Pancreatic cancer and biliary cancer are among the most lethal types of human cancers. The Bardeesy laboratory has developed a series of genetically engineered mouse models to define the role of key gene mutations in driving these cancer types. Current projects focus on defining roles for cancer genes in controlling the way cells modulate their growth and utilize energy in response to available nutrients, and on identifying epigenetic regulators responsible for changes in cellular differentiation state that lead to cancer initiation and maintenance.

Epigenetic drivers of pancreatic and biliary cancer

An important area of current focus in our lab is to elucidate the epigenetic regulators of pancreatic cancer and biliary cancers, with particular attention paid to factors that subvert normal differentiation pathways and that reprogram cancer cell metabolism. As part of these efforts, we defined the tumorigenic role of a number of chromatin-modifying enzymes that are deregulated in pancreatic cancer progression, KDM2B. This histone demethylase is a major regulator both of polycomb repressor complexes that override cancer cell differentiation states and of a distinct program controlling metabolic homeostasis. In biliary cancer, there are recurrent mutations in the IDH1 and IDH2 genes. Mutant IDH proteins in IHCC and other malignancies acquire a novel enzymatic activity allowing them to convert alpha-ketoglutarate (αKG) to 2-hydroxyglutarate (2HG), which inhibits the activity of multiple αKG-dependent dioxygenases, including the JmjC family histone demethylases. We are focusing on how IDH mutations affect epigenetic programs and regulation of cellular identity in the liver.

Targeting master regulators of metabolic reprogramming in PDAC

In order to couple rapid growth with available nutrients, cancers employ profoundly altered networks of biosynthetic and catabolic pathways. This requirement for metabolic reprogramming is particularly acute in PDAC, which is characterized by hypoxia and limited nutrient availability, and activates anti-oxidant gene expression and autophagy (cellular self-catabolism) as necessary adaptive metabolic changes. While these pathways offer attractive new therapeutic targets, the underlying mechanisms driving altered PDAC metabolism are unclear. We have focused on identifying master transcriptional regulators that broadly orchestrate metabolic reprogramming in PDAC.
Selected Publications:


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