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Chapter

Perspective Chapter: Molecular Pathology of Lung Cancer

Shivani Gandhi, Ishani Gupta, Reetika Menia and Raman Kumar

Abstract

Lung cancers, due to delays in diagnosis and availability of limited treatment resources, have become the leading cause of cancer-related death globally. With the recent advances in the identification of molecular mechanisms and profile of lung cancer, the understanding of novel characteristics of the molecular pathology of lung cancers as well as knowledge of driver mutations has been enhanced that has led to the development and success of targeted strategies against lung cancer. Diagnosis and treatment of this heterogeneous group of cancer have been revolutionized with the advent of the identification of genetic alterations. This chapter will summarize the etiopathogenesis, current knowledge depicting the series of events associated with the development of lung cancer, the molecular mechanism of most common and relevant genetic alterations in lung cancer along with a brief about the use of targeted therapies in lung cancer patients.

Keywords: molecular, pathology, lung cancers, molecular mechanism, tumor suppressor genes

1. Introduction

Lung cancer is one of the most frequently diagnosed cancers worldwide and is the leading cause of cancer-related mortality, late diagnoses being one of the commonest reasons for this. A total of 13% of new cases of cancer as well as 19% of deaths related to cancer are attributed to lung cancers globally. A total of 1.8 million new cases of lung cancer were estimated in the year 2012. Cancer-related mortality due to lung cancer is common in men, with the highest number of cases being reported from Mizoram in both males and females (age-adjusted rate 28.3 and 28.7 per 100,000 population in males and females, respectively). A total of 6.9% of all new cases of cancer and 9.3% of deaths related to cancer are constituted by lung cancer alone in India in both men and women. The 5-year survival rate is less than 15%, despite significant advances in both diagnostic and therapeutic approaches [1–3].

With the identification of the molecular profile of lung cancer, the understanding of molecular pathology has also been enhanced. Many genetic alterations in the cancer stem cells have been revealed with the help of molecular studies and these cancer stem cells play an important role to produce clones of cancer cells to form tumor mass. Many genetic driver mutations have been identified with the help of
combined genomic and transcriptomic sequencing studies and these driver mutations undergo stepwise accumulation resulting in the development of lung cancer. Molecular-targeted therapies have been identified to predict the response in patients of lung cancers to these targeted therapies with the advent and identification of driver mutations. The identification and knowledge of the molecular pathology of lung cancers have further led to the modification in the histological classification of cancers of the lung. A huge success rate has been observed in the development as well as approval of the targeted therapies and approach with the improved understanding in the identification of the genetic signature and the pathogenesis of molecular mechanism in approximately 20% of squamous cell carcinoma (SCC) and 60% of adenocarcinoma of lung. Dramatic response rates along with improved progression-free survival (PFS) have been observed with the use of targeted therapies in patients of lung cancers harboring mutations of genes like epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) gene. Therefore, molecular testing is now being routinely used to guide the clinical care of lung cancer patients to predict one’s therapeutic response [4–9].

Lung cancers have been classified into several histological subtypes based on the molecular profiles and targetable genetic alterations in lung cancer. It is a heterogeneous disease that shows variation in clinical features and biological behavior. Heterogeneity in the molecular mechanism reflects the molecular changes that occur in different subtypes of lung cancer. Genetic abnormalities associated with the development of cancer include a gain of function mutation of oncogenes like EGFR, BRAF, KRAS, AKL, MET, HER-2, loss of function mutation of tumor suppressor genes like TP53, PTEN, STK11, expression of growth factor, and their receptors. Targeted therapies are highly dependent upon molecular pathology; thus, the thorough understanding and knowledge of the molecular mechanism of different types of lung cancer is an integral part to understand the biological behavior and predict the response of cancer to the targeted therapy. With the identification of genetic mutations involved in particular cancer, the biological behavior of lung cancer can be determined which is essential for the diagnostic and therapeutic strategies that can target molecular aberrations.

In addition to the well-known genetic alterations in lung cancer that have been previously identified such as BRAF, EGFR & KRAS, many other genetic alterations such as ERBB2, RET, JAK2, DDR2 that occur in low frequency but are recurrent have also been identified with the help of genomic studies that have led to the development of targeted approach against lung cancers [10–13].

2. Etiology of lung cancer

In addition to cigarette smoking, which is one of the well-known carcinogens, there are many other environmental as well as genetic factors that contribute to lung cancer, discussed as under:

2.1 Smoking

Smoking alone accounts for approximately 90% cases of lung cancer and the risk is directly proportional to the duration of smoking and the number of cigarettes smoked/day. The risk of lung cancer is the same with cigar and pipe smoking as it is with cigarette smoking. Smoking of low-tar or “light” cigarettes also increases
the risk of lung cancer as much as regular cigarettes. Menthol cigarette smoking increases the risk even more as menthol may allow people to inhale more deeply.

2.2 Secondhand smoke

   With the passive smoking risk of lung cancer increases by 20 to 30%. More than 7000 deaths from lung cancer each year occur due to secondhand smoke.

2.3 Exposure to radon

   Radon is a naturally occurring radioactive gas that is formed by the breakdown of uranium in soil and rocks. Uranium miners have small but significant risk of lung cancer due to exposure to radon. In Europe, 2% of all deaths from lung cancer in smokers were due to appreciable hazards from residential radon.

2.4 Exposure to asbestos

   With exposure to asbestos, the risk of lung cancer is further increased and is seen more in smokers. The risk of lung cancer with asbestos exposure is directly proportional to the dose concentration and the type of asbestos fiber.

2.5 Exposure to other cancer-causing agents in the workplace

   Metal exposure such as chromium, nickel, arsenic, and polycyclic aromatic hydrocarbons is also associated with lung cancer.

2.6 Previous radiation therapy to the lungs

   Radiation exposure for non-lung cancer treatment, like non-Hodgkin’s lymphoma and breast cancer, also increases the risk of lung cancer. Certain disorders of the lung like idiopathic pulmonary fibrosis increase the risk of lung cancer independent of smoking.

2.7 Air pollution

   Air pollution is also an important risk factor for lung cancer. Around 5% of all deaths from lung cancer may occur due to outdoor air pollution worldwide.

2.8 Personal or family history of lung cancer

   First-degree relatives of lung cancer patients have an increased risk to develop cancer.

2.9 Other lung diseases and airways obstruction

   Some non-malignant diseases like COPD are associated with an increased risk for lung cancer. Tobacco smoking is the primary risk factor causing both lung cancer and COPD. Patients with interstitial fibrosis are at an increased risk of lung cancer.

2.10 Genetic factors

   Susceptibility to lung cancer is determined by host genetic factors. Tobacco smokers with genetic susceptibility are at a higher risk.
3. Molecular mechanism of lung cancer

Molecular aberrations in oncogenes, proto-oncogenes as well as tumor suppressor genes have been recognized broadly in the pathogenesis of lung cancer. Gain of function mutation of oncogenes, and loss of function mutation of tumor suppressor genes result in the accumulation of multiple genetic abnormalities over a period of time that act by causing cellular alterations such as loss of function mutation of TP53, Rb genes is common in small-cell carcinoma whereas gain of function mutation of genes encoding tyrosine kinase receptors is seen in adenocarcinoma as depicted in Figure 1. Accumulation of multiple genetic abnormalities forms an initiating step for tumor progression. Some of the genetic alterations involved in lung cancer progression are discussed as follows.

4. Oncogene/proto oncogene

4.1 KRAS

KRAS is a member of the RAS family of proto-oncogenes, which also includes HRAS and NRAS. These three RAS genes encode monomeric GTPases that play a critical role in controlling the signal transduction pathways, regulate cell proliferation, differentiation, and cell survival. RAS proteins are bound to guanosine diphosphate (GDP) and are inactive in normal quiescent cells. On binding of the growth factor to the growth factor receptor, there is a transition to the active guanosine triphosphate (GTP) bound form that leads to the formation of an activated RAS-GTP complex, and this complex further bind to activate a number of other downstream signaling pathways such as RAF/MEK/MAPK/RAS PI3K/AKT pathways. Downstream signaling of pathways is initiated via KRAS incited by various growth factor receptors including EGFR and thus constitutive activation of this protein overcomes the need for growth

![Figure 1](image-url)

*Figure 1.* Molecular pathogenesis of lung cancer.
factor-mediated signaling. Activating RAS mutations alter the GTPase activity of the protein, thus hampering the inactivation of active RAS-GTP to GDP which leads to an increase in the downstream growth-promoting signaling pathway. In lung cancer, RAS/RAF/MEK/MAPK signal transduction cascade plays a pivotal role (Figure 2).

Activating KRAS mutation is the commonest oncogenic alteration in lung adenocarcinoma, which occurs in about 25–40% of cases, while mutations of HRAS and NRAS are very rare. KRAS mutation is more frequently observed in males and smokers. A total of 0–15% cases of adenocarcinoma in never smokers reported KRAS mutation. In squamous cell carcinoma or small-cell carcinoma, KRAS mutation is very rare or absent. KRAS mutations primarily occur at codon 12, occasionally at codon 13, and very rare at codon 61. The most common mutations in KRAS are G to T transversions (~84%) in smokers, while never smokers have G to A transitions. EGFR and KRAS mutations are mutually exclusive, although there may be rare exceptions to this. A literature review has suggested that KRAS mutant tumors are resistant to the EGFR tyrosine kinase inhibitors (TKIs), as the mutations in KRAS lead to constitutive activation of the pathways, which are downstream of EGFR. In lung cancer, the high frequency of KRAS mutations makes it an ideal target for the treatment of cancer [14–23].

4.2 EGFR

EGFR is a member of erbB family having closely related receptor tyrosine kinases, which also includes erbB1 (also known as EGFR), erbB2 (HER2), erbB3, and erbB4. EGFR has an extracellular ligand binding domain, a transmembrane portion, and intracellular tyrosine kinase and regulatory domains. On binding of a specific ligand (e.g., epidermal growth factor), there occurs a conformational change and phosphorylation of the intracellular domain occurs, which leads to downstream signal transduction by various pathways that include PI3K/AKT/mTOR, RAS/RAF//MAPK, and JAK/STAT signaling pathways. Depending on the pathway undertaken, the end result is cell proliferation or cell maintenance by inhibition of apoptosis (Figure 3).
DNA mutations in EGFR can occur in the extracellular region or intracellular portions of the protein. In 43–89% cases of non-small-cell lung cancer, overexpression of EGFR or mutations in intracellular EGFR have been observed. Mutations in the EGFR tyrosine kinase domain are observed in around one-quarter of NSCLC and are associated with increased receptor expression in 75% of cases. Exon 19 frame deletions and exon 21 point mutation are the most common domain mutations in EGFR tyrosine kinase leading to the substitution of leucine at codon 858 in place of arginine, as a result of which signal transduction pathways get activated resulting in increased proliferation of cells and inhibition of apoptosis irrespective of the presence of ligand at extracellular site. Mutations in exons 18 and 21 are less commonly observed.

All EGFR mutations are observed in adenocarcinoma of the lung, although they can also be seen in adenosquamous carcinomas. EGFR mutations are more commonly observed in young female patients with no history of smoking but there can be exceptions to this. EGFR mutations are very rarely observed in pure squamous cell carcinoma of the lung. In patients who develop resistance to EGFR TKIs, secondary mutations in EGFR are observed, the commonest is the T790M activating point mutation in exon 20 [17, 18, 24–29].

4.3 BRAF

BRAF is a proto-oncogene that encodes a serine/threonine protein kinase that is a downstream effector protein of RAS and it transduces the signal through the mitogen-activated protein kinase pathway, which promotes cell proliferation and survival. Phosphorylation of downstream mediators MEK1 and MEK2 occurs on activation of BRAF, which subsequently activates ERK1 and ERK2, which take part in the regulation of growth-regulating proteins such as c-JUN and ELK1. BRAF-activating mutations lead to an increase in the kinase activity that exhibits transforming activity in vitro.

BRAF mutations are most commonly noted in melanoma, and they can also occur in about 3% cases of NSCLC. The mutations seen in NSCLC differ from those

Figure 3. 
EGFR signal transduction in cancer cells.
in melanoma and colorectal carcinoma. In lung adenocarcinoma, V600E mutations in exon 15 are most commonly seen accounting for 50% of BRAF mutations, which are followed by G469A in exon 11 and D594G in exon 15. In NSCLC BRAF mutations occur either in the kinase domain (such as V600E, D594G, and L596R) or in the G-loop of the activation domain of the gene (such as G465V and G468A). BRAF and EGFR mutations are mutually exclusive. Non-V600E BRAF mutations are observed in current or former smokers, while V600E mutations are more common in female never smokers. BRAF mutations act as an important therapeutic target in NSCLC [14, 21, 30, 31].

4.4 MEK

MEK1 (also known as MAPK1) is a serine–threonine kinase that acts as an important downstream target of RAS activation. MEK1 further activates MAPK2 and MAPK3 that are downstream of BRAF. In lung adenocarcinoma, somatic mutations of MEK1 are reported rarely and they are mostly activating mutation in exon 2 [27, 32].

4.5 Met

MET is located on chromosome 7q21-q31 and acts as a protooncogene that encodes a membrane tyrosine kinase receptor that is also known by the name hepatocyte growth factor receptor. Hepatocyte growth factor binds to its ligand, there occurs a sequence of events which are homodimerization of receptor, activation of kinase, and downstream signaling through PI3K/AKT/RAS/RAF/MEK/MAPK and c-SRC kinase pathways. Gene amplification of MET is observed in NSCLC. MET copy number is increased more commonly in SCC than ADC and is mutually exclusive with KRAS mutations. Amplification of MET results in overexpression of MET protein and thus activation of downstream signaling pathways. MET amplification is a known mechanism of secondary EGFR-TKI resistance. In this scenario, the amplification of MET drives and maintains the PI3K/AKT pathway bypassing the EGFR blockade by TKIs, which suggests concomitant MET inhibition may be a way of overcoming TKI resistance [33–36].

4.6 HER-2

The human epidermal growth factor receptor 2 (HER2/ERBB2) is a part of the ERBB family of receptors which encodes a membrane-bound receptor tyrosine kinase. Unlike other members of ERBB receptors, it does not bind directly to the ligand but can form heterodimers with other ligand-bound members of the receptor family. On activation, there occurs signaling through PI3K, MAPK, and JAK/STAT pathways. HER2 activation is seen in only a few cases of lung cancers with 20% of the case showing overexpression, gene amplification in 2%, and activating mutations in 1.6–4% of NSCLC. HER2 mutations are most commonly observed in adenocarcinoma and this mutation occurs mostly in tumors that are wild type for EGFR and KRAS and they are observed in the female gender, Asian ethnicity, and non-smokers, which is similar to the clinical profile of EGFR mutant tumors [37–41].

4.7 ROS1

ROS1, a proto-oncogene, belongs to receptor tyrosine kinase of the insulin family receptor and is located on chromosome 6q22. The rearrangement was initially described in glioblastoma involving the ROS1-FIG gene fusion.
More recently, ROS1 fusions were identified as potential driver mutations in an NSCLC cell line (HCC78; SLC34A2-ROS1) and an NSCLC patient sample (CD74-ROS1). These fusions result in tyrosine kinase activation, although the details of the downstream signaling transduced by ROS1 fusion are not fully understood yet.

Patients with ROS1 rearrangements are significantly younger, more likely to be never smokers, and overrepresented in the Asian race. Also, ROS-positive lung cancer patients are associated with sensitivity toward TKIs, specifically crizotinib, with a patient demonstrating prompt and durable complete response to therapy [42–44].

4.8 Ret

It is a proto-oncogene that encodes for receptor tyrosine kinase and is located on chromosome 10q11.2. The chromosomal rearrangements involving RET gene and kinesin family 5B (KIF5B) & coiled-coil domain containing-6 (CCDC6) resulting in KIF5B-RET and CCDC6-RET fusion genes have been identified in 70 to 90% and 10 to 25% of lung tumors, respectively.

As a result of chromosomal rearrangements, there is overexpression of RET protein. The RET fusion is found in 1–2% of NSCLC, particularly in younger, non-smoking patients with adenocarcinoma histology, and is associated with increased risk of brain metastases and patients with RET fusions show minimal response to immunotherapy [43–46].

4.9 ALK

ALK encodes for receptor tyrosine kinase. Mutation of the ALK gene is associated with 4% of unselected NSCLC approximately. EML4-ALK fusion gene that is found in a subset of lung cancers occurs because of chromosomal rearrangements forming EML4–ALK fusion gene that is involved in the activation and upregulation of RAS/RAF1/MAP2K1/MAPK1 pathway that is involved in cell proliferation as well as cell survival.

Lung cancers associated with ALK rearrangements are more common in young patients with male dominance who are more commonly non-smokers or light smokers. These tumors show typical histology characterized by the presence of mucin as well as the solid pattern of tumor growth comprising of signet cells in the Western population or acinar growth pattern in Asian patients. They are commonly diagnosed at an advanced stage of clinical presentation. The response rate to chemotherapy as well as the overall survival rate in patients with ALK rearrangement is prompt and comparable [42, 47–50].

4.10 DDR2

The DDR2 gene is a tyrosine kinase receptor, present on the long arm of chromosome 1 (1q23.3). It is involved in cell proliferation, survival, and migration by promoting matrix metalloproteinase expression. DDR2 mutation is associated with 3.8% of cases of squamous cell carcinoma. DDA2 mutations have also been observed in a few cases of NSCLC. It acts as an oncogene and its over expression promotes cell survival and proliferation in SCC lungs [51–53].

4.11 FGFR

FGFR belongs to the receptor tyrosine kinase family and is one of the most promising predictive biomarkers in lung cancer. There is overexpression and gain of function
mutation of FGFR in lung cancer. Fibroblast growth factors bind with FGFR causing the activation and upregulation of JAK–STAT/MAPK/P3K-AKT pathway causing cell proliferation, angiogenesis, differentiation, and survival. Multiple FGFR aberrations are present in Sq-NSCLC tumors—alterations (mutations and fusions), amplification, and mRNA/protein over-expression—but their predictive potential is unclear. FGFR1 amplification is seen in 22% of lung squamous cell carcinoma patients. Mutations are more common in non-smokers than smokers, with more advanced TNM stages. FGF mutations in small-cell carcinoma lung is associated with poor prognosis [54–56].

5. Tumor suppressor genes

5.1 TP53

TP53 (Tumor protein 53) is a tumor suppressor gene located on chromosome 17p13. It encodes a protein containing DNA binding, transcriptional activation, and oligomerization domains. The encoded protein regulates the expression of certain target genes involved in cell cycle arrest, DNA repair, or metabolic changes. It also regulates the expression of genes engaged in promoting growth arrest in the G1 phase or cell death in response to genotoxic stress. P53 is thus known as “the guardian of the genome.” P53 prevents the damaged cells from undergoing mitosis. On entering the G2 phase, p53 blocks cells at the G2 checkpoint, by inhibiting the cyclin-dependent kinase required to enter mitosis. This ability of p53 to inhibit cellular proliferation or induce apoptosis is suppressed by the HDM2 protein product. There is proteosome-dependent degradation and downregulation of p53 expression caused by HDM2 protein. Also, p53 itself causes the activation of HDM2 protein by binding directly with HDM2 protein resulting in the upregulation of HDM2. Thus, p53 downregulates its own expression, and as a result of which, p53 levels in normal cells are merely detectable because of this autoregulatory mechanism. Damaged DNA induces TP53 activation leading to cell cycle arrest by inducing the expression of cyclin-dependent proteins, which inhibit cell cycle progression.
kinase inhibitors, which may cause DNA repair or apoptosis (Figure 4). One of the most common abnormalities noted in lung cancer is the inactivation of TP53 with a hemizygous deletion of 17p13, containing the locus of TP53, which accounts for 90% of mutations of small-cell carcinomas and about 65% of NSCLC. Missense mutations involving TP53 have been known to be associated with 80–100% of small-cell lung carcinomas. In NSCLC mutations or proteins, accumulation has been known to occur more commonly in SCC than in ADC. Also, mutations of TP53 were found in at least 81% of SCCs in a meta-analysis by the cancer genome atlas (TCGA). Exposure to tobacco and smoking has also been noted to be associated with the varied nature of the mutation spectrum as smoking-associated cancers have a higher propensity of G to T transversions compared to G to C transversions due to the presence of polycarb- bonates associated with tobacco smoke. Also, G to A transitions at CpG dinucleotides are more commonly seen in never smokers. Mutations of EGFR and KRAS can also occur in association with TP53, and also, loss of function mutation of TP53 has been associated with poor response to treatment [57–64].

5.2 LKB1 (STK11)

The LKB1 is a tumor suppressor gene located on chromosome 19p13.3. It was thought to be involved as the causative agent behind Peutz-Jeghers syndrome through a germline-inactivating mutation. LKB1 mutation is typically rare in most types of cancer, except pancreatic cancer and NSCLC. It was found that LKB1 possesses inactivating mutations in NSCLC tumors. Inactivation of LKB1 is known to be more common in adenocarcinomas than in squamous cell carcinomas at a rate of 34 and 19%, respectively. LKB1 in lung cancer may be inhibited by a variety of somatic mutations or deletions that produce truncated proteins causing inactivation of LKB1 in about 11–30% of lung ADC. It is thought to be the third commonest genetic aberration in lung ADC after TP53 and KRAS. There are few studies in the literature supporting the association between LKB1 mutations and a history of smoking in men. Also, a correlation with KRAS mutations has been reported [65–67].

5.3 PTEN

PTEN, a tumor suppressor gene, is located on the long arm of chromosome 10 and encodes for lipid and protein phosphatases. This phosphatase causes the dephosphorylation of PIP3 as a result of which there is downregulation in the expression of PI3K/AKT/mTOR signaling pathway. Thus, the loss of function mutation of PTEN results in unrestricted upregulation and activation of signaling pathways causing uncontrolled cell proliferation, resulting in tumor mass. Some lung cancers are associated with PTEN mutations or deletions. PTEN mutations are more common in smokers than non-smokers, present in 10.2% cases of SCC lung as compared to 1.7% cases of adenocarcinoma lung. Overall, PTEN mutations are seen in 5% cases of NSCLC, in which 75% cases of NSCLC show reduced protein expression [68, 69].

5.4 PI3K

The PI3K/mTOR/AKT pathway is an important signal transduction pathway involved in the regulation of cell proliferation, differentiation, survival, adhesion, and motility. Both NSCLC and small-cell carcinoma have been known to be associated with alterations in this pathway. A variety of membrane tyrosine kinase receptors
including EGFR, vascular endothelial growth factor receptors, insulin-like growth factor receptors, HER2, and platelet-derived growth factor receptors has been known to activate this pathway. Activation of tyrosine kinase receptors results in the phosphorylation of PIP2 (phosphatidylinositol 4, 5-bisphosphate) to PIP3 (phosphatidylinositol 3,4,5-triphosphate) with the help of enzymes phospho inositol 3 kinase (PI3K). PI3K and mTOR further cause phosphorylation of PIP3. Downstream regulation of AKT is caused by mTOR, which is a serine/threonine kinase. Activation and upregulation of AKT result in cell proliferation and survival. Also, upregulation of other pathways like RAF/MAPK/RAS results in direct activation of PIP3 [70–73].

6. Therapeutic approach

Targeted drug therapy is recommended for the treatment of lung cancers. It is primarily used to treat non-small-cell lung cancers that constitute 80–85% of lung cancers. It targets the abnormalities in tumor cells without damaging the healthy cells. Biomarker testing is emerging as a tool in targeted therapy for testing patients who have abnormalities in their DNAs, which can be detected after looking for changes in the tumor cells. These changes can be additions, deletions, point mutations, rearrangements, or genetic alterations in the DNA. These changes are targeted in most lung cancer treatments. Targeted therapy is often associated with fewer side effects as they focus on the specific target that is mutated in the cell. These drugs target the pathways involved in lung adenocarcinomas. A number of pathways have been implicated in the causation of lung cancer such as EGFR, PI3K/AKT/mTOR, NTRK/ROS1, and RAS–MAPK, which have been targeted for the treatment purpose. Targeted therapy drugs have now replaced chemotherapy as the first-line treatment, such as EGFR inhibitors erlotinib, gefitinib, PI3K/AKT/mTOR inhibitors everolimus, and NTRK/ROS1 inhibitors entrectinib. These drugs have been found to be clinically beneficial and safer than conventional chemotherapy in the treatment of lung cancer [74, 75].

7. Conclusion

The knowledge of the large genomic data including the role of oncogenes, proto-oncogenes as well as tumor suppressor genes has markedly improved the understanding of the pathogenesis of lung cancers to develop more effective targeted therapies. The recent development in molecular testing technologies has led to the identification of genetic alterations. In addition to the above-mentioned molecular biomarkers, efforts are going on in an extensive manner to identify additional aberrations that can be further explored and used in the targeted therapy of lung cancer. This will further help to improve the available treatment strategies, tailor targeted therapies, and provide newer treatment avenues.
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