Identification of MicroRNAs Regulated by Oncogenic KRAS in Pancreatic Cancer

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INTRODUCTION: KRAS–induced pancreatic cancer is a very common disease, for which, currently, no effective therapy is available. Intense efforts are underway to identify KRAS targets that play a crucial role in oncogenesis. One promising KRAS-regulated pathway that has so far been overlooked is the microRNA pathway; microRNAs involved in the malignant transformation triggered by KRAS remain largely unknown. **GOALS:** Our goal is to identify microRNAs regulated by oncogenic KRAS in pancreatic cells that contribute to the oncogenic phenotype. **METHODS AND RESULTS:** For that purpose we used an Agilent microarray platform to compare microRNA expression between an immortalized human primary pancreatic epithelial cell line (HPDE) and its isogenic KRAS-transformed counterpart (HPDE-KR). Using this approach, we identified 17 upregulated microRNAs and 3 downregulated microRNAs in HPDE-KR cells. Differential expression was validated by qPCR in the isogenic HPDE and HPDE-KR lines of the following upregulated microRNAs: 139-3p, 19b-3p, Let7b, 100-5p, 29b-3p and 130a-3p. A second approach used to identify microRNAs regulated by KRAS was to perform a metanalysis of published microarray datasets comparing pancreatic cancer patient samples to non-cancerous pancreatic tissues. Nine microRNAs were identified by both approaches (microarray and metanalysis), including the validated microRNAs 29b-3p and 130a-3p. In order to confirm that these microRNAs were in fact regulated by KRAS, we used KRAS positive MiaPaca pancreatic cells to generate stable lines with doxycycline-inducible expression of two different short hairpin RNAs targeting KRAS. Inhibition of KRAS expression by doxycycline led to a decrease in expression of microRNAs 19b-3p, 100-5p, Let7b and 130a-3p, thus corroborating the results obtained in the HPDE/HPDE-KR cells. **CONCLUSIONS:** Taken together, these results suggest that the abovementioned microRNAs are KRAS targets in pancreatic cancer. Further understanding of their biological function, as well as the targets they regulate in this setting, could uncover novel pathways for pancreatic cancer therapy.

Keywords: KRAS, microRNAs, pancreatic cancer

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