

IN THE SPOTLIGHT

A New Target for Therapy in Squamous Cell Carcinoma of the Lung

Kadoaki Ohashi and William Pao

Summary: Investigators report the identification of novel somatic mutations in the *DDR2* kinase gene in squamous cell carcinoma of the lung. Cellular, biochemical, and human data suggest that tumor cells harboring *DDR2* mutations have increased sensitivity to existing tyrosine kinase inhibitors, providing rationale for clinical trials of agents that inhibit *DDR2* kinase in the disease. *Cancer Discovery*; 1(1); 23-4. ©2011 AACR.

Commentary on Hammerman et al., p. 78(1).

In this issue of *Cancer Discovery*, Hammerman and colleagues (1) report that mutations in the gene encoding the discoidin domain receptor 2 (*DDR2*) kinase identify a novel therapeutic target in squamous cell lung cancer.

Lung cancer is the leading cause of cancer-related death in the United States and worldwide. Until the last decade, treatment decisions for patients were largely based on histologic considerations. Those with small-cell lung cancer (SCLC; now ~10% of cases) were treated in one way and those with non-small cell lung cancer (NSCLC) in another. In major trials, investigators studied patients with NSCLC as one disease entity regardless of whether they had adenocarcinoma (50% of lung cancers), squamous cell carcinoma (SCC; 30%), or large-cell carcinoma (10%). However, recent clinical and translational studies have demonstrated that this approach is no longer applicable. First, the antiangiogenesis agent bevacizumab was approved for use in nonsquamous NSCLC; use in SCC was restricted because of increased bleeding risks (2). Second, the multitargeted antifolate pemetrexed was approved for use in only nonsquamous NSCLC; in several studies (2), pemetrexed did not show a benefit in patients with squamous cell tumors. Third, most targetable mutant kinases, such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and HER2, were found in lung adenocarcinomas and only rarely in other histologic subtypes (3). Such advances seem to have left SCC as the “odd man out.”

Although the lung adenocarcinoma genome has been characterized extensively (4), less is known about specific genetic alterations, especially “driver mutations,” in SCC of the lung. Large-scale genomic studies in the latter have been hampered by difficulty obtaining samples with high tumor content and minimal necrosis. Nevertheless, some efforts are beginning to

bear fruit. SCC of the lung may be categorized into distinct subsets based on mRNA expression patterns (5). Recent molecular analyses have identified genes that may play important roles in lung squamous cell tumorigenesis (e.g., *SOX2*, *p63*, *BRF2*, *GRM8*, *BAI*). Perhaps more clinically applicable, some potentially targetable alterations in genes encoding kinases have been identified in lung SCC, including *FGFR1*, *EGFRvIII*, and *PIK3CA* (Table 1). Whereas *EGFRvIII* and *PIK3CA* mutations are relatively uncommon, focal *FGFR1* amplification occurs in up to 22% of SCC cases. Importantly, cells with *FGFR1* amplification may be dependent on fibroblast growth factor receptor (FGFR) signaling for survival and are sensitive to FGFR inhibitors, many of which are in clinical development (6).

Hammerman and colleagues (1) describe driver mutations involving another kinase in SCC of the lung. Using dideoxynucleotide-based re-sequencing, they screened 201 genes (including those that encode the tyrosine kinome) in 20 primary lung SCC samples and matched normal controls, and identified somatic missense mutations in 25 genes, including 2 in *DDR2*. In a secondary screen of 48 SCC samples that included 13 cell lines, they found 4 additional *DDR2* mutations. They then sequenced *DDR2* in a validation cohort of 222 primary lung SCC samples and identified another 5 samples with mutation, resulting in an overall frequency of 3.2% (9 of 227) in primary lung SCC samples. In total, 11 novel *DDR2* mutations were found throughout the entire gene, not just in exons encoding the kinase domain. Mutations did not correlate with amplification or overexpression of the gene. *DDR2* mutations also had no correlation with gender or smoking history.

DDR2 is the second member of the *DDR* kinase family, which possess a motif in their extracellular domains with homology to the *Dictyostelium discoideum* protein discoidin-I. *DDR* kinases are widely expressed in human tissues, are activated by collagens, and have roles in cell adhesion. *DDR1* and *DDR2* mutations have been reported previously in multiple tumor types including lung cancer (7), but they are rare and have not been functionally characterized. In the study by Hammerman and colleagues (1), the mutants that were studied biologically had transforming ability. Tumor cell lines harboring activating *DDR2*

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Table 1. Potential targetable driver mutations in squamous cell carcinoma of the lung

Gene	Frequency (%)	Drug	Reference
<i>FGFR1</i> amplification	22	FGFR TKIs	Weiss et al. (6)
<i>EGFRvIII</i> mutations	5	EGFR TKIs	Ji et al. (10)
<i>PIK3CA</i> mutations	3.6	PI3K inhibitors	Yamamoto et al. (11)
<i>EGFR</i> kinase domain mutations	3.4	EGFR TKIs	Miyamae et al. (12)
<i>DDR2</i> mutations	3.2	Dasatinib, nilotinib	Hammerman et al. (1)

Abbreviation: TKI, tyrosine kinase inhibitor.

mutations displayed increased sensitivity *in vitro* and *in vivo* to multiple tyrosine kinase inhibitors, including the 3 small molecules dasatinib, nilotinib, and AP24534, which are more commonly known for their ability to inhibit ABL kinase activity but appear to have “off-target” anti-*DDR2* activity. Interestingly, the authors identified one patient with lung SCC whose tumor harbored a *DDR2* mutation and responded significantly to treatment with dasatinib and erlotinib. The patient’s tumor did not have any *EGFR* kinase domain mutation associated with sensitivity to erlotinib, suggesting that the tumor responded to dasatinib because of its dependency on mutant *DDR2*.

The new findings raise many questions. Are *DDR2* mutations specific to SCC of the lung, or will they also be found in other cancer types? In lung cancer, will ethnic differences be found in the frequency of *DDR2* mutations, as for *EGFR*, *KRAS*, and *LKB1* mutations in lung adenocarcinoma? Are *DDR2* mutations overlapping with *FGFR1* amplification, *EGFRvIII* mutations, and/or *PIK3CA* mutations? Are all *DDR2* mutants equally sensitive to dasatinib? What signaling pathways are activated by *DDR2* mutants? A previous phase II study of dasatinib in NSCLC showed only 1 partial response among 34 patients (8); was this result negative due to lack of studying the appropriate molecularly enriched cohort of patients (i.e., patients with *DDR2* mutant tumors)? Because dasatinib induces pleural effusion as a problematic toxicity, do more potent *DDR2* inhibitors with fewer side effects exist?

The findings by Hammerman and colleagues (1) offer a promise of the translational knowledge that may soon emerge from the ongoing Cancer Genome Atlas project on SCC of the lung (9). Whereas this study used targeted dideoxynucleotide-based re-sequencing of only 201 genes, future efforts will deliver portraits of whole exomes and/or whole genomes. We look forward to a more comprehensive picture of the lung SCC genome, so that SCC of the lung no longer is the odd man out in terms of therapeutic options.

Disclosure of Potential Conflicts of Interest

W. Pao received consulting fees (Astra-Zeneca, Bristol-Myers Squibb, Symphony Evolution, and MolecularMD) and grant support (Xcovery, Astra-Zeneca, and Enzo). K. Ohashi disclosed no potential conflicts of interest.

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