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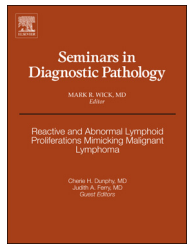

Current concepts on the molecular pathology of non-small cell lung carcinoma

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ABSTRACT

Recent advances in the understanding of the complex biology of non-small cell lung carcinoma (NSCLC), particularly activation of oncogenes by mutation, translocation and amplification, have provided new treatment targets for this disease, and allowed the identification of subsets of NSCLC tumors, mostly with adenocarcinoma histology, having unique molecular profiles that can predict response to targeted therapy. The identification of specific genetic and molecular targetable abnormalities using tumor tissue and cytology specimens followed by the administration of a specific inhibitor to the target, are the basis of personalized lung cancer treatment. In this new paradigm, the role of a precise pathology diagnosis of lung cancer and the proper handling of tissue and cytology samples for molecular testing is becoming increasingly important. These changes have posed multiple new challenges for pathologists to adequately integrate routine histopathology analysis and molecular testing into the clinical pathology practice for tumor diagnosis and subsequent selection of the most appropriate therapy.

Abbreviations: *ALK*, anaplastic lymphoma kinase gene; AMP, Association of Molecular Pathology; ASCO, American Society of Clinical Oncology; *BRAF*, v-raf murine sarcoma viral oncogene homolog B gene; CAP, College of American Pathologists; CNB, core-needle biopsies; *DDR2*, discoidin domain receptor 2 gene; *EGFR*, epidermal growth factor receptor gene; FFPE, formalin fixed and paraffin embedded; *FGFR1*, fibroblast growth factor receptor type 1 gene; FNA, fine needle aspirations; *HER2*, human epidermal growth factor receptor 2 gene; IASLC, International Association for the Study of Lung Cancer; IHC, immunohistochemistry; KIF5B, kinesin family member 5B gene; KRAS, Kirsten rat sarcoma viral oncogene homolog; MALDI-TOF MS, matrix assisted laser desorption/ionization-time of flight mass spectrometry; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NSCLC, non-small cell lung carcinoma; PCR, polymerase chain reaction; *PI3K*, phosphatidylinositol 3-kinase gene; *PIK3CA*, Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha, gene; *PTEN*, phosphatase and tensin homolog gene; qRT-PCR, quantitative reverse transcription polymerase chain reaction; *ROS1*, c-ros 1 gene; SCLC, small cell lung carcinoma; TKI, tyrosine kinase inhibitor; WHO, World Health Organization

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Introduction

Lung cancer is the leading cause of deaths in the United States and worldwide.[1] The high mortality associated with lung cancer is in part due to late diagnosis after regional or distant spread of the disease.[2] From biological and clinical perspectives, lung cancer is a heterogeneous disease with multiple histological subtypes, being the most frequent non-small cell lung carcinoma (NSCLC). Traditionally, NSCLC has been used to designate tumors that exhibit histological and cytological features different from small cell carcinoma (SCLC). Most NSCLCs can be grouped into three main categories: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma; however, there are other less frequently diagnosed histologic types.[3] Nowadays, due to the utilization of new therapeutic strategies and molecular diagnostic testing in NSCLC, particularly adenocarcinomas,[4] it is imperative that pathologists are more specific in the diagnosis of subtypes of NSCLC, and they should make sure that there is sufficient tissue or cytology sample for molecular testing.

In this review, we described the most frequently described targetable genetic abnormalities in NSCLC and discuss the current status and challenges of molecular testing in this disease, including the implementation of new molecular methodologies to better predict the outcome of the disease and select the appropriate therapy.

Clinically relevant molecular abnormalities of NSCLC

During the last decade, multiple molecular abnormalities affecting oncogenes and tumor suppressor genes have been described in NSCLC.[5,6] Of these, several gene mutations, amplifications, and rearrangements have been identified as potential molecular targets. Here, we review the characteristics of key cancer-related genes that have been emerged as potential targets in NSCLC using either tyrosine kinase inhibitors (TKIs) or monoclonal antibodies.

Epidermal growth factor receptor gene (EGFR)

Mutations of *EGFR* in lung cancer are mostly limited to the first four exons of the tyrosine kinase domain (exons 18–21). The most frequent mutations are in-frame deletions in exon 19 (44% of all mutations) and missense mutations in exon 21 (41% of all mutations). These mutations are frequently diagnosed in lung adenocarcinomas (~20–48% vs. other NSCLC histologies ~2%), and strongly correlate with never-smoking status (50–60%), female gender (40–60%), and East Asian ethnicity (30–50%).[7] There are some reports suggesting that *EGFR* mutations are encountered most frequently in lung adenocarcinomas with non-mucinous differentiation and with a lepidic or papillary predominant pattern.[8,9] Activating *EGFR* mutations are biologically important because most of them have enhanced tyrosine kinase activity in response to epidermal growth factor stimulation.[2,10] *EGFR* mutations are diagnosed mostly using gene sequencing methodologies, although quantitative (q)PCR-based assays are also available (Fig. 1). There are some antibodies that identify mutant EGFR proteins, but they have not shown to be clinically useful.

The presence of these *EGFR* mutations is clinically relevant because they have been associated with sensitivity to small molecule TKIs (gefitinib and erlotinib).[11–13] Unfortunately, some patients with activating *EGFR* mutations who respond initially to EGFR TKIs subsequently relapse.[14] This resistance appears to occur through a range of different mechanisms, including most frequently, a second *EGFR* mutation (50%) in exon 20 (*T790M* and *D761Y*),[15] as well as other molecular mechanisms that include amplification of the *MET* oncogene

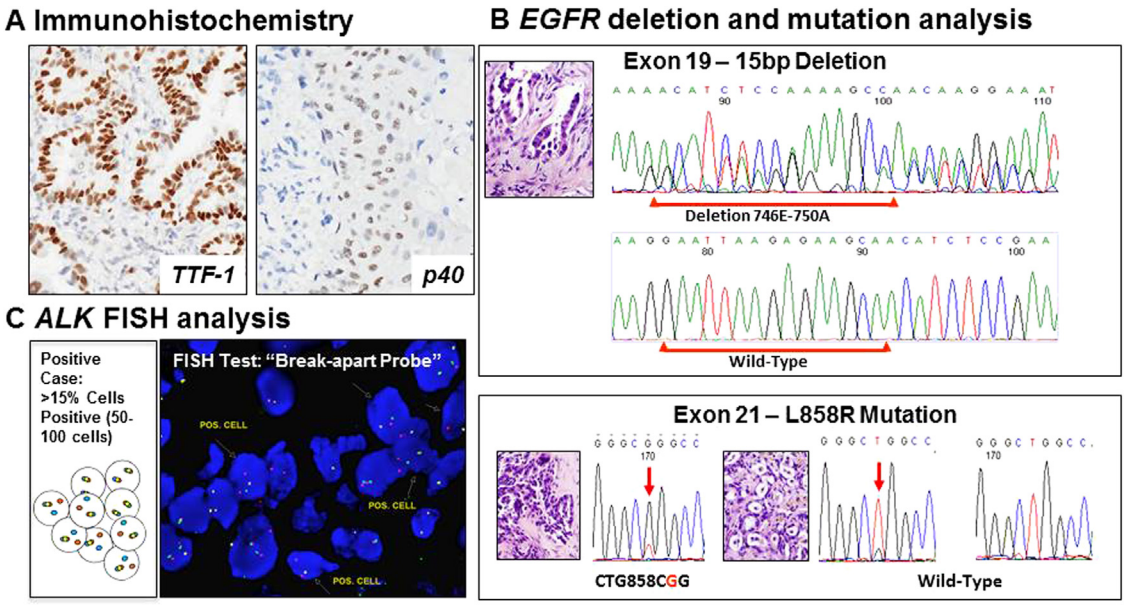

Fig. 1 – Histology section-based molecular tests for NSCLC. (A) Immunohistochemistry panel: thyroid transcription factor (TTF-1) is a marker of adenocarcinoma, and *p40* (*p63*) is a marker of squamous cell carcinoma. (B) *EGFR* mutation analysis and (C) *EML4–ALK* fusion fluorescent in situ hybridization (FISH) analysis.