Investigation of MicroRNAs as Relevant KRAS-targets in Pancreatic Ductal Adenocarcinoma.

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INTRODUCTION: *KRAS* oncogenic mutations are found in over 90% of pancreatic ductal adenocarcinomas (PDACs), and no effective therapies are available for KRAS-induced malignancies. Even though efforts are underway to target KRAS-induced oncogenesis, microRNAs involved in the malignant transformation triggered by KRAS remain largely unknown. Using a microarray platform to compare microRNA expression between engineered isogenic pancreatic epithelial cell lines, which differ only by expression of the KRAS oncoprotein, we have previously identified 20 KRAS-regulated microRNAs. **GOALS:** The goal of this study was to validate the expression and function of the KRAS-regulated microRNA network in cells derived from human PDAC tumors. **METHODS AND RESULTS:** For that purpose we used 2 different approaches. First, we used RNA interference to inhibit KRAS expression in KRAS-positive PANC-1 and MIAPaCa-2 PDAC cells. As expected based on our previous microarray data, inhibition of KRAS expression decreased expression of microRNAs miR-100-5p and miR-130a-3p. Furthermore, KRAS inhibition led to increased expression of CSF1 and Smad4, which are validated miR-130a-3p targets. Unexpectedly, transfection of PDAC cells with miR-130a-3p mimic double-stranded oligonucleotides decreased clonogenic growth, suggesting a tumor suppressor role for this microRNA. Nonetheless, inhibition of miR100-5p expression with an antagomiR oligonucleotide decreased clonogenic growth, suggesting that this microRNA contributes to KRAS-induced oncogenesis in PDAC. For the second approach, using the QIAGEN Ingenuity Pathways Analysis Database, we performed *in sillico* analysis of all up-regulated microRNAs identified by our previous microarray experiment to identify the microRNA targets most likely to be regulated by KRAS. The most commonly regulated target was the PTEN phosphatase, which was targeted by 7 different microRNAs. PTEN is a well-known tumor suppressor and KRAS targeting by RNA interference in PDAC cells increases PTEN protein levels. **CONCLUSIONS:** Taken together, these results suggest that oncogenic KRAS regulates microRNAs that synergistically or individually contribute to the malignant phenotype in PDAC.

Keywords: KRAS, microRNAs, pancreatic cancer

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