KRAS-mediated suppression of PP2A-B56a promotes pancreatic tumorigenesis.

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Protein phosphatase 2A (PP2A) is a major serine/threonine phosphatase that regulates many cellular pathways including KRAS, a protein whose oncogenic mutation is prevalent in 95% of patients with Pancreatic Ductal Adenocarcinoma (PDAC). Previous research has identified a decrease in global PP2A activity, as well as an increase in expression of PP2A inhibitors, in PDAC cell lines. These studies suggest that suppression of PP2A activity may be important in PDAC maintenance. While global PP2A has tumor suppressive capabilities, the regulation of specific pathways by PP2A can change based on PP2A holoenzyme composition. Specifically, the B56α subunit of the heterotrimeric PP2A holoenzyme has been shown to negatively regulate cellular transformation and has decreased expression in PDAC, indicating that B56α suppression may aid in PDAC tumorgenicity. Therefore, there is a critical need to understand the mechanisms that alter PP2A function and substrate targeting. *Our research aims to investigate the impact of oncogenic KRAS on PP2A-B56α activity and how suppression of B56α impacts the initiation and progression of PDAC.* Our preliminary studies suggest that induction of $KRAS^{G12D}$ increases the expression of cancerous inhibitor of PP2A (CIP2A), indicating that PP2A suppression may be an early event in PDAC initiation. Consistent with this hypothesis, our *in vivo* data show that the loss of B56α in the context mutant KRAS accelerates PDAC initiation, increasing the formation of precursor lesions. Together, these studies identify PP2A as a critical regulator of KRAS-induced tumorigenesis and suggest that therapeutic reactivation of PP2A may be a novel therapeutic strategy in PDAC patients.