

Fendrich V, Oh E, Bang S, Karikari C, Ottenhof N, Bisht S, Lauth M, Brossart P, Katsanis N, Maitra A, Feldmann G (2011). Ectopic overexpression of Sonic Hedgehog (Shh) induces stromal expansion and metaplasia in the adult murine pancreas. *Neoplasia* Oct;13(10): 923-30.

Ligand-dependent activation of the Hedgehog (Hh) signaling pathway has been implicated in both tumor initiation and metastasis of pancreatic ductal adenocarcinoma (PDAC). Prior studies in genetically engineered mouse models (GEMMs) have assessed the role of Hh signaling by cell autonomous expression of a constitutively active Gli2 within epithelial cells. On the contrary, aberrant pathway reactivation in the human exocrine pancreas occurs principally as a consequence of Sonic Hh ligand (Shh) overexpression from epithelial cells. To recapitulate the cognate pathophysiology of Hh signaling observed in the human pancreas, we examined GEMM where Hh ligand is conditionally overexpressed within the mature exocrine pancreas using a tamoxifen-inducible Elastase-Cre promoter (Ela-CreERT2;LSL-mShh). We also facilitated potential cell autonomous epithelial responsiveness to secreted Hh ligand by generating compound transgenic mice with concomitant expression of the Hh receptor Smoothed (Ela-CreERT2;LSL-mShh;LSL-mSmo). Of interest, none of these mice developed intraductal precursor lesions or PDAC during the follow-up period of up to 12 months after tamoxifen induction. Instead, all animals demonstrated marked expansion of stromal cells, consistent with the previously described epithelial-to-stromal paracrine Hh signaling. Hh responsiveness was mirrored by the expression of primary cilia within the expanded mesenchymal compartment and the absence within mature acinar cells. In the absence of cooperating mutations, Hh ligand overexpression in the mature exocrine pancreas is insufficient to induce neoplasia, even when epithelial cells coexpress the Smo receptor. This autochthonous model serves as a platform for studying epithelial stromal interactions in pancreatic carcinogenesis.