancer Institute, a biomarker is any molecule in the blood or other bodily fluids or tissues that can be used to diagnose or monitor a disease. As it turns out, there are a lot of different aspects of cancer biology that tumor biomarkers can shed light on. In addition to aiding in the detection of cancer at an early stage, these markers can also be used to make prognostic predictions about the severity of the disease and the likelihood of a favorable or unfavorable prognosis associated with a particular tumor. Predictive biomarkers assess the likely effectiveness of a treatment, which is yet another major application. Tumor biomarkers provide important clinical data that can be used to determine the most effective treatment for a patient, paving the way for individualized cancer care. Tumor biomarkers can be divided into a few categories: genetics, epigenetics, proteomics, metabolomics, and imaging technology.

8.1. DNA methylation as a tumor biomarker

All human cancers share a common epigenetic aberration now thought to be crucial to the development of the disease. Through the use of high-throughput techniques like microarrays and next-generation sequencing, we are learning more and more about the degree to which cancer cells undergo epigenetic reprogramming. The chemical covalent modification of cytosine known as DNA methylation is the most extensively researched epigenetic process in the mammalian genome at the present time. Specifically, it is the modification of CpG dinucleotides by adding a methyl group (CH3) to the fifth carbon of cytosine bases that are 5 from guanosine. CpG islands are small areas of the genome where CpG dinucleotides are highly clustered (CGIs). CGIs are rare (less than 1% of the genome), but when they are present, they tend to be in unmethylated areas near gene promoters in healthy adult cells. At general, increased methylation (hypermethylation) in the promoter region of a gene results in decreased expression, but methylation in the transcribed region (gene body) has a variable influence on gene expression.

The methylation signature of cancer cells is abnormal; they exhibit global hypomethylation and hypermethylation of tumor suppressor genes (TSGs). In NSCLC, there is a high prevalence of global hypomethylation, which is linked to genomic instability and abnormal amplification of oncogenic gene isoforms. Both high-throughput techniques and target-based strategies have been used to identify a significant number of abnormal methylation genes in lung cancer. Additionally, methylation has been mentioned as an early stage in the development of lung tumors. The early hypermethylation of p16, which greatly contributes to its transcriptional silencing, is a well-known case. APC, DAPK1, RASSF1A and H-cadherin are some other examples. There is already a very broad number of possible indicators for lung cancer diagnosis, prognosis, and prognostic information thanks to the abundance of high-throughput and gene-focused techniques.

DNA hypermethylation is a promising tumor biomarker since it is almost always present in malignant tissues. DNA methylation boasts several advantages over other types of molecular markers like mRNA and proteins. For starters, DNA methylation is chemically stable and can endure extreme circumstances for extended periods of time since it is a covalent change of DNA. A second advantage is that it is simple to amplify and detect. Thirdly, Aberrant methylation of specific CGIs occurs far more frequently than cancer-specific mutations, which are dispersed

across multiple genes. Furthermore, such methylation can be uncovered by genome-wide screening methods. The use of methylation-specific PCR for the detection of aberrant methylation has become widespread, even in situations where methylated sequences are scarce. Since methylation has been detected in non-neoplastic tissues and in the early stages of carcinogenesis, it can serve as a very early indicator of neoplastic change. Noncore regions of p16 are methylated, for instance, in 17 percent of cases of pulmonary hyperplasia, 24 percent of cases of pulmonary dysplasia, and 50 percent of cases of lung cancer in situ. In contrast to point mutations, which can occur anywhere throughout the gene sequence, DNA methylation typically impacts larger segments of DNA within promoters. As a result, methylation profiling is more efficient and cost-effective than mutation profiling. Powerful new methods for detecting DNA methylation have emerged in recent years, including sodium bisulfite (SB) conversion, restriction genomic scanning, and CGI microarrays. SB conversion is merely the first step in some of the listed experiments, such as methylation-specific PCR, and is not a DNA methylation detection approach in and of itself. Since 'converted' DNA can be used in numerous PCR-based procedures after being treated with SB, CGI methylation can discriminate between normal and abnormal methylation patterns. A diagnostic tool for DNA methylation should be sensitive and repeatable enough for routine use, with standardized processes that are quick and can be automated. The current principle widely used, quantitative methylation-specific PCR (qMSP), appears to retain many of these properties and has shown extremely high performance in clinical samples including bronchial washings and plasma. These assays, however, still have ways to go before they can be considered "excellent clinical laboratory practice."

There are three distinct clinical applications for the study of aberrant DNA methylation in the context of cancer diagnosis. Primarily, it is possible to diagnose cancer cells in biopsies or bodily fluids by detecting cell-free DNA (cfDNA) that circulates in plasma and is specifically present in cancer cells. Second, abnormal methylation at specific CGIs can be used as a prognostic or predictive marker in the management of treatment and follow-up of diagnosed cases, such as histological type, differentiation, aggressive behavior, response to chemotherapy regimens, or association with adverse drug effects. Third, abnormal methylation of some CGIs in noncancerous tissues may be employed as a cancer risk sign if this phenomenon is linked to the development of cancer.

DNA methylation has emerged as a promising epigenetic biomarker that has the potential to enhance both the early identification of cancer and the treatment of patients who have been diagnosed with the disease. However, the main questions that circulate now are that if it is simple enough to development or if it will be clinically acceptable everywhere. There has recently been research on the DNA methylation profile that separates NSCLC with epithelial-like characteristics from NSCLC with mesenchymal-like characteristics, which respond differently to anti-EGFR therapy. This was accomplished by first conducting a genome-wide analysis in NSCLC cell lines with epithelial and mesenchymal phenotypes. Methylation findings were confirmed by direct sequencing of cloned segments, and the most discriminatory differentially methylated areas labeled the cell lines as epithelial or mesenchymal. Ten of the 13 most discriminative genes were successful at classifying cell lines using qMSP tests, and seven were linked to in vitro erlotinib resistance. Analysis of NSCLC cell lines, raw tumors, and biopsies from chemo resistant patients revealed that ERB2 and ZEB2 methylation status was predictive of an epithelial-like phenotype and might be used for diagnostic reasons when examined more closely using pyrosequencing and quantitative methylation-specific PCR. Computational approaches for improved biomarkers selection, performance evaluation, and assay design are needed to simplify similar procedures for the identification and validation of biomarkers based on DNA methylation. The importance of long-term, retrospective investigations is being emphasized. It is necessary to confirm these findings in studies with strong statistical power before attempting to create assays for routine clinical usage.

8.2. Circulating Tumor DNA

Because blood is a possible source of minimally invasive samples, namely circulating tumor DNA (cfDNA) in serum or plasma or DNA extracted from peripheral blood leucocytes, and because it has become obvious that hypermethylation may be found in tumor-derived DNA circulating in plasma or serum of cancer patients, there has been a considerable increase in blood-based DNA methylation tests in clinical research over the last decade. It is not completely understood how DNA gets into the bloodstream. Possible explanations for the detection of cfDNA in blood plasma or serum include the active release of tumor DNA and the passive leaking of DNA after the necrosis or apoptosis of neoplastic cells. Only recently has the methylation status of SOX17 been

shown to be the first indicator of whether or not cfDNA is linked to circulating tumor cells from the same patients. The genetic and epigenetic characteristics of the primary tumor source are preserved in cfDNA. It is important to note that serum cfDNA differs from plasma cfDNA in a number of ways, the most notable being that serum cfDNA concentrations are higher. The presence of extra DNA in the serum has been linked to the clotting process. The disease and the circulating cfDNA are better reflected by the lower concentrations of cfDNA in plasma than in serum. Numerous loci have been discovered to be methylated in the plasma/serum of NSCLC patients, which points to new potential diagnostic and prognostic targets. DNA methylation of SHOX2 has recently been identified as a biomarker that can differentiate between malignant lung illness and controls with a sensitivity of 60% and a specificity of 90%, as shown in a study by Kneip et al. More advanced stages of cancer were recognized with greater sensitivity than earlier ones, including stages II (72%), III (55%) and IV (83%). Compared to adenocarcinomas, small-cell lung cancer and squamous cell carcinoma were recognized with higher sensitivity. This research suggests that the degree of SHOX2 DNA methylation in the plasma of lung cancer patients can be used as a biomarker for the detection of malignant lung disease. To better understand how this panel of indicators might be used in the diagnosis of lung cancer, a small sample of patients' serum was analyzed for the methylation status of six genes (APC, CDH1, MGMT, DCC, R ASSF1A, and AIM1). A total of 35.5 percent of the 76 patients with lung cancer were accurately detected, indicating that DCC offers a high level of specificity (100 percent). However, the use of this strategy for early identification and surveillance of lung cancer requires evaluation in a larger test set.

8.3. Methylation of miRNA loci as Novel Biomarkers in Lung Cancer

Different types of circulating RNA were discovered in human serum. These included microRNAs, piwi-interacting RNAs, transfer RNAs, snoRNAs, and snRNAs. Due to their exceptional stability under adverse conditions and resistance to circulating RNAses, circulating microRNAs (c-miRNAs) are often discussed in the literature as promising possibilities for developing lung cancer diagnostics. Almost all human cells passively (in apoptotic bodies, complexed with AGO proteins) or actively (in exosomes/microvescicles) produce C-miRNAs, which can affect tissue homeostasis

through paracrine signaling or initiate pathogenic pathways like neoplastic transformation and tumor growth. It was discovered that tumor cells, CAFs, and blood cells all produce miRNAs into the microenvironment, most of which make their way then into the bloodstream.

MicroRNAs (miRNAs) are being studied as potential novel epigenetic regulators of gene expression due to their participation in a wide variety of cellular biological processes that promote cancer phenotypes and oncogenic changes. While hypermethylation of miR-124a in lung adenocarcinomas causes Rb phosphorylation and CDK6 activation, the miRNA-29 family may correct aberrant methylation in lung cancer by targeting the 3'-untranslated region of DNMT3A and DNMT3B, which are often increased in lung cancer and are linked with poor prognosis. Overexpression of miR-29 suppresses lung carcinogenesis via restoring normal methylation in non-small cell lung cancer (NSCLC) by re-expressing methylated silenced TSGs. Clarifying the connection that exists between DNA methylation and miRNAs will, when taken as a whole, contribute to a better understanding of how to create tumor biomarkers that are more comprehensive.

9. Present Therapeutic Scenario

As discussed in the previous text, lung cancer is basically in two types- 1. Small Cell Lung Cancer (SCLC) and 2. Non-Small Cell Lung Cancer (NSCLC). These categories are mainly done from the location and microscopical viewpoint of cancer cells. Compared to SCLC, NSCLS is more prevalent. After the diagnosis, lung cancer treatment and therapies are done according to the staging. The process of staging is done by determining the extent of its spread in the lymph nodes, lungs, and other body parts. Surgery, chemotherapy, radiation therapy, targeted therapy, or a combination of these treatments may be used to treat NSCLC patients.

Chemotherapy and radiation therapy are frequently used in the treatment of people with SCLC (*How Is Lung Cancer Diagnosed and Treated? | CDC*, n.d.). Surgery is chosen as a treatment option for non-metastatic NSCLC based on the volume of the tumor, how it affects nearby tissues, and the amount of surgery required to entirely remove the tumor given the patient's health or medical operability. The patient is referred for final non-surgical care with radiotherapy if the tumor is not entirely resectable or the patient cannot be operated on medically (Chaft et al., 2021).

Patients with lung cancer are typically older than those with breast or colon cancer, are more likely to smoke, and have higher rates of heart disease and emphysema. These factors contribute to increased all-cause mortality as well as debility brought on by surgery, particularly pneumonectomy. Together, these variables make cytotoxic medications less tolerable, which have, up until the last ten years, been these patients' best alternative. Surgery has become more precise, and as a result, morbidity after surgery has decreased and the survival of patients treated solely through surgery is improving stage by stage. The same is true for radiotherapy, where advances in methods have led to higher tumor-targeting radiation fields that are more conformal, as well as significantly lower toxicities when using intensity-modulated radiation treatment as opposed to 2D or 3D methods (Chaft et al., 2021). MRI-guided radiation and proton therapy have the potential to significantly enhance dose delivery.

9.1. Radiation Therapy

Applying high-energy X-rays to a tumor to reduce it is known as radiation treatment. Since it only affects the tumor location, it is regarded as a local treatment and is typically used in conjunction with surgery, alternative chemotherapy, or as a neo-adjuvant therapy to help in surgery by lowering the size of a tumor (C. Y. Huang et al., 2017a). For high-risk individuals with early-stage lung cancer, stereotactic body radiation therapy (SBRT) has been suggested as an alternate local therapeutic option (Crabtree et al., 2010). Stereotactic radiosurgery harms the targeted cells' DNA, much like other radiation treatments do. Tumors then begin to contract as a result of the afflicted cells' inability to proliferate. One to five treatments are often required for body radiation. The absence of an incision makes SBRT different from conventional surgery. Instead, intense radiation doses are directed at the afflicted area using 3D imaging in SBRT (*Stereotactic Body Radiotherapy - Type - Mayo Clinic*, n.d.). The results of SBRT and surgical resection have not been directly compared. Clinical stage IA illness patients who underwent surgery fared better in a random comparison than those who underwent stereotactic body radiation therapy in terms of health and local tumor control (Crabtree et al., 2010). Tumor radio-resistance, systemic tumor progression, and local or distant metastases frequently restrict the therapeutic effectiveness of radiotherapy alone in the treatment of locally or regionally advanced lung cancer (C. Y. Huang et al., 2017a). However, there is no such thing as complete resistance to radiation therapy. Radiation therapy will

always have to be somewhat indiscriminate and unselective in order to eliminate chronic, drug-resistant tumor stem cell reservoirs (Henning et al., 2013).

9.2. Chemotherapy

Chemotherapy is a medicinal therapy that uses potent chemicals to kill body's rapidly proliferating cells. Since cancer cells grow and proliferate significantly more quickly than the majority of body cells, chemotherapy is most frequently utilized to treat cancer. Chemotherapy medications come in a wide variety. A number of malignancies can be treated with chemotherapy medications either alone or in combination (*Chemotherapy - Mayo Clinic*, n.d.). Cell division and DNA replication are inhibited by conventional anticancer chemotherapy drugs. The microtubule dynamics of the mitotic spindle may also be the target of several of these substances. Taxanes, nucleoside analogues, topoisomerase inhibitors, platinum compounds, and vinca alkaloids are some of the early anticancer medications still in use today. They significantly extend patient survival and have excellent curative benefits (Ke & Shen, 2017). The benefits of chemotherapy-based treatment seem to have peaked in the regimens of the present therapeutic scenario of lung cancer. Chemotherapy has relied on natural substances for the past 30 years. Researchers in biology are now better able to examine how natural substances might be used to treat or prevent a variety of malignant conditions (C. Y. Huang et al., 2017). By interfering with the production of DNA, RNA, or proteins or by impairing the proper operation of the preformed molecule, traditional chemotherapy drugs largely disrupt the macromolecular synthesis and function of malignant cells (M. T. Amjad et al., 2022).

Based on their modes of action, anticancer medications currently fall into a number of different types, which include the following: a) alkylating agents that damage DNA; b) anti-metabolites that replace the normal building blocks of RNA and DNA; c) antibiotics that interfere with the enzymes involved in DNA replication; d) topoisomerase inhibitors that inhibit either topoisomerase I or II, which are the enzymes involved in unwinding DNA during replication and transcription; e) mitotic inhibitors that inhibit mitosis and cell division; and f) corticosteroids, which are used for the treatment of cancer and to relieve the side effects from other drugs (C. Y. Huang et al., 2017).

Drug name	Generic name	Use
Xeloda	Capecitabine	Anti-Metabolites
Avastin	Bevacizumab	VEGF/VEGFR Inhibitors
Tarceva	Erlotinib	EGFR Inhibitors
Cytoxan	Cyclophosphamide	Alkylating Agents
Taxol	Paclitaxel	Mitotic Inhibitors
Taxotere	Docetaxel	Mitotic Inhibitors
Gemzar	Gemcitabine	Antimetabolites
Erbitux	Cetuximab	EGFR Inhibitors
Alimta	Pemetrexed	Antimetabolites
Navelbine	Vinorelbine	Mitotic Inhibitors
Platinol	Cisplatin	Alkylating Agents
Trexall	Methotrexate	Antimetabolites, Antipsoriatics, Antirheumatics
Ethyol	Amifostine	Antineoplastic Detoxifying Agents
Iressa	Gefitinib	EGFR Inhibitor
Neosar	Cyclophosphamide	Alkylating Agents
Platinol-AQ	Cisplatin	Alkylating Agents
Photofrin	Porfimer	Miscellaneous Antineoplastics
Onxol	Paclitaxel	Mitotic Inhibitors

Table 3: Chemotherapy Drugs currently being used in Lung cancer treatment (C. Y. Huang et al., 2017).

Current recommendations state that a platinum agent-based doublet, such as cisplatin or carboplatin, should be used in conjunction with a third-generation cytotoxic medication, gemcitabine, a taxane (paclitaxel, docetaxel), or vinorelbine. The clinical outcome of cisplatin doublets is marginally better than carboplatin-based chemotherapy without being associated with an increase in severe adverse effects, according to meta-analyses of randomized clinical studies comparing the two drugs (C. Y. Huang et al., 2017). Bevacizumab, a monoclonal antibody that targets the vascular endothelial growth factor (VEGF), was authorized in late 2006 for use in conjunction with the chemotherapeutic drugs paclitaxel and carboplatin for the first-line treatment of patients with non-squamous NSCLC (Alan Sandler et al., 2006; Cohen et al., 2007). A number of anticancer medications used to treat lung cancer, including bleomycin, doxorobucin, etoposide (VP-16), cisplatin, and methotrexate, have been found to increase the expression of the Fas ligand (FasL) on the surface of cells that express the Fas receptor. This finding raises the possibility that apoptosis by these medications may be mediated by Fas cross-linking. Those with a positive K-ras mutation respond well to platinum medications, however, patients with enhanced Her-2 expression do not respond well to many medicines. Additionally, taxanes are more beneficial when

p27 expression is elevated, whereas taxanes are ineffective for patients who have a positive beta-tubulin mutation. Finally, patients that exhibit a lot of excision repair protein (ERCC1) would not benefit from cisplatin or other platinum medicines (C. Y. Huang et al., 2017). Anticancer agents have long been found in natural substances. Traditional Chinese medicine (TCM) has been used for many years in China and other countries to treat malignancies (Hsiao & Liu, 2010).

9.3. Targeted Therapy

One kind of cancer treatment is called targeted therapy. Drugs are used to specifically target the genes and proteins that support the growth and survival of cancer cells. By focusing on certain cells, such as blood vessel cells, targeted therapy can influence the tissue habitat in which cancer cells proliferate (*What Is Targeted Therapy? | Cancer.Net*, n.d.). The specific targets of the cancer disease are the focus of certain novel methods of cancer treatment. Targeted therapy has an impact on a variety of molecular targets and signaling cascades. The anticancer effects of targeted therapy were mediated by a number of pathways, including reduction of proliferation, induction of apoptosis, suppression of metastasis, control of immunological function, and reversal of multidrug resistance (Ke & Shen, 2017).

Tyrosine-kinase inhibitors (TKIs), which target mutant oncogenes, and monoclonal antibodies, which block immunological checkpoints have significantly increased the arsenal of drugs used to treat metastatic non-small-cell lung cancer (NSCLC) (Chaft et al., 2021). Gefitinib and erlotinib, which suppress the tyrosine kinase activity of the epidermal growth factor receptor, are frequently prescribed to people with non-small-cell lung cancer. Sadly, innate and acquired resistance restricts the effectiveness of EGFR-TKIs. Autophagy has been suggested to play a part in the drug resistance of tumor cells as a unique cytoprotective mechanism for tumor cells to survive under adverse settings. As scientists first report that the PI3K/Akt/mTOR signaling pathway was also inhibited together with the high degree of autophagy that was induced by Gefitinib or Erlotinib. It's interesting to note that even after EGFR expression was lowered with EGFR-specific siRNAs, EGFR-TKIs can still cause cell autophagy. Scientists also discovered that EGFR-TKIs can induce autophagy in lung cancer cells and that inhibiting autophagy enhanced EGFR-TKIs' ability to limit proliferation. Thus, inhibiting autophagy offers a potentially effective means of enhancing the

effectiveness of EGFR-TKIs in the treatment of patients with advanced non-small-cell lung cancer (Han et al., 2011).

9.4. Immunotherapy

The development of lung cancer depends not only on the changing genomes and molecular characteristics of cancer cells but also on how those cells interact with the environment around the tumor, particularly the immune system (Hirsch et al., 2017). Numerous ligands and receptors that block or stimulate the immunological synapse have been the target of immunotherapy strategies. The co-opting of certain immune-checkpoint pathways by malignancies as a significant immunological resistance strategy is now well established, notably against T cells that are specifically reactive to tumor antigens. Since many immunological checkpoints are triggered by ligand-receptor interactions, they are easily inhibited by antibodies or controlled by recombinant ligands or receptors. The first immunotherapeutic in this class to receive US Food and Drug Administration (FDA) approval was Cytotoxic T-Lymphocyte-associated Antigen 4 (CTLA4). The possibility for enhancing anticancer immunity and producing long-lasting clinical responses is shown by preliminary clinical findings using blockers of additional immune-checkpoint proteins, such as programmed cell death protein 1 (PD1) (Pardoll, 2012). Advanced lung cancer and other tumors are currently managed in a significant way by antibody-directed treatments against these checkpoints, which have demonstrated amazing early effectiveness in several malignancies (Postow et al., 2015). Several monoclonal antibodies directed to the PD-1 receptor are nivolumab, pembrolizumab, or its ligand PD-L1 are atezolizumab, durvalumab, avelumab have reached the clinic and others are in preclinical development (Hirsch et al., 2017). About 14–20% of individuals with advanced NSCLC who had previously received treatment responded quickly and effectively to these drugs in early clinical studies (Rizvi et al., 2015).

Ipilimumab, an anti-cytotoxic T-lymphocyte antigen-4 antibody, has demonstrated sustained improvements and prolonged survival for a subgroup of patients with advanced melanoma as a result of recent advances in converting the early development of immunomodulatory antibodies in the clinic. According to further research, immune checkpoint antibodies with a similar function—more specifically, those that target the programmed death-1 pathway—have activity in non-small cell lung cancer (Forde et al., 2014).

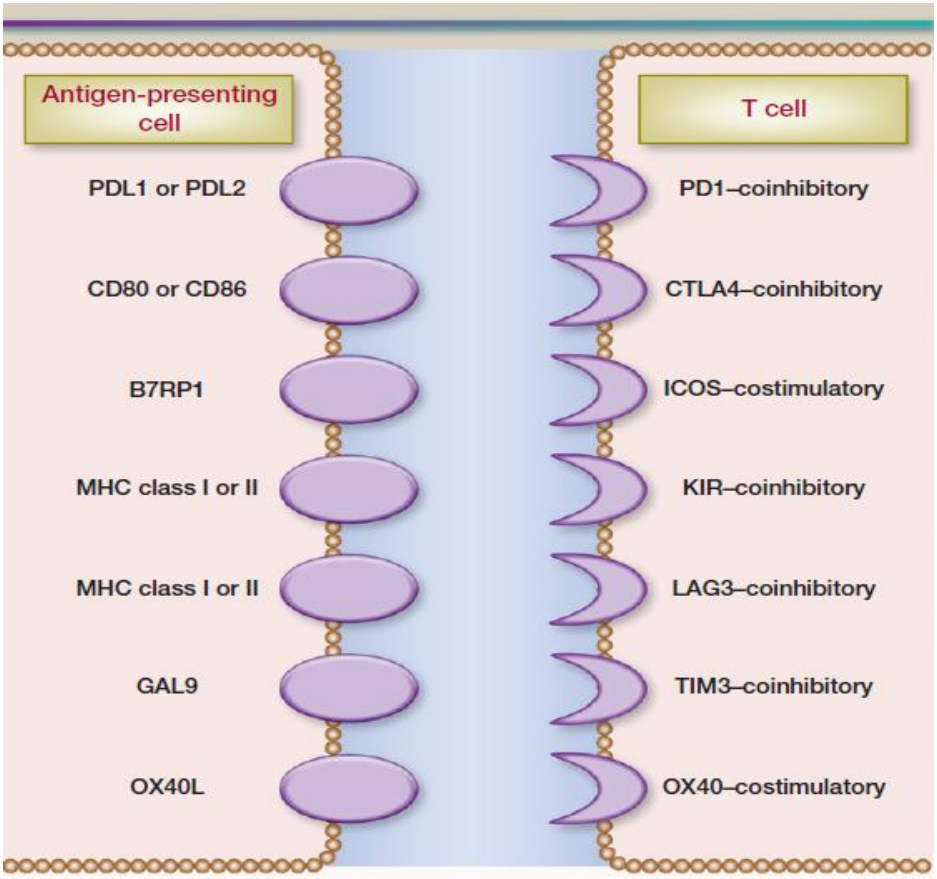

Figure 13: Selected immune checkpoints for which modulating molecules are in late preclinical or clinical development. B7RP1, B7-related protein-1; ICOS, inducible T-cell co-stimulator; KIR, killer cell immunoglobulin–like receptor; LAG3, lymphocyte activation gene 3; GAL9, galectin-9; TIM3, T-cell immunoglobulin domain and mucin domain 3; OX40L, OX40 ligand (Forde et al., 2014).

10. Future Perspectives

The health systems bear a heavyweight in terms of mortality and morbidity due to lung cancer. Finding the root cause and early diagnosis can be the key to the treatment of this deadly disease. A lot of advancements have been developed to understand its nature and to treat this disease. Researchers supported by the NCI (National Cancer Institute) are advancing our knowledge of lung cancer prevention, detection, and treatment. There has been significant improvement because researchers are now able to pinpoint numerous genetic changes that can promote the development of lung cancer. Finding early signs of lung cancer has been the subject of extensive investigation.

The National Lung Screening Trial (NLST), sponsored by the NCI, demonstrated that individuals with a history of heavy smoking can be screened for lung cancer using low-dose CT scans. Researchers are currently working to improve CT screening so that it can more accurately detect

the presence of cancer. Researchers are working to create or improve sputum and blood tests that could be used to find lung cancer early. There are two ongoing research areas: 1) An early diagnosis of lung cancer can be achieved by analyzing blood samples to see if tumor cells or molecular markers are present. 2) Sputum samples are examined for the presence of aberrant cells or molecular markers that reveal people who may require further investigation (*Advances in Lung Cancer Research - NCI*, n.d.).

Machine Learning is another advancement in the field of lung cancer. Through the use of machine learning, computers can learn to make predictions about the future. Researchers are employing computer algorithms to develop computer-aided programs that can detect lung cancer in CT scans more accurately than radiologists or pathologists can. For instance, in one artificial intelligence study, scientists taught a computer program to accurately identify two forms of lung cancer and cancer-related genetic alterations with 97% accuracy (*Advances in Lung Cancer Research - NCI*, n.d.).

There're numerous developments have been done also in the lung cancer treatment section. Surgery, radiation, chemotherapy, targeted therapy, immunotherapy, and combinations of these treatments are available for treating lung cancer. Scientists now have some encouraging findings for advanced-stage lung cancer, even though researchers are still searching for novel therapeutic options for all stages of the disease. As discussed before, in order to combat cancer, immunotherapies collaborate with the body's immune system. Today's research on lung cancer treatments places a lot of emphasis on them. There are currently clinical trials looking at new immunotherapy combinations with or without chemotherapy to treat lung cancer. For the treatment of lung cancer, immune checkpoint inhibitors include- Atezolizumab (Tecentriq), Cemiplimab (Libtayo), Durvalumab (Imfinzi), Nivolumab (Opdivo), Pembrolizumab (Keytruda).

With less damage to healthy cells, targeted treatments locate and target certain cancer cell types. For advanced lung cancer, numerous targeted medicines have just become accessible, and more are currently being developed. Some specific lung cancer therapies include the following:

The cancer-causing change in the ALK (Anaplastic Lymphoma Kinase) gene is the focus of ALK inhibitors. For the 5% of patients with lung cancer who have an ALK gene mutation, these medications are still being improved. Some recently approved ALK inhibitors are- Alectinib (Alecensa), Brigatinib (Alunbrig), Lorlatinib (Lorbrena). The blood-brain barrier-crossing capacity of these most recently approved ALK inhibitors has improved over that of earlier

versions. This development is important since disease progression frequently takes place in the brain in non-small cell lung cancer patients with ALK mutations.

On cancer cells, EGFR may be present in higher concentrations than usual, stimulating their growth and division. The following EGFR-targeting medicines have been authorized for the treatment of lung cancer- Afatinib (Gilotrif), Dacomitinib (Vizimpro), Erlotinib (Tarceva), Gefitinib (Iressa), Osimertinib (Tagrisso).

The ROS1 gene is changed in a small number of non-small cell lung cancer patients. For patients with these changes, entrectinib (Rozlytrek) and crizotinib (Xalkori) are approved medicines.

Treatment for some patients with non-small cell lung cancer has been approved using a combination of the drugs dabrafenib (Tafinlar), which targets a particular mutation in the BRAF gene, and trametinib (Mekinist), which targets a protein called MEK (*Advances in Lung Cancer Research - NCI*, n.d.).

Numerous NCI-funded scientists are working to find better ways to combat lung cancer on the NIH campus as well as in other countries across the world. Research that focuses on fundamental issues, such as the biological causes of cancer and the societal variables that influence cancer risk, is often conducted. Additionally, others are more clinical in nature, aiming to transform fundamental knowledge into better patient results. Both small cell lung cancer preventive, screening, and therapy trials as well as non-small cell lung cancer trials are available and more research and studies are going on (*Advances in Lung Cancer Research - NCI*, n.d.).

11. Conclusion

The epigenetic modifications that occur within cancer cells are a major contributor to intratumoral heterogeneity. This heterogeneity is largely caused by the many variables that exist within the lung tumor and immunological microenvironment. Effective therapeutic targeting of the epigenome shows promise for influencing both cancer and the immune system. Understanding the precise underlying and acquired epigenetic alterations during various treatments is necessary for clinical benefit to be realized. In order to successfully treat lung cancer, researchers will need to reprogramme the epigenome in a very targeted and nuanced way. The most recent advancements in the subset of NSCLC patients with oncogenic driver changes have provided significant clinical

patient benefit and developed a customized therapy approach. The therapy landscape of oncogenic-dependent non-small cell lung cancer is becoming an increasingly complex one. Since extensive data from studies performed with next-generation sequencing or other current technologies are continually published, the patterns of the co-occurrence of druggable genetic abnormalities in NSCLC are partially elucidated and constantly updated. This is vital for gaining a complete understanding of the molecular epidemiology and clinical implications of NSCLC. This review paper provided a comprehensive understanding of the molecular association of lung cancer, including the current landscape of lung cancer research for the development of novel targeted gene therapy and the future perspective that further research can bring.

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