Endocrine-exocrine signaling drives pancreatic cancer progression

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Background/Significance to NETs: The predominant histologic subtypes of pancreatic cancer, pancreatic ductal adenocarcinoma (PDAC) and pancreatic neuroendocrine tumors (PNET) are thought to originate from independent cellular compartments comprised of the exocrine (acinar cells/ducts) and endocrine (islets) pancreas, respectively. Recent ultrastructural and perfusion studies have identified bidirectional endocrine-exocrine blood flow, but whether and how intra-pancreatic endocrine-exocrine signaling contributes to PNET and PDAC progression is not known. Understanding these mechanisms could reveal novel strategies for PNET prevention and therapy.

Materials and Methods/Experimental Approach: To determine whether endocrine-exocrine crosstalk could drive pancreatic tumor development, we generated a new obesity-driven mouse model of pancreatic cancer, since obesity is a major host risk factor for both PDAC and PNET and places a significant physiologic stress on both the endocrine and exocrine pancreas. We crossed the leptin-deficient (*ob/ob*) model of obesity with an oncogenic *Kras*-driven model (*KC*: *Pdx1-Cre; Kras*$^{LSL\text{-}G12D}$) of PDAC, which faithfully mimics the genetic and histologic features of the human disease. We induced weight loss using adeno-associated virus-mediated leptin gene therapy or caloric restriction and analyzed tumor progression by histology. We performed molecular analyses of mouse and human PDAC tumors and sera using exome sequencing, RNA-sequencing, immunohistochemistry, and ELISA and assessed islet gene expression in obese and non-obese conditions by single-cell RNA-sequencing.

Results: Findings from autochthonous mouse models demonstrated that obesity accelerates pancreatic ductal tumorigenesis, while genetic or dietary weight loss intercepts tumor development, consistent with a causal and reversible role for obesity in early PDAC progression. Molecular analyses defined obesity-driven microenvironmental alterations that foster tumorigenesis rather than new driver mutations, including perturbations in the expression of hormones and genes involved in hormone processing and secretion. Specifically, we identified obesity-induced islet beta cell expression of the hormone cholecystokinin (CCK) and showed that islet CCK itself is sufficient to promote *Kras*-driven pancreatic tumorigenesis. Single-cell analyses of islet cells further identified potential beta cell-intrinsic and extrinsic factors that drive islet hormonal adaptation including CCK production.

Conclusions/Next Steps: Our results highlight how endocrine-exocrine crosstalk may drive pancreatic cancer development by uncovering a previously unappreciated intra-pancreatic signaling axis. Given the bidirectional blood flow between the endocrine and exocrine pancreas,

these data support a plausible new mechanism for PNET formation through reciprocal exocrine signaling, which deserves further exploration. Furthermore, our findings underscore the potential of targeting aberrant islet hormone production using PNET therapies, such as somatostatin analogues, as a novel approach for PDAC prevention and therapy.