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The Hedgehog signaling pathway is overexpressed in a variety of cancers, leading to hyperactivation of target genes in Hh responding cells. In a number of cancers, the responding cells are stromal fibroblasts that are found near Hh ligand-expressing epithelial cells. This paracrine mechanism is one of many cell-cell interactions that take place between epithelial and mesenchymal cells. Through its role as a master regulator of other transcription factors, Hh pathway activation can have extremely potent effects on cell proliferation, behavior and survival. In pancreatic ductal adenocarcinoma (PDA), paracrine signaling from neoplastic epithelial cells to fibroblasts controls the development and maintenance of stromal desmoplasia, a very prominent feature of these tumors. We previously found that stromal desmoplasia in PDA contributes to primary chemoresistance by interfering with drug delivery. Inhibiting the Hh pathway with a targeted inhibitor of Smoothened (Smo) depleted the stroma from pancreatic tumors arising in a genetically engineered mouse model. This had the effect of facilitating drug delivery to the tumor parenchyma, ultimately aiding in their treatment and leading to prolonged survival. However, the precise molecular mechanisms by which Smo inhibitors target desmoplasia is unclear.

We propose to learn more about how Smo inhibitors affect stromal cells by examining the functional and molecular consequences of Smo inhibition in a genetically engineered mouse model of PDA. We will use ex vivo molecular techniques to dissect the downstream signalling pathways initiated by Hh signalling.

Another effect of Smo inhibition in pancreatic tumors is the restoration of tissue vascularization, which is oddly low in pancreatic cancer. This paradoxical result is at odds with the known roles of the Hh pathway during angiogenesis. We hypothesize that angiogenesis occurs after Smo inhibition due to the relief of an anti-angiogenic signal provided by fibroblasts. We will test this by using hedgehog-independent means of depleting the stroma, and by examining several possible stroma-mediated mechanisms using tissues derived from genetically engineered mice.

These experiments will leverage our expertise in mouse modeling, preclinical therapeutics and molecular biology to determine the basic mechanisms of Smo inhibition in pancreatic cancer and other systems employing paracrine Hh signaling. Currently, 25 different clinical trials have been initiated to investigate Smo inhibitors in 9 different cancers, including PDA. The experiments proposed here will aid our understanding of their results and assist in the design of future trials. More generally, we will learn about the relationship between epithelial and mesenchymal cells and the pathways that promote stromal desmoplasia in cancer.