Review

Squamous Cell Carcinoma of the Lung: Molecular Subtypes and Therapeutic Opportunities

Pablo Perez-Moreno1,2, Elisabeth Brambilla3,4, Roman Thomas5–9, and Jean-Charles Soria1,2

Abstract

Lung cancer is the leading cause of cancer-related deaths worldwide. Next to adenocarcinoma, squamous cell carcinoma (SCC) of the lung is the most frequent histologic subtype in non–small cell lung cancer. Encouraging new treatments (i.e., bevacizumab, EGFR tyrosine kinase inhibitors, and ALK inhibitors) have afforded benefits to patients with adenocarcinoma, but unfortunately the same is not true for SCC. However, many genomic abnormalities are present in SCC, and there is growing evidence of their biologic significance. Thus, in the short term, the molecular characterization of patients with SCC in modern profiling platforms will probably be as important as deciphering the molecular genetics of adenocarcinoma. Patients with SCC of the lung harboring specific molecular defects that are actionable (e.g., fibroblast growth factor receptor 1 amplification, discoidin domain receptor 2 mutation, and phosphoinositide 3-kinase amplification) should be enrolled in prospective clinical trials targeting such molecular defects. Clin Cancer Res; 18(9); 2443–51. ©2012 AACR.

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide (1, 2). Non–small cell lung cancer (NSCLC) accounts for 85% of all lung cancers. Adenocarcinoma and squamous cell carcinoma (SCC) are the most frequent histologic subtypes, accounting for 50% and 30% of NSCLC cases, respectively. Although the incidence of lung SCC is decreasing as a consequence of changes in tobacco consumption habits, SCC is still a major health issue (3, 4). Despite the recognition of histologic subtypes, the concept of “one size fits all” governed decisions for many years (5). Encouraging new treatments [i.e., bevacizumab, EGFR tyrosine kinase inhibitors (TKI), and ALK inhibitors] have afforded benefits to patients with adenocarcinoma, but unfortunately the same is not true for SCC. A correct histologic diagnosis is becoming increasingly important because it may predict response and toxicity to different therapies (6, 7).

Trials evaluating targeted therapies have failed to identify any benefits in patients with SCC, and the standard first-line treatment administered to such patients is chemotherapy doublets. Moreover, figitumumab, an antibody targeting insulin-like growth factor I receptor, combined with chemotherapy, showed nonsignificantly worse survival when compared with chemotherapy alone in a phase III trial (8). Remarkably, patients with SCC are at higher risk of bleeding complications if they are exposed to bevacizumab. It is important to note that the development plans for all VEGF receptor (VEGFR) TKIs combined with chemotherapy in the SCC subtype have been halted due to higher mortality rates. Bleeding and cavitation are also induced by VEGFR TKIs, but this is probably not the only explanation for the increased toxicity in the SCC subtype. Thus, SCC represents an important field in which new therapeutic options are awaited.

The purpose of this article is to review the genetic alterations that seem actionable (from a therapeutic perspective) and could potentially define different molecular subtypes of SCC, rendering them eligible for personalized treatment strategies.

Histologic Subtypes of SCC

SCCs are tumors that arise from bronchial epithelial cells through squamous metaplasia/dysplasia and are therefore characterized by keratinization and/or intercellular bridges, their most common features. However, the mere presence of at least 10% of the tumor bulk exhibiting these differentiation features is required for a diagnosis of SCC on resected specimens. The diagnosis of poorly differentiated SCC is made when the differentiated squamous component is minimal. This implies that many small biopsy specimens may appear as NSCLC, because large-cell carcinoma is not accepted as a diagnosis in small specimens. An immunohistochemistry (IHC) panel together with a mucin stain can help identify NSCLC subtypes (9). The expression of p63...
Translational Relevance

Squamous cell carcinoma (SCC) of the lung is the second most frequent histology in non–small cell lung cancer (NSCLC). Over the past decade, new approaches targeting specific pathways in NSCLC have emerged, but very few advances have been made in the treatment of SCC. Advances in translational research have revealed significant differences in molecular pathways among subtypes of NSCLC, and these genomic alterations have significant effects on tumor growth. Thus, a molecular characterization of SCC is essential to understand the biologic relevance and the true frequency of each alteration. Patients with SCC of the lung harboring specific molecular defects that are actionable (e.g., fibroblast growth factor receptor 1 amplification, discoidin domain receptor 2 mutation, and phosphoinositide 3-kinase amplification) should be enrolled in prospective clinical trials targeting such molecular defects.

Membrane receptor alterations

Fibroblast growth factor receptor 1 (FGFR1) is a transmembrane tyrosine kinase receptor that plays a role in normal physiologic functions, and evidence exists for deregulated signals in the pathogenesis of many different cancer types. It signals downstream through 4 different pathways: RAS–RAF–mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)–AKT, STAT, and phospholipase Cγ (22). In a study using lung cancer cell lines with FGFR1 amplification and mice engrafted with FGFR1-amplified cells, Weiss and colleagues (23) showed that tumor growth is dependent on FGFR1 activation. Treatment with specific blockers resulted in tumor growth inhibition or shrinkage. In lung SCC, the frequency of FGFR1 amplification by FISH (Fig. 2) is 22%, whereas in adenocarcinoma it is much lower, and this high frequency of amplification was found by other authors (23–25).

The discoidin domain receptor 2 (DDR2) is a tyrosine kinase that binds collagen as its endogenous ligand, and when activated interacts with Src and Shc (26, 27). Mutations may alter kinase activity, ligand binding, or DDR2 localization (28, 29). In a study by Hammerman and colleagues (30), mutations were found in 11 of 290 SCC samples (3.8%). Lung SCC cell lines harboring DDR2 mutations were selectively killed by RNA interference or dasatinib. In addition, tumors established from a DDR2 mutant cell line were shown to be sensitive to dasatinib in xenograft models. By contrast, xenografts with nonmutant tumors were insensitive to treatment. This response was also seen in a pretreated patient with SCC who carried a DDR2
mutation and had a long-term response on erlotinib plus dasatinib, which suggests that DDR2 mutations may be clinically relevant.

MET is a proto-oncogene that encodes a transmembrane tyrosine kinase receptor for the hepatocyte growth factor. MET amplification serves as a mechanism of gefitinib resistance by activating ERBB3 signaling (31). In cells with MET gene amplification, MET is highly activated, and cell proliferation and survival are dependent on this activated MET kinase (32). Inhibition of MET in amplified cell lines leads to reduced cell growth and apoptosis (33). The frequency of MET gene copy-number gains is between 3% and 21%, with no differences between adenocarcinoma and SCC, although it seems to be more prevalent in smokers (34, 35). Despite these results, it is estimated that true MET amplifications are rare in lung cancer, occurring at a frequency of ~2% for adenocarcinoma and somewhat less than that for SCC. This may be because there is a low-level copy-number gain of MET in a much higher percentage of the tumors, but the biologic implications are unclear. In lung cancer, the estimated frequency of mutations is low (1% for SCC

Table 1. Frequency of selected genetic abnormalities in NSCLC

<table>
<thead>
<tr>
<th>Genetic abnormality (references)</th>
<th>Gene location</th>
<th>SCC</th>
<th>Adenocarcinoma</th>
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<tr>
<td>TP53 (36, 71)</td>
<td>17p13.1</td>
<td>51%</td>
<td>36%</td>
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<tr>
<td>PIK3CA amplification (51, 52, 54)</td>
<td>3q26.3</td>
<td>33%</td>
<td>6%</td>
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<td>SOX2 amplification (23, 24)</td>
<td>3q26.3-q27</td>
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<tr>
<td>FGFR1 amplification (24, 25)</td>
<td>8p12</td>
<td>22%</td>
<td>1%</td>
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<tr>
<td>PTEN mutation (36, 61)</td>
<td>10q23.3</td>
<td>10%</td>
<td>2%</td>
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<tr>
<td>MET amplification (34, 35)</td>
<td>7q31.1</td>
<td>3%–21%</td>
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<tr>
<td>PTEN loss (59, 62)</td>
<td>10q23.3</td>
<td>8%–20%</td>
<td>8%–20%</td>
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<tr>
<td>KRAS mutation (36)</td>
<td>12p12.1</td>
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<td>21%</td>
</tr>
<tr>
<td>Variant III mutation (36)</td>
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<td>5%</td>
<td>Very rare</td>
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<tr>
<td>LKB1 mutation (70)</td>
<td>19p13.3</td>
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<td>23%</td>
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Figure 1. Frequencies of potentially actionable/targetable genetic abnormalities present in SCC of the lung. amp, amplified; mut, mutant.
The phosphatase and tensin homolog (PTEN) is a phosphatase that plays a tumor-suppressive role. In the cytoplasm it plays the role of a phosphatase: It dephosphorylates PIP3 into phosphatidylinositol-3,4-bisphosphate (PIP2), thereby inhibiting PI3K-AKT signaling (57). Additionally, nuclear compartmentalization of PTEN is a key component of its tumor-suppressive activity, because it positively regulates APC/C-CDH1 in a phosphatase-independent manner to promote the down-regulation of its targets and tumor suppression (58). The loss of PTEN activity leads to hyperactivation of the PI3K–AKT pathway. Loss of PTEN can occur at the genomic level or by alternative mechanisms such as promoter hypermethylation, alternative splicing of pre-mRNA, and post-translational modifications. PTEN inactivation occurs more frequently at the protein level than at the genomic level, and promoter methylation is found in 35% of PTEN-negative NSCLC (59, 60). PTEN mutations have been described in 10% of lung SCC samples, compared with 2% of adenocarcinomas (36, 61). At the genomic level, PTEN loss is seen in 8% to 20% of both histologic subtypes (59, 62).

The BRAF protein is a cytoplasmic serine/threonine kinase that plays an important role in the RAS–mitogen-activated protein kinase (MAPK) signaling pathway (63). BRAF mutations are associated with increased kinase activity that leads to constitutional activation of MAPK2 and MAPK3, and they are mutually exclusive to EGFR and KRAS mutations. Mutations are seen in ~2% of patients and are quite similar in both adenocarcinoma and SCC. Approximately 90% of mutations found in lung cancer do not involve the mutation commonly seen in melanoma (V600E), and this may have biologic and therapeutic implications (64, 65).

EML4-ALK is an aberrant fusion gene that encodes a cytoplasmatic chimeric protein with constitutive kinase activity. This gene fusion has potent oncogenic activity in animal models and cell lines, and inhibition of ALK leads to a substantial tumor response. This fusion is uncommon, occurring in ~2% to 7% of cases of NSCLC, and is more prevalent in people who never smoked or in light smokers and in patients with adenocarcinoma. In lung SCC, the estimated prevalence is ~1% (66–68).

Serine/threonine kinase 11 (STK11/LKB1) is a tumor-suppressor gene that phosphorylates AMPK. It regulates cell-cycle arrest, p53-mediated apoptosis, and the induction of cell polarity (69). Somatic mutations of LKB1 are present in 5% of lung SCCs and 23% of adenocarcinomas, and they are associated with resistance to EGFR inhibitors and sensitivity to Her2-targeted therapy (43–49).

**Signaling pathway alterations**

Phosphoinositide 3-kinase catalytic α (PI3KCA) encodes for the class IA PI3Kα catalytic subunit p110α. Mutations are seen in ~2% to 3% of SCCs; however, the precise frequency remains to be determined in sufficiently powered studies that are currently ongoing (36, 50–52). The mutational status of PI3KCA is not exclusive to EGFR or KRAS (53). PI3KCA copy-number gains are more frequent in SCC (33.1%) than in adenocarcinoma (6.2%) or small-cell lung cancer lines [4.7% (51, 52, 54)]. Because the PI3KCA gene is located close to the SOX2 lineage transcription factor gene, which is frequently amplified in SCC, it is not clear whether these amplifications are functionally associated with PI3K dependency. In SCC cell lines, mutations or copy-number gains confer a growth advantage (52).

The v-akt murine thymoma viral oncogene homolog 1 (AKT1) gene encodes for protein kinase B α (PKBα), which is involved in the PI3K signal transduction pathway (55). The somatic mutation E17K in the AKT1 gene was found in 1% of lung SCCs but not in adenocarcinoma (56).

The v-akt murine thymoma viral oncogene homolog 2 (AKT2) gene encodes for protein kinase B β (PKBβ), which is involved in the PI3K signal transduction pathway (55). The somatic mutation E17K in the AKT1 gene was found in 1% of lung SCCs but not in adenocarcinoma (56).

**Transcription factor alterations**

The p53 gene, located on chromosome 17p13.1, codes for a multifunctional DNA sequence-specific nuclear phosphoprotein that is essential for maintaining the integrity of the genome. In lung cancer, the frequency of p53 mutation is between 30% and 50%. In the COSMIC database, the rate of TP53 mutation in SCC of the lung is 51% (36). The spectrum of somatic mutations observed in p53 in SCC...
is characterized by a high proportion of C:G > A:T transversions and is compatible with the mutagenic effects of tobacco carcinogens (71). Loss of p53 pathway function can also be related to HDM2 amplification/overexpression when p53 is wild type.

Sex-determining region Y-Box 2 (SOX2) is a transcription factor that plays a role in squamous differentiation of the esophagus and lung. The amplification of the SOX2 gene is the most frequent chromosome gain seen in SCC of the lung, with a frequency of 23% as shown by single-nucleotide polymorphism arrays and FISH (23, 24, 72). Suppression of SOX2 in amplified SOX2 cells has greater antiproliferative effects compared with other genes on 3q26.33, and SOX2 amplification and overexpression are involved in maintaining stem cell properties in SCC (24, 72).

### Therapeutic Opportunities

The advent of targeted therapies has revolutionized cancer treatment. In lung adenocarcinoma, significant improvements in outcomes can be achieved when targeted therapies are used in populations of patients who have been selected based on the molecular profile of their tumor. Unfortunately, this is not true for patients with lung SCC, whose treatment cannot be selected based on the molecular

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Abbreviations: AB, antibody; CT, combined therapy; HS, histologic selection or stratification; KI, kinase inhibitor; MOA, mechanism of action; MT, monotherapy; NCTID, National Cancer Trial Identification; Ph, phase of clinical development.
Clinical Cancer Research

4XL147 is an oral inhibitor of PI3K that has shown signs of inhibition is still debated (83). PF-04691502, an oral SCC; however, their predictive value for sensitivity to PI3K inhibition can be used when the purpose is to inhibit the PI3K–AKT pathway. The E17K mutation found in SCC does not alter the sensitivity of AKT to ATP competitive inhibitors, but it does alter the sensitivity to allostERIC kinase inhibitors (85). MK-2206 is an allostERIC inhibitor of AKT that is being tested in a phase II trial in lung cancer. GDC-0068 is an oral, selective, ATP-competitive AKT inhibitor that is currently in a phase I trial.

Until now, targeting of p53 has proved to be highly disappointing; however, a new era may emerge with the use of hdm2 inhibitors such as RG7112 and MK-8242, which are currently in the phase I setting. RG7112 was tested in patients with liposarcomas (a frequently HDm2-amplified tumor), but with no prescreening for p53 status (86).

Finally, targeting BRAF was tested in unselected patients with NSCLC. Sorafenib, a multitKINase BRAF inhibitor, failed to show a survival advantage when added to first-line chemotherapy in advanced NSCLC (87). GS2118436, a selective inhibitor of BRAF that showed activity in non-V600 BRAF mutant melanoma, is under investigation in a phase II trial in patients with NSCLC and BRAF mutations (88).

Conclusions

Although the incidence of adenocarcinoma is on the rise, lung SCC is currently the second most frequent histologic subtype and the leading one in developing countries. Encouraging new treatments have afforded a benefit to patients with adenocarcinoma, but unfortunately the same is not true for SCC. Chemotherapy is still the gold standard for first-line treatment in advanced SCC of the lung. To date, no single phase III trial involving targeted therapies has identified a benefit in this subpopulation; moreover, some trials showed augmented toxicity in comparison with the population with nonsquamous disease.

Increasing information from basic, translational, and clinical research is changing the approach to patient care in cancer. The historical classification of lung cancer is histology based, but modern pathology needs to bring histology and genomics closer together. A correct histologic diagnosis can help guide the choice of a selected pool of aberrations to be screened. The recognition of molecular
subtypes may identify tumors with different biologic behaviors, and molecular profiling together with an appropriate histologic diagnosis potentially can be used to select the right targeted therapy.

Over the past few years, investigators have described many genomic alterations in SCC. Preclinical data for some of these alterations is promising, and it has been shown that many such aberrations can make a cancer cell become addicted to a specific pathway. How much of this molecular deciphering will translate to actionable targets and therapeutic success remains to be established. Amplification of MET or FGFR1, both of which are found frequently in SCC of the lung, makes the amplified cells become dependent on that pathway, and clinical data concerning MET and FGFR1 inhibition are encouraging. Dasatinib and imatinib inhibit cells carrying DDR2 mutations, which are detected more often in SCC than in adenocarcinoma. In the short term, the molecular characterization of patients with SCC in modern profiling platforms will therefore be as important as deciphering the molecular genetics of adenocarcinoma. Patients with SCC of the lung should not be denied molecular testing, because such an approach may provide new therapeutic opportunities for such patients. Patients with SCC of the lung harboring specific molecular defects that are actionable (i.e., FGFR1, DDR2, and PI3K) should be enrolled in prospective clinical trials targeting such defects.

Disclosure of Potential Conflicts of Interest
R. Thomas receives consulting and lecture fees from Sanofi-Aventis, Merck, Roche, Boehringer Ingelheim, AstraZeneca, and Atlas-Biologs. No other potential conflicts of interest were disclosed.

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