

UNRAVELLING THE MOLECULAR BASIS OF LUNG CANCER: PATHWAYS TO PROGRESS

Tanya Das¹, Priyankar Pal^{*}

¹Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Barrackpore Kolkata 700121

^{1*}Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Barrackpore, Kolkata 700121

^{*}Corresponding Author at: Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Barrackpore, Malir Math, Kolkata, Bara Kanthalia, West Bengal 700121

^{*}Corresponding Email: priyankarpal97@gmail.com

ABSTRACT

Lung cancer remains one of the primary causes of cancer-related deaths worldwide. The disease's intricacy stems from its heterogeneity, which includes numerous genetic, epigenetic, and molecular mechanisms. This review delves into the critical molecular mechanisms driving lung cancer progression, such as genetic mutations, epigenetic changes, signal transduction pathways, and immune evasion strategies. Understanding these pathways sheds light on targeted medicines and personalized medicine methods for lung cancer treatment. Key oncogenic drivers, including KRAS, EGFR, and TP53 mutations, as well as ALK and ROS1 rearrangements, are highlighted for their role in cell cycle dysregulation, apoptosis evasion, and increased metastatic potential. Epigenetic modifications, such as DNA methylation, histone acetylation, and non-coding RNAs, contribute to gene expression changes in lung cancer cells. Dysregulated signaling pathways, including PI3K/AKT/mTOR, RAS/RAF/MEK/ERK, and Notch, are investigated regarding tumor development, angiogenesis, and therapeutic resistance. Furthermore, the review emphasizes the heterogeneity of lung cancer and the interaction of the tumor microenvironment,

immune evasion, and therapy resistance. Recent advances in targeted therapeutics and immunotherapies are briefly discussed, focusing on the implications for personalized medicine. The goal of the review is to offer a thorough grasp of the biology of lung cancer, opening the door for innovative treatment approaches that will enhance patient outcomes.

Keywords: *Immune evasion, Lung cancer, Oncogenic drivers, Personalized medicine, Targeted therapies, Tumor microenvironment*

INTRODUCTION:

Lung cancer is the leading cause of cancer-related fatalities worldwide, accounting for around 1.6 million deaths annually. Approximately 85 % of NSCLC refers to a range of histological subtypes, with the most frequent being lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC). Tobacco use is the leading cause of lung cancer, accounting for about 80% of cases in the US and other nations where smoking is prevalent. Smoking is linked to all main histological subtypes of NSCLC, including small cell lung cancer (SCLC), however, LUSC and SCLC have a larger connection than LUAD, which is the most prevalent histology in nonsmokers.

Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are the two main forms of lung cancer, which cause more than 2 million new cases each year. Because of aggressive disease progression and delayed detection, survival rates are still low despite advancements in treatment. Numerous pathways essential to the pathophysiology of lung cancer have been revealed by molecular research, providing possible targets for treatment.

Genetic Mutations in Lung Cancer:

1) Oncogenes and Tumor Suppressors

a) KRAS mutations: KRAS is frequently mutated in NSCLC, leading to uncontrolled cell proliferation via the MAPK and PI3K-AKT pathways.

b) EGFR mutations: Mutations in EGFR contribute to constitutive activation of tyrosine kinase signaling, promoting tumor growth and survival.

c) TP53 mutations: Loss of TP53 function disrupts cell cycle control and apoptosis, enhancing tumor aggressiveness.

2. Fusion Proteins

a) ALK and ROS1 fusions: These gene rearrangements are frequent in a subgroup of non-small cell lung cancer (NSCLC) and endorse oncogenesis by activating constitutive kinase activity.

3) Epigenetic Alterations

a) DNA Methylation

Tumor suppressor genes like CDKN2A are silenced by hypermethylation, which promotes unregulated cell proliferation.

b) Histone Modification

Changes in histone acetylation and methylation affect gene expression and chromatin structure. For instance, a poor prognosis is linked to histone deacetylase (HDACs) overexpression.

c) Non-coding RNAs

Lung cancer is regulated by long non-coding RNAs (lncRNAs) and microRNAs (miRNAs). For example, miR-21 targets tumor suppressors such as PTEN to promote invasion and proliferation.

4. Signal Transduction Pathways

a) MAPK/ERK Pathway

Mutations in KRAS and EGFR cause aberrant signaling in this system, which encourages the growth and survival of tumor cells.

b) PI3K-AKT-mTOR Pathway

Angiogenesis, metabolism, and cell growth are all supported when mutations or amplifications activate this pathway

c) Wnt/ β -Catenin Pathway

Dysregulated Wnt signaling promotes invasion, metastasis,

and the characteristics of cancer stem cells.

5.Immune Evasion Mechanisms

a).Immune Checkpoint Dysregulation

Lung malignant cells use immunological checkpoints, such as PD-1/PD-L1, to elude immune detection.

b)Tumor Microenvironment

The tumor microenvironment (TME) facilitates immune evasion by attracting immunosuppressive cells such as regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSCs).

6. Therapeutic Implications

a) Targeted Therapies

Treatment approaches for certain subtypes of lung cancer have changed as a result of tyrosine kinase inhibitors (TKIs) that target EGFR, ALK, and ROS1.

b)Immunotherapy

Nivolumab and pembrolizumab are examples of immune checkpoint inhibitors that have demonstrated potential in boosting immune responses against lung cancer.

c).Epigenetic Drugs

To reverse the epigenetic silencing of tumor suppressor genes, researchers are investigating the use of HDAC inhibitors and DNA methyltransferase inhibitors.

ROLE OF TUMOR SUPPRESSOR GENE

In human lung tumors, allele loss in the short arm of chromosome 3 at 3p21.3.1 is the first premalignant chromosomal abnormality. This loss of heterozygosity happens in almost all cases of small-cell lung cancer (95%) Additionally, some smokers and ex-smokers have normal bronchial epithelium.²⁻⁴ According to homozygous deletion research about three lung cancers, the smallest deletion area specific to the 370 kb span of established SCLC cell lines (GLC20, NCI-H740, and NCI H1450) contains 19 genes

(RBM6, RBM5, SEMA3F, GNAT1, NAT1/SLC38A3/G17, GNAI2, SEMA3B, IFRD2, HYAL3, FUS2/NAT6, HYAL1, HYAL2, FUS1/TUSC2, RASSF1/123F2, BLU/ZMYND10, NPRL2/TUSC4, 101F6/ TSP10/CYB561D2, PL6/TMEM115, and CACNA2D2), and 3 open reading frames encoding hypothetical proteins (LOC100129060, LOC100287609, and C3orf45/FLJ38608).Five

Regarding regulating processes like cell differentiation, proliferation, signal transduction, and apoptosis, most of the 19 genes exhibit variable levels of tumor suppressor activity. It has been proposed that these genes work together as a sizable, cohesive, biologically functionally diverse tumor suppressor unit.³

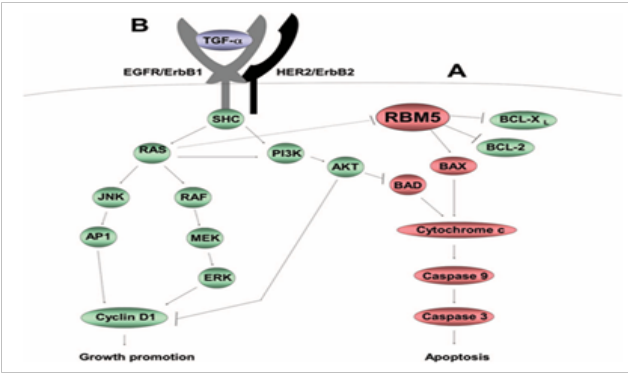


FIGURE 1. The relationship between transforming growth factor (TGF)-and RBM5 signaling and the modulation of apoptosis. A Proapoptotic activity associated with RBM5 overexpression is related to the down-regulation of BCL-XL and up-regulation of BAX expression, and antisense RBM5 overexpression is related to the up-regulation of BCL-2 expression. Overexpressed RBM5 increases cytochrome c release from the mitochondria and activation of caspases 9 and 3. B, activating mutations in epidermal growth factor receptor (EGFR), HER2, or KRAS result in increased growth and decreased apoptosis. For instance, RBM5 expression is down-regulated by the RAS activating mutant RAS(G12V), which would inhibit apoptosis. Likewise, increased EGFR and

HER2 activities can lead to phosphorylation – and subsequent inhibition of – the proapoptotic activity associated with the BCL2-associated agonist of cell death.

ROLE OF ONCOGENE

Therapeutic Targeting of Oncogenes

Small Molecule Inhibitors; Erlotinib, afatinib, and Osimertinib are first, second, and third-generation EGFR TKIs. ALK inhibitors include brigatinib and crizotinib.

Antibody-Based Therapies

Monoclonal antibodies that target HER2 for uncommon HER2 mutations.

Combination Therapies

TKIs and immune checkpoint inhibitors work in concert

Overcoming Drug Resistance

Next-generation inhibitors that target resistant mutations are being developed (for example, EGFR C797S).

FUTURE PROSPECTS

Advancements in the understanding of molecular mechanisms underlying lung cancer provide an optimistic outlook for precision medicine. Future research should integrate multi-omics approaches, such as genomics, proteomics, and metabolomics, to uncover novel biomarkers and therapeutic targets. Artificial intelligence and machine learning hold the potential to revolutionize diagnostic accuracy and treatment personalization. Additionally, developing combination therapies addressing resistance mechanisms and targeting tumor microenvironments will enhance treatment efficacy. Expanding immunotherapy options and exploring epigenetic modulation as therapeutic avenues are promising strategies. Collaborative efforts in clinical trials will be crucial to accelerating the transition of these discoveries into clinical practice.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENT

I would like to express my sincere gratitude to Swami Vivekananda University for providing me with the opportunity to undertake this review paper. My heartfelt thanks go to my mentor Priyankar Pal sir, for his invaluable guidance, support, and encouragement throughout this project. His expertise and insights have been instrumental in shaping the direction and quality of this work.

References

- Siegel, R. L., et al. (2024). Cancer statistics, 2024. CA: A Cancer Journal for Clinicians, 74(1), 7-30. <https://doi.org/10.3322/caac.21763>
- Herbst, R. S., et al. (2018). Lung cancer. The New England Journal of Medicine, 378(2), 172-183. <https://doi.org/10.1056/NEJMr1614347>
- Dela Cruz, C. S., et al. (2011). Lung cancer: Epidemiology, etiology, and prevention. Clinics in Chest Medicine, 32(4), 605-644. <https://doi.org/10.1016/j.ccm.2011.09.001>
- Govindan, R., et al. (2012). Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell, 150(6), 1121-1134. <https://doi.org/10.1016/j.cell.2012.08.024>
- Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: The next generation. Cell, 144(5), 646-674. <https://doi.org/10.1016/j.cell.2011.02.013>
- Molina, J. R., et al. (2008). Non-small cell lung cancer: Epidemiology, risk factors, treatment, and survivorship. Mayo Clinic Proceedings, 83(5), 584-594. <https://doi.org/10.4065/83.5.584>
- Travis, W. D., et al. (2015). The 2015 World Health Organization classification of lung tumors. Journal of Thoracic Oncology, 10(9), 1243-1260. <https://doi.org/10.1097/JTO.0000000000000630>
- Zappa, C., & Mousa, S. A. (2016). Non-small cell lung cancer: Current treatment and future advances. Translational

Lung Cancer Research, 5(3), 288-300. <https://doi.org/10.21037/tlcr.2016.06.07>

Reck, M., et al. (2013). Management of non-small-cell lung cancer: Recent developments. *The Lancet*, 382(9893), 709-719. [https://doi.org/10.1016/S0140-6736\(13\)61502-0](https://doi.org/10.1016/S0140-6736(13)61502-0)

Goldstraw, P., et al. (2016). The IASLC lung cancer staging project: Proposals for revision. *Journal of Thoracic Oncology*, 11(1), 39-51. <https://doi.org/10.1016/j.jtho.2015.09.009>

Lynch, T. J., et al. (2004). Activating mutations in the epidermal growth factor receptor underlying responsiveness to gefitinib. *New England Journal of Medicine*, 350(21), 2129-2139. <https://doi.org/10.1056/NEJMoa040938>

Pao, W., et al. (2004). EGF receptor gene mutations are common in lung cancers from “never smokers.” *Proceedings of the National Academy of Sciences*, 101(36), 13306-13311. <https://doi.org/10.1073/pnas.0405220101>

Jones, P. A., & Baylin, S. B. (2007). The epigenomics of cancer. *Cell*, 128(4), 683-692. <https://doi.org/10.1016/j.cell.2007.01.029>

Brambilla, E., et al. (2001). Molecular biology of lung cancer. *Clinics in Chest Medicine*, 22(1), 1-15. [https://doi.org/10.1016/S0272-5231\(05\)70067-5](https://doi.org/10.1016/S0272-5231(05)70067-5)

Cancer Genome Atlas Research Network (2012). Comprehensive molecular profiling of lung adenocarcinoma. *Nature*, 511(7511), 543-550. <https://doi.org/10.1038/nature13385>

Rauch, T. A., et al. (2012). DNA methylation biomarkers in lung cancer. *Cancer Biomarkers*, 10(3-4), 181-189. <https://doi.org/10.3233/CBM-2012-0242>

Martinez-Cardus, A., et al. (2016). Epigenetic mechanisms in lung cancer chemoresistance. *Epigenomics*, 8(5), 713-732. <https://doi.org/10.2217/epi-2016-0004>

Sun, S., et al. (2007). Squamous cell carcinoma—Recent advances in lung cancer research. *New England Journal of Medicine*, 357(23), 2429-2437. <https://doi.org/10.1056/NEJMra043659>

Lam, B., et al. (2013). MicroRNAs in lung cancer—From biological functions to therapeutic applications. *Journal of Thoracic Oncology*, 8(11), 1246-1256. <https://doi.org/10.1097/JTO.0b013e3182a22019>

- Politi, K., & Herbst, R. S. (2015). Lung cancer in the era of precision medicine. *Clinical Cancer Research*, 21(10), 2213-2220. <https://doi.org/10.1158/1078-0432.CCR-14-245321>.
- Engelman, J. A., et al. (2007). MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science*, 316(5827), 1039-1043. <https://doi.org/10.1126/science.1141478>
- Roberts, P. J., & Der, C. J. (2007). Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. *Oncogene*, 26(22), 3291-3310. <https://doi.org/10.1038/sj.onc.1210421>
- Gainor, J. F., & Shaw, A. T. (2013). Emerging paradigms in the development of resistance to tyrosine kinase inhibitors in lung cancer. *Journal of Clinical Oncology*, 31(31), 3987-3996. <https://doi.org/10.1200/JCO.2012.45.2029>
- Rosell, R., et al. (2009). Predictive biomarkers for customizing chemotherapy in lung cancer. *Expert Review of Respiratory Medicine*, 3(5), 425-434. <https://doi.org/10.1586/ers.09.41>
- Katayama, R., et al. (2012). Mechanisms of acquired resistance to EGFR tyrosine kinase inhibitors in lung cancer. *Cancer Science*, 103(11), 1991-1996. <https://doi.org/10.1111/cas.12021>
- Aviel-Ronen, S., et al. (2006). K-ras mutations in non-small-cell lung carcinoma. *Pathology*, 38(6), 555-558. <https://doi.org/10.1080/00313020601024042>
- Yuan, M., et al. (2020). Targeting KRAS mutant cancers with small molecules. *Annual Review of Cancer Biology*, 4(1), 117-137. <https://doi.org/10.1146/annurev-cancerbio-030419-033020>
- Wu, P., et al. (2021). Signal pathways in lung cancer. *Frontiers in Oncology*, 10, 978. <https://doi.org/10.3389/fonc.2020.01172>
- Zou, H., et al. (2019). The role of Wnt signaling in lung cancer. *Molecular and Cellular Biology*, 39(7), e00178-18. <https://doi.org/10.1128/MCB.00178-18>
- Lovly, C. M., & Carbone, D. P. (2011). Lung cancer signaling pathways. *Journal of Clinical Oncology*, 29(35), 5899-5908. <https://doi.org/10.1200/JCO.2010.33.1165>
- Reck, M., et al. (2016). Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer.

New England Journal of Medicine, 375(19), 1823-1833. <https://doi.org/10.1056/NEJMoa1606774>

Hellmann, M. D., et al. (2018). Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *New England Journal of Medicine*, 378(22), 2093-2104. <https://doi.org/10.1056/NEJMoa1716948>

Topalian, S. L., et al. (2012). Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *New England Journal of Medicine*, 366(26), 2443-2454. <https://doi.org/10.1056/NEJMoa1200690>

Borghaei, H., et al. (2015). Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *New England Journal of Medicine*, 373(17), 1627-1639. <https://doi.org/10.1056/NEJMoa1507643>

Ferrara, N., et al. (2004). Tumor angiogenesis and lung cancer. *Nature Medicine*, 10(10), 1095-1106. <https://doi.org/10.1038/nm1123>

Galon, J., et al. (2012). Immunoscore and its potential in cancer. *Journal of Clinical Oncology*, 30(33), 4099-4101. <https://doi.org/10.1200/JCO.2012.44.1239>

Gandhi, L., et al. (2018). Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *New England Journal of Medicine*, 378(22), 2078-2092. <https://doi.org/10.1056/NEJMoa1801005>

Chen, D. S., & Mellman, I. (2017). Elements of cancer immunity and the cancer-immune set point. *Nature*, 541(7637), 321-330. <https://doi.org/10.1038/nature21349>

Zhang, L., et al. (2021). Immune evasion in lung cancer. *Cancer Research*, 81(1), 13-20. <https://doi.org/10.1158/0008-5472.CAN-20-2012>

Sharma, P., et al. (2017). Immune checkpoint therapy in lung cancer. *Science*, 355(6330), 1217-1224. <https://doi.org/10.1126/science.aaj1899>

Mok, T. S., et al. (2009). Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *New England Journal of Medicine*, 361(10), 947-957. <https://doi.org/10.1056/NEJMoa0810699>

Yu, H. A., et al. (2013). Acquired resistance of EGFR-mutant lung cancer to tyrosine kinase inhibitors. *Journal of Clinical Oncology*, 31(8), 1070-1080. <https://doi.org/10.1200/>

JCO.2012.44.6916

Wang, Z., et al. (2020). Targeting drug resistance in EGFR-mutant lung cancer. *Cancer Discovery*, 10(8), 1154-1165. <https://doi.org/10.1158/2159-8290.CD-19-1427>

Planchard, D., et al. (2016). Dabrafenib plus trametinib in BRAF V600E-mutant metastatic NSCLC. *Lancet Oncology*, 17(7), 984-993. [https://doi.org/10.1016/S1470-2045\(16\)30146-2](https://doi.org/10.1016/S1470-2045(16)30146-2)

Ramalingam, S. S., et al. (2019). Osimertinib in untreated EGFR-mutated advanced NSCLC. *New England Journal of Medicine*, 382(1), 41-50. <https://doi.org/10.1056/NEJMoa1913662>

Rosell, R., et al. (2012). Erlotinib in mutated lung cancer: Lessons learned. *Journal of Thoracic Oncology*, 7(2), S130-S134. <https://doi.org/10.1097/JTO.0b013e31824abf8e>

Wu, Y. L., et al. (2018). Dacomitinib versus gefitinib in EGFR-mutated NSCLC. *Lancet Oncology*, 19(11), 1454-1467. [https://doi.org/10.1016/S1470-2045\(18\)30608-3](https://doi.org/10.1016/S1470-2045(18)30608-3)

Camidge, D. R., et al. (2012). Crizotinib in ALK-positive lung cancer. *New England Journal of Medicine*, 368(25), 2385-2394. <https://doi.org/10.1056/NEJMoa1214886>

Shaw, A. T., et al. (2014). Ceritinib in ALK-rearranged non-small-cell lung cancer. *New England Journal of Medicine*, 370(13), 1189-1197. <https://doi.org/10.1056/NEJMoa1311107>

Horn, L., et al. (2018). First-line atezolizumab in extensive-stage small-cell lung cancer. *New England Journal of Medicine*, 379(23), 2220-2229. <https://doi.org/10.1056/NEJMoa1813427>