Commentary

Targeting metabolic peculiarities: a potentially novel therapeutic approach for KRAS-mutant lung cancer?

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Lung cancer is a leading cause of cancer-related mortality particularly in its advanced stages (1). The search for more effective therapies to improve the outcome of advanced non-small cell lung cancer (NSCLC) patients is a real hardship for the cancer research community (2). Profound understanding of NSCLC pathobiology has facilitated largely the development of a more personalized style of therapy (3).

Aberrations of the mitogen-activated protein kinase (MAPK) pathway have been reported as an important event in many disease states (4,5). RAS proteins are a family of small GTPases which play a pivotal role in this pathway (6). The three RAS subfamilies which have been evaluated extensively in humans are KRAS, NRAS and HRAS (7).

KRAS-driven NSCLC patients are estimated to represent a considerable portion of the total NSCLC population particularly adenocarcinomas (8); and approximately 97% of KRAS mutations in NSCLC involve codons 12 or 13 (9). Clinically, smokers and female NSCLC patients were more likely to harbor KRAS mutations (10).

However contrary to other driver mutations in NSCLC like EGFR or ALK, no KRAS-targeted therapy has been approved till the moment; and the search for one is immensely ongoing (11). One potential reason behind the failure of direct targeting of these mutations is that KRAS mutations impair GTPase binding and thus RAS remains in a GTP-bound state, which is hard to target with small molecules (12). Accordingly, alternative indirect methods have been experimented to target KRAS-driven NSCLC; most notably by targeting MEK or RAF (which are downstream mediators in the MAPK pathway) (13).

A number of MEK inhibitors have shown promise in preclinical models of KRAS-mutant NSCLC (like selumetinib and trametinib) (14-16). Initial clinical data with these agents in various combinations have been encouraging and the results of a number of other randomized trials are awaited to better assess MEK inhibitors in this setting (17-19).

The letter by Kerr and coworkers published recently in Nature is exploring a totally different aspect of KRAS-mutant NSCLC (20). They showed that KRASG12D/G12D homozygous cells exhibit a glycolytic switch associated with increased channeling of glucose-derived metabolites into the tricarboxylic acid cycle and glutathione biosynthesis. They have observed these changes in spontaneous advanced murine lung tumors (which show a high frequency of KRASG12D copy gain), but not in the corresponding early tumors (KRASG12D heterozygous). These findings provide an important insight into therapeutically relevant metabolic pathways in KRAS-mutant NSCLC and its exploitation may provide a novel therapeutic strategy for these patients. Moreover, these findings suggest that KRAS-mutant NSCLC may be classified on a metabolic basis which may have also prognostic and therapeutic implications. Further preclinical and clinical studies are needed in order to confirm the present findings as well as evaluate the clinical utility of them.

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Footnote

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