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TITLE
Evaluation of the Transcriptional Repressor REST during Acinar to Ductal Metaplasia

HYPOTHESIS:
We hypothesize that REST helps maintain appropriate pancreatic-cell identity that is critical for preventing the early stages of pancreatic ductal adenocarcinoma development.

BACKGROUND/AIMS:
The 5-year survival of Pancreatic Ductal Adenocarcinoma (PDAC) has remained flat-lined at only 3%-7% over the past three decades. While the later stages of PDAC have been characterized, a comprehensive understanding of early events in pancreatic cancer development is lacking. The large body of published research in transgenic mouse models indicates that pancreatic lesions originate from the acinar cells that transdifferentiate into ductal-like cells, a process known as acinar to ductal metaplasia (ADM). Therefore, maintaining appropriate acinar cell organization and identity is a crucial step in preventing ADM and PDAC development. While the transcriptional repressor REST is well characterized as a long-term gene silencer of neuronal genes in non-neuronal cells, the role of REST in pancreatic acini remains largely unexplored.

METHODS:
To investigate the necessity of REST activity in ADM progression, we developed a novel mouse model (p48-Cre⁺⁻/REST⁺⁻) with conditional knockout of Rest expression within pancreas acinar cells. The degree of REST knockout was characterized at the gene expression and protein level using qPCR and Western Blot, respectively. The effect of REST knockout during induced ADM in vitro was assessed using the ADM assay on primary p48-Cre⁺⁻/REST⁺⁻ pancreas acini. The role of REST during ADM in vivo was determined by inducing acute pancreatitis in mice using the cholecystokinin analog caerulein.

RESULTS & CONCLUSIONS
The high Cre-mediated efficiency of Rest exon 2 knockout results in decreased Rest expression at the mRNA and protein level within the pancreas. Data to establish a phenotype for REST knockout in pancreatic acini are contradictory. While REST knockout prevents ADM in vitro, REST ablation accelerates acute pancreatitis in mice treated with caerulein. Future studies will cross the p48-Cre⁺⁻/REST⁺⁻ mice with transgenic mice harboring an activating Kras mutation to study the role of Rest in PDAC progression.