chemotherapy agents performed quite differently in squamous carcinomas versus adenocarcinomas, firmly established the need for modifications in the then-existing 2004 WHO lung cancer classification system. The revised 2011 classification system, developed jointly by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society, provides an integrated approach to the classification of lung adenocarcinomas that includes clinical, molecular, radiographic, and pathologic information. It also recognizes that most lung cancers present in an advanced stage and are often diagnosed based on small biopsies or cytologic specimens, rendering clear histologic distinctions difficult if not impossible.

Previously, in the 2004 classification system, tumors *failing* to show definite glandular or squamous morphology in a small biopsy or cytologic specimen were simply classified as *non-small-cell carcinoma, not otherwise specified*. However, because the distinction between adenocarcinoma and squamous carcinoma is now viewed as critical to optimal therapeutic decision making, the modified classification approach recommends these lesions be further characterized using a limited special stain workup. This distinction can be achieved using a single marker for adenocarcinoma (thyroid transcription factor-1 or napsin-A) plus a squamous marker (p40 or p63) and/or mucin stains. The modified classification system also recommends preservation of sufficient specimen material for appropriate molecular testing necessary to help guide therapeutic decision making (see below).

Another significant modification to the WHO classification system is the discontinuation of the terms *bronchioloalveolar carcinoma* and *mixed-subtype adenocarcinoma*. The term *bronchioloalveolar carcinoma* was dropped due to its inconsistent use and because it caused confusion in routine clinical care and research. As formerly used, the term encompassed at least five different entities with diverse clinical and molecular properties. The terms *adenocarcinoma in situ* and *minimally invasive adenocarcinoma* are now recommended for small solitary adenocarcinomas (≤3 cm) with either pure lepidic growth (term used to describe single-layered growth of atypical cuboidal cells coating the alveolar walls) or predominant lepidic growth with ≤5 mm invasion. Individuals with these entities experience 100% or near 100% 5-year disease-free survival with complete tumor resection. *Invasive adenocarcinomas*, representing more than 70–90% of surgically resected lung adenocarcinomas, are now classified by their predominant pattern: lepidic, acinar, papillary, and solid patterns. Lepidic-predominant subtype has a favorable prognosis, acinar and papillary have an intermediate prognosis, and solid-predominant has a poor prognosis. The terms *signet ring* and *clear cell adenocarcinoma* have been eliminated from the variants of invasive lung adenocarcinoma, whereas the term *micropapillary*, a subtype with a particularly poor prognosis, has been added. Although *EGFR* mutations are encountered most frequently in nonmucinous adenocarcinomas with a lepidic- or papillary-predominant pattern, most adenocarcinoma subtypes can harbor *EGFR* or *KRAS* mutations. The same is true of *ALK, RET,* and *ROS1* rearrangements. What was previously termed *mucinous bronchioloalveolar carcinoma* is now called *invasive mucinous adenocarcinoma*. These tumors generally lack *EGFR* mutations and show a strong correlation with *KRAS* mutations. Overall, the revised WHO reclassification of lung cancer addresses important advances in diagnosis and treatment, most importantly, the critical advances in understanding the specific genes and molecular pathways that initiate and sustain lung tumorigenesis resulting in new "targeted" therapies with improved specificity and better antitumor efficacy.

IMMUNOHISTOCHEMISTRY

The diagnosis of lung cancer most often rests on the morphologic or cytologic features correlated with clinical and radiographic findings. Immunohistochemistry may be used to verify neuroendocrine differentiation within a tumor, with markers such as neuron-specific enolase (NSE), CD56 or NCAM, synaptophysin, chromogranin, and Leu7. Immunohistochemistry is also helpful in differentiating primary from metastatic adenocarcinomas; thyroid transcription factor-1 (TTF-1), identified in tumors of thyroid and pulmonary origin, is positive in over 70% of pulmonary adenocarcinomas and is a reliable indicator of primary lung cancer, provided a thyroid primary has been excluded. A negative TTF-1, however, does not exclude the possibility of a lung primary. TTF-1 is also positive in neuroendocrine tumors of pulmonary and extrapulmonary origin. Napsin-A (Nap-A) is an aspartic protease that plays an important role in maturation of surfactant B7 and is expressed in cytoplasm of type II pneumocytes. In several studies, Nap-A has been reported in >90% of primary lung adenocarcinomas. Notably, a combination of Nap-A and TTF-1 is useful in distinguishing primary lung adenocarcinoma (Nap-A positive, TTF-1 positive) from primary lung squamous cell carcinoma (Nap-A negative, TTF-1 negative) and primary SCLC (Nap-A negative, TTF-1 positive). Cytokeratins 7 and 20 used in combination can help narrow the differential diagnosis; nonsquamous NSCLC, SCLC, and mesothelioma may stain positive for CK7 and negative for CK20, whereas squamous cell lung cancer often will be both CK7 and CK20 negative. p63 is a useful marker for the detection of NSCLCs with squamous differentiation when used in cytologic pulmonary samples. Mesothelioma can be easily identified ultrastructurally, but it has historically been difficult to differentiate from adenocarcinoma through morphology and immunohistochemical staining. Several markers in the last few years have proven to be more helpful including CK5/6, calretinin, and Wilms tumor gene-1 (*WT-1*), all of which show positivity in mesothelioma.

MOLECULAR PATHOGENESIS

Cancer is a disease involving dynamic changes in the genome. As proposed by Hanahan and Weinberg, virtually all cancer cells acquire six hallmark capabilities: self-sufficiency in growth signals, insensitivity to antigrowth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. The order in which these hallmark capabilities are acquired appears quite variable and can differ from tumor to tumor. Events leading to acquisition of these hallmarks can vary widely, although broadly, cancers arise as a result from accumulations of gain-of-function mutations in oncogenes and loss-of-function mutations in tumor-suppressor genes. Further complicating the study of lung cancer, the sequence of events that lead to disease is clearly different for the various histopathologic entities.

The exact cell of origin for lung cancers is not clearly defined. Whether one cell of origin leads to all histologic forms of lung cancer is unclear. However, for lung adenocarcinoma, evidence suggests that type II epithelial cells (or alveolar epithelial cells) have the capacity to give rise to tumors. For SCLC, cells of neuroendocrine origin have been implicated as precursors.

For cancers in general, one theory holds that a small subset of the cells within a tumor (i.e., "stem cells") are responsible for the full malignant behavior of the tumor. As part of this concept, the large bulk of the cells in a cancer are "offspring" of these cancer stem cells. While clonally related to the cancer stem cell subpopulation, most cells by themselves cannot regenerate the full malignant phenotype. The stem cell concept may explain the failure of standard medical therapies to eradicate lung cancers, even when there is a clinical complete response. Disease recurs because therapies do not eliminate the stem cell component, which may be more resistant to chemotherapy. Precise human lung cancer stem cells have yet to be identified.

Lung cancer cells harbor multiple chromosomal abnormalities, including mutations, amplifications, insertions, deletions, and translocations. One of the earliest sets of oncogenes found to be aberrant was the MYC family of transcription factors (*MYC, MYCN*, and *MYCL*). *MYC* is most frequently activated via gene amplification or transcriptional dysregulation in both SCLC and NSCLC. Currently, there are no MYC-specific drugs.

Among lung cancer histologies, adenocarcinomas have been the most extensively catalogued for recurrent genomic gains and losses as well as for somatic mutations (Fig. 107-2). While multiple different kinds of aberrations have been found, a major class involves "driver mutations," which are mutations that occur in genes encoding signaling proteins that when aberrant, drive initiation and maintenance of tumor cells. Importantly, driver mutations can serve as potential Achilles' heels for tumors, if their gene products can be targeted