The Molecular Pathology of Lung Cancer

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KEYWORDS

• Lung carcinoma • Lung adenocarcinoma • EGFR • KRAS • ALK • MET • Histology

Key points

- Molecular analysis of lung adenocarcinoma permits targeted therapeutic approaches and is associated with improved outcomes.
- Epidermal growth factor receptor mutation correlates with lepidic/papillary/acinar/micropapillary adenocarcinoma subtypes and Kirsten rat sarcoma viral oncogene homolog mutation with solid-subtype and invasive mucinous adenocarcinoma; however, individual cases may show significant variation from published correlations.
- Intratumoral genomic heterogeneity contributes to the morphologic heterogeneity seen on pathology.
- A variety of molecular testing methods may be used for detection of common genomic alterations in lung cancer; massively parallel sequence may supersede many polymerase chain reaction–based targeted approaches, but use of a combination of methods is likely to provide the greatest clinical and technical sensitivity.

ABSTRACT

Advances in lung cancer genomics have revolutionized the diagnosis and treatment of this heterogeneous and clinically significant group of tumors. This article provides a broad overview of the most clinically relevant oncogenic alterations in common and rare lung tumors, with an emphasis on the pathologic correlates of the major oncogenic drivers, including *EGFR*, *KRAS*, *ALK*, and *MET*. Illustrations emphasize the morphologic diversity of lung adenocarcinoma, including genotype-phenotype correlations of genomic evolution in tumorigenesis. Molecular diagnostic approaches, including PCR-based testing, massively parallel sequencing, fluorescence in situ hybridization, and immunohistochemistry are reviewed.

OVERVIEW

Lung cancer ranks as the second most common form of cancer across all races and ethnicities in the United States.[1] The main types of lung cancer are adenocarcinoma, squamous cell carcinoma (SQC), large cell carcinoma, and high-grade neuroendocrine tumors, including small cell lung carcinoma (SCLC) and large cell neuroendocrine carcinoma.[2] Each lung cancer type has relatively unique clinicopathologic and molecular associations. Epidemiology studies have shown that the incidence of lung SQC has trended down and adenocarcinoma has trended up over the past few decades,[3] presumably reflecting shifts in smoking patterns and cigarette design in the form of changing chemical components and more effective filters.[4]

Despite an overall annual decrease in incidence, lung cancer remains a top cause of cancer-related deaths, affecting both men and women, a large age range, and smokers and nonsmokers. However, lung cancer–specific mortality has begun to decline in the past decade. This change is attributable both to earlier tumor detection using high-resolution chest computed tomography (CT) screening[5,6] and to routine use of therapies targeting specific tumor genomic alterations.[7]

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Lung adenocarcinoma in particular is defined by a variety of mutually exclusive oncogenic driver alterations, the most common of which occur in the *Kirsten rat sarcoma viral oncogene homolog* (*KRAS*), *epidermal growth factor receptor* (*EGFR*), and *anaplastic lymphoma kinase* (*ALK*) genes, with the latter 2 concentrated in never smokers. Tumors harboring activating alterations in *EGFR* and *ALK*, as well as in other oncogenes, including *ROS1*, *RET*, *BRAF*, *ERBB2*, and *MET*, may respond to targeted inhibitors; the evidence for their association with a survival benefit has led to national guidelines recommending testing for *EGFR* and *ALK* alterations in all patients with metastatic lung adenocarcinoma before initiating first-line therapy.[8,9] Other lung carcinomas, including SQC, SCLC, and large cell carcinoma, tend to occur in heavy smokers and often lack a clear oncogenic driver. These tumors characteristically have high rates of *TP53* mutations and overall high mutational frequencies reflecting smoking-related mutagenesis.[10,11]

ASSOCIATED GENETIC ALTERATIONS

ADENOCARCINOMA

Our understanding of the genomic underpinnings of lung cancers has been advanced significantly by numerous large-scale sequencing efforts.[10–12] In adenocarcinoma, such efforts have confirmed the prevalence of established oncogenic driver alterations (**Table 1**) and have uncovered additional layers of genomic complexity, with probable implications for response to targeted therapies. *TP53* mutations are reported in 50% of lung adenocarcinoma, frequently overlapping with a variety of oncogenic driver alterations. Other commonly mutated genes in lung adenocarcinoma, such as *STK11*, *KEAP1*, *NF1*, *PIK3CA*, and *PTEN*, likely facilitate, rather than drive, tumorigenesis.[12] These alterations may nonetheless have prognostic and predictive implications. *STK11* is significantly co-mutated with *KRAS* in smokers and associated with worse outcomes.[13] Animal studies suggest that the presence of *STK11* mutations confer relative resistance to MEK inhibitors in *KRAS*-mutated lung adenocarcinomas.[14] Mutations in *PIK3CA*, *PTEN*, and *AKT1* are detected in a minority of *EGFR*-mutated lung adenocarcinoma and appear to confer relative resistance to EGFR tyrosine kinase inhibitors (TKIs).[15,16]

SQUAMOUS CELL CARCINOMA

Despite advances in genomics and precision medicine, efforts to apply targeted therapies outside of lung adenocarcinoma have largely been disappointing. A subset of SQC harbors oncogenic alterations, including in fibroblast growth factor receptor (FGFR) family members, PI3K/PTEN/AKT pathway, and *discoidin domain receptor tyrosine kinase 2* (*DDR2*) (**Table 2**); however, overall it is unclear that these alterations, existing as they do on a background of high mutational burden, near universal TP53 dysregulation, and multiple concomitant oncogenic mutations, will be readily targetable using a single inhibitor.[10] *FGFR1* amplification in particular has been examined as a biomarker for FGFR inhibitor therapy; in vitro studies suggest that *FGFR1*-amplified lung cancers are sensitive to a variety of targeted inhibitors,[17,18] but there are few data on the efficacy of these drugs in practice. Further, some studies suggest that FGFR1 mRNA and protein expression are better predictors of sensitivity to FGFR inhibitors than copy number.[19] Fortunately, the efficacy of immune checkpoint inhibitors, such as pembrolizumab and nivolumab, both programmed death-1 (PD-1) inhibitors, offers new therapeutic promise for patients with SQC.[20,21]

SMALL CELL LUNG CARCINOMA/LARGE CELL NEUROENDOCRINE CARCINOMA

Small cell lung carcinoma is typically centrally located and highly associated with a heavy smoking history, with only 2% of SCLC occurring in never smokers.[22] *TP53* and retinoblastoma 1(*RB1*) are inactivated in essentially all cases, on a background of a high somatic mutation rate consistent with smoking-related mutagenesis.[11] Amplification of MYC family oncogenes occurs in 3% to 7% of SCLC; in vitro studies suggest this is a targetable alteration[23] but there is limited evidence for clinical efficacy of agents targeting MYC. The profound cell cycle dysregulation seen in SCLC contributes to the distinct clinical presentation of rapid tumor growth, high proliferative index, and exquisite sensitivity to chemoradiotherapy, with inevitable relapse. In contrast to SCLC, large cell neuroendocrine carcinoma shows large cells with ample cytoplasm growing in nests with central comedo-type necrosis. This tumor type arises predominantly in the peripheral lung and has historically been considered a form of non–small cell carcinoma, with a prognosis intermediate between non–small cell and SCLC.[2] Genomic profiling studies have revealed that it is most closely related to SCLC, with loss of *TP53* and *RB1*, as well as a similar copy number profiles.[24] However, in practice this is a relatively rare diagnosis and systematic data are lacking to guide clinical therapy; current practice guidelines