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A Second Site *Kras^{G12D}* Mutation that Impairs PI3K Binding Rescues Embryonic Lethality, Abrogates Myeloproliferative Disease, and Delays Lung Tumorigenesis

Jasmine C. Wong*, Pedro A. Perez-Mancera*, Jangkyung Kim, Kuang-Yu Jen, Scott C. Kogan, Ari J. Firestone, Eric A. Collisson, David A. Tuveson, Kevin Shannon (*- equal contribution)

Phosphatidylinositol 3-kinase (PI3K) signaling is essential for *RAS*-driven transformation. To directly investigate the role of oncogenic K-Ras binding to PI3K in development and tumorigenesis, we generated *Kras$^{G12D/+,Y64G/+}$* mice that express, from the endogenous locus, a K-Ras oncoprotein that also contains a "second site" amino acid substitution at tyrosine 64 (Y64G) that disrupts the interaction between oncogenic K-Ras and PI3K. Surprisingly, *Kras^{G12D,Y64G}* mice are viable, fertile, and phenotypically unremarkable, although they are born at a lower than expected Mendelian frequency (26% versus the expected 50% on a C57BL/6 strain background). As opposed to the enhanced proliferative rate observed in mouse embryonic fibroblasts (MEFs) from *K-Ras^{G12D}* mice, *Kras^{G12D,Y64G}* MEFs exhibit wild-type rates of proliferation. Detailed analysis of the hematopoietic compartment in *Kras^{G12D,Y64G}* mice reveals a reduced proportion of long-term hematopoietic stem cells, but no evidence of the aggressive myeloproliferative neoplasm observed when a conditional mutant *Kras^{G12D}* is activated in hematopoietic cells. Consistent with these observations, bone marrow cells isolated from *K-Ras^{G12D,Y64G}* mice exhibit a normal pattern of myeloid progenitor colony growth in response to cytokine stimulation. In contrast to the lack of observed hematologic malignancy, 100% of *Kras^{G12D,Y64G}* mice we examined at 1 year of age showed lung lesions, ultimately succumbing to lung tumors with a median survival of 496 days. Despite the ubiquitous *Kras^{G12D,Y64G}* expression, these mice survive longer than models with mosaic, adenoviral-Cre recombinase-controlled *Kras^{G12D}* (median survival of 185 days). The majority of the lung lesions that arise in *Kras$^{G12D, Y64G}$* mice are low grade, classified pathologically as atypical lymphoid proliferation or papillary adenomas; a few adenocarcinomas are also observed. These studies reinforce the importance of oncogenic KRas-mediated activation of PI3K for transformation and demonstrate that expressing a Y64G amino acid substitution in the context of oncogenic *Kras^{G12D}* normalizes cell proliferation, rescues embryonic lethality, abrogates myeloid disease, and attenuates lung tumorigenesis. Beyond the bone marrow and lung, this mutant strain is a potent genetic tool for dissecting the role of aberrant PI3K signaling in pancreatic, colon, and other tissues characterized by tumors driven by somatic *KRAS* mutations, and also have implications for treating human cancers with *KRAS* mutations.