CRKL as a Lung Cancer Oncogene and Mediator of Acquired Resistance to EGFR Inhibitors: Is It All That It Is Cracked Up to Be?

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Summary: Cheung and colleagues demonstrate that amplified CRKL can function as a driver oncogene in lung adenocarcinoma, activating both RAS and RAP1 to induce mitogen-activated protein kinase signaling. In addition, they show that CRKL amplification may be another mechanism for primary or acquired resistance to epidermal growth factor receptor kinase inhibitors. Cancer Discovery; 1(7):560–1. © 2011 AACR.

Commentary on Cheung et al., p. 608 (1).

In this issue of Cancer Discovery, Cheung and colleagues (1) report evidence that CRKL amplification may be another mechanism for primary or acquired resistance to EGFR inhibitor kinase inhibitors. Cheung and colleagues (1) report a prevalence of 3% in tumors (on the basis of their previous data; ref. 5) and 7% (6/84) in cell lines. This finding is similar to other independent series, including that of Chitale and colleagues (6), who noted narrow amplicons encompassing CRKL in 6% of lung adenocarcinomas, and that of Kim and colleagues (2), who reported a frequency of 3%. In addition, approximately 2- to 3-fold more cases harbor broader gains of 22q; the CRKL dependence of such tumors will also be important to assess because it would impact on the size of the patient subset in terms of future targeted clinical approaches.

Is amplified CRKL a driver oncogene of the same rank or stature as mutant epidermal growth factor receptor (EGFR)? One of the notable features of major driver oncogenes (EGFR, KRAS, HER2, BRAF) in lung adenocarcinoma is their mutual exclusivity. Cheung and colleagues (1) report that focal CRKL amplification is mutually exclusive with EGFR mutation and EGFR amplification. However, of the 6 lung cancer cell lines found in this study to have focal gains of CRKL, 2 contain other major driver oncogenes (KRAS G13D in HCC515, BRAF G469A in H1755; refs. 7, 8). Interestingly, both cell lines demonstrated clear dependence on CRKL in functional assays. Perhaps CRKL amplification is more akin to PIK3CA mutations, which often, but not always, are concurrent with other major driver oncogenes (9). Intriguingly, of the same 6 cell lines, at least 4 are known to have inactivating mutations in LKB1(7), suggesting another potentially cooperating interaction to explore functionally. The investigators do provide functional evidence for another potentially important cooperating lesion, namely loss of NF1, and go on to show that 1 of 3 CRKL-amplified tumors also harbored an inactivating mutation of NF1 (1). Clearly, the cooperative effects of CRKL gain and overexpression on various oncogenic lesions in these signaling pathways will require further work.

More broadly, the findings of Cheung and colleagues heighten the potential interest of CRKL gains in other cancers and of gains of other signaling adapter molecules. In a survey of genomic copy number data on more than 3,000 specimens from 26 types of cancer, Beroukhim and colleagues (10) found CRKL at the epicenter of 1 of the top 12 most commonly amplified regions in multiple cancer types, including lung cancers, melanoma, ovarian cancer, and colorectal cancer. More generally, these investigators also found that regions of statistically significant gain across different cancers were significantly enriched for genes associated with the Gene Ontology term molecular adaptor activity (10). In addition to CRKL, these genes included IRS2, GRB2, GRB7, GAB2, and TRAF6, among others. Like CRKL, several of these have been shown to have oncogenic properties when gained or overexpressed, for instance, IRS2 and TRAF6 (11, 12).

Finally, could secondary amplification of CRKL represent yet another mechanism of acquired resistance to EGFR kinase inhibitors? Cheung and colleagues show that overexpression of CRKL decreases sensitivity to the EGFR inhibitor gefitinib in experiments based on introducing a CRKL expression
plasmid into the gefitinib-sensitive, EGFR-mutant HCC827 cell line (1). It will be of interest to see whether secondary amplification of CRKL ever emerges spontaneously after long-term selection of EGFR mutant cell lines in the presence of EGFR inhibitor, like the 2 major mechanisms of resistance, the EGFR T790M mutation and MET amplification (13–15). The spectrum of acquired resistance mechanisms for EGFR inhibitors has recently been more accurately defined by 2 large series in which the authors analyzed rebiopsy specimens from patients who progressed (16, 17). When high-sensitivity assays are used, the EGFR T790M or other rare second-site mutations are detected in 60% to 70% of patients (16). Another 10% of cases show acquired MET amplification, small cell transformation, or epithelial–mesenchymal transition (17), leaving approximately 25% to 30% of cases in which the precise mechanism of acquired resistance remains unknown.

In this context, it is notable that Cheung and colleagues also report the identification of 1 patient with acquired resistance to an EGFR inhibitor whose rebiopsy specimen showed a modest gain in CRKL copy number, possibly attributable to chromosome 22 polysomy, relative to the pretreatment baseline sample. Thus, it will be important to examine additional acquired resistance samples for such gains and to define their relationship to EGFR T790M. Likewise, it will be of interest to assess the status of CRKL in tumor biopsies from patients with EML4-ALK–positive lung cancer presenting acquired resistance to crizotinib, especially those lacking ALK mutations (18–20), because the biology of CRKL-induced resistance should in principle also apply to this subset. It is increasingly clear that the delineation of molecular subsets of lung cancer has dramatically clarified its biologic and clinical heterogeneity, leading to new therapeutic opportunities (21); the elucidation of the subset of lung cancers with focal CRKL amplification represents a further advance in this direction.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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