IN THE SPOTLIGHT

RAF/MEK Dependence of KRAS-Mutant Pancreatic Ductal Adenocarcinomas

Aphrothiti J. Hanrahan and David B. Solit

Summary: Studies using genetically engineered mouse models indicate that RAF activation is sufficient to induce pancreatic intraepithelial neoplasms, suggesting that mitogen-activated protein kinase (MAPK)/extracellular signal–regulated kinase (ERK) kinase (MEK) inhibitor–based combination approaches may have clinical use in patients with pancreatic ductal adenocarcinomas. Cancer Discov; 2(8); 666–9. ©2012 AACR.

Commentary on Collisson et al., p. 685 (1).

Thirty years have passed since missense mutations in RAS were first identified as the transforming factors in the Harvey and Kirsten strains of the mouse sarcoma virus. Somatic mutations of the 3 RAS genes have since been shown to be among the most prevalent somatic alterations in human cancer. Studies using genetically engineered mouse models (GEMM) of pancreatic and lung cancer, among others, have confirmed that mutant RAS contributes to cancer initiation and maintenance of the transformed phenotype even in the setting of established, metastatic disease. These results have prompted intensive academic- and industry-led efforts to identify direct inhibitors of oncogenic RAS. These efforts have failed to date likely due to the high affinity of the RAS–GTP interaction, as have efforts to selectively inhibit the posttranslational modifications required for RAS activation. The latter approach was ineffective in KRAS- and NRAS-mutant tumors as geranylgeranyl modification can substitute for farnesylation in targeting KRAS and NRAS to the plasma membrane.

An alternate approach is to target the effector pathways responsible for RAS-mediated transformation. Biochemical studies have identified more than 20 distinct RAS effector molecules, the best characterized of which include the RAF proteins, the phosphatidylinositol 3-kinases (PI3K), and the RAL exchange factors. Our understanding of the contribution of individual RAS effectors to transformation remains incomplete, but is likely influenced by the spatial/temporal availability of effectors, the presence or absence of extracellular stimuli, and the pattern of coincident mutational events. In this issue of Cancer Discovery, Collisson and colleagues (1) set out to investigate which of the various RAS effectors are required for tumor initiation and progression in pancreatic ductal adenocarcinoma (PDA). An in-depth focus on PDA is justified by the high rate of KRAS mutation in this disease (>90%) and the urgent need to develop effective therapies for this common and almost universally lethal cancer.

Prior studies using GEMMs have shown that expression of mutant Kras leads to the formation of multifocal pancreatic intraepithelial neoplasms (PanIN; ref. 2). Furthermore, coincident loss of Ink4a/Arf or Tp53 function results in the development of invasive pancreatic adenocarcinomas that phenocopy the human disease (3, 4). To determine whether RAF activation is sufficient to initiate pancreatic tumor formation, the authors generated mice with constitutive or conditional expression of BrafV600E in pancreatic cells. The V600E mutation accounts for more than 90% of the Braf mutations found in human tumors and locks the kinase into a constitutively active conformation. In the BrafCA mouse model generated by Dankort and colleagues (5), the BrafCA allele contains an insert that includes a floxed cassette containing exons 15 to 18 of human wild-type BrafcdNA upstream of a modified exon 15, which harbors the V600E mutation. The wild-type Braf allele is expressed before Cre-mediated recombination, but upon expression of Cre, the wild-type exon 15 to 18 insert is excised, and the expression of BrafV600E is initiated under the control of the endogenous Braf promoter. Targeted expression of BrafV600E using this model in the mouse lung leads to the development of benign lung tumors that progress to adenocarcinoma in the setting of concomitant loss of Tp53 or Ink4A/Arf (5). Similarly, conditional melanocyte-specific expression of BrafV600E in mice using this model results in benign melanocytic hyperplasia, which in the setting of coincident Pten loss progresses to invasive melanoma (6).

In the current study, Collisson and colleagues (1) express BrafV600E in the mouse pancreas by crossing BrafCA mice

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recently shown to prolong the survival of patients with metastatic melanoma whose tumors harbored *BRAF* V600E/K mutations (10). On the basis of these results, U.S. Food and Drug Administration approval for the use of trametinib in patients with BRAF-mutant melanoma is anticipated. Notably, 22 patients with pancreatic cancer were treated with trametinib within the context of the phase I trial of this agent (11). One patient achieved a partial response and several additional patients were noted to have minor responses or stable disease. Although these results are disappointing in light of the GEMM studies reported by Collisson and colleagues (1), they are consistent with studies of human cancer cell lines conducted by this group and others showing that in contrast to BRAF-mutant cell lines, which are with rare exception sensitive to MEK inhibition, KRAS-mutant cell lines exhibit variable sensitivity to MEK inhibitors. The basis for this heterogeneity of MEK dependence in KRAS-mutant cell lines has been explored in colorectal cancer cell lines and in this context can be attributed, in part, to the presence of PIK3CA co-mutation in some models (12). While PIK3CA mutations are rarely observed in pancreatic cancers, Collisson and colleagues (1) show that MEK inhibition in KRAS-mutant PDA cell lines is associated with a reciprocal increase in the expression of phosphorylated AKT and that cotreatment with a selective inhibitor of AKT is associated with synergy in many, but not all, models.

In sum, the results reported by Collisson and colleagues (1) in concert with the clinical experience to date indicate that despite the sufficiency of RAF activation for PanIN development, MEK inhibitor–based combination approaches will be needed to induce durable tumor regressions in most patients with KRAS-mutant PDA. Future laboratory studies will be needed to define the molecular basis for the variable response of KRAS-mutant PDA tumors to MEK inhibition, as such studies would aid in the development of rational MEK inhibitor–based combination strategies.
Disclosure of Potential Conflicts of Interest

D.B. Solit is a consultant/advisory board member for Roche and GlaxoSmithKline. No potential conflicts of interest were disclosed by the other author.

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