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Defining the mechanisms of pancreatic cancer susceptibility in patient-derived organoid models

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Scientific Abstract:

Deaths from pancreatic ductal adenocarcinoma (PDA) continue to rise; PDA will soon become the second leading cause of cancer-related death. Pancreatitis, or pancreatic inflammation, is a common condition with an incidence five-fold higher than PDA. Both PDA and pancreatitis exhibit similar features, often confounding early detection approaches for PDA. Despite its late diagnosis, studies have demonstrated that the development of an overt pancreatic malignancy takes over a decade, highlighting the need and the possibility of early detection in at-risk populations. In addition, pancreatitis is the gateway to PDA in mice and a risk factor for PDA in patients. Therefore, prevention approaches for PDA necessitate discovery of treatment options for pancreatitis and a better understanding of the factors that promote cancer. Understanding the mechanisms by which pancreatitis increases susceptibility to transformation has been hampered by a lack of physiologically relevant models and difficulty accessing patient samples.

With the advent of organoid technology, we can create organoids from small amounts of material with high efficiency from both normal pancreata and PDA. We will create a living biobank of pancreatitis organoids to delineate their unique molecular features. These pancreatitis organoids will facilitate the identification of biomarkers that discriminate between benign and malignant disease. We will determine if pancreatitis organoids exhibit distinct underlying genetic programs that are associated with increased risk for transformation. A deeper understanding regarding the pathways that are enriched in pancreatitis and how underlying gene expression programs influence susceptibility to tumorigenesis will identify potential intervention targets for PDA prevention.

Lay Abstract:

Pancreatic cancer (PDA) is a deadly malignancy. Most PDA patients are diagnosed with late-stage disease and no longer benefit from surgery, the only curative treatment for this disease. Early detection would greatly increase the number of patients who receive this life-saving surgery. Unfortunately, diagnostic tests with the necessary specificity for pancreatic cancer are not available. This is due in part to the difficulty in discriminating between pancreatic cancer and pancreatitis. Pancreatitis is a common type of pancreatic inflammation that resolves naturally in most patients and has a low mortality rate. However, it shares several features with PDA, including the development of fibrotic scar tissue, making it difficult to distinguish between patients with pancreatitis and PDA. We propose to make models from pancreatitis patients that will enable in depth comparison to a collection of models already generated from normal pancreas and pancreatic cancer patients. This will facilitate the discovery of biomarkers that are unique to pancreatic cancer and can be used for early detection.

Several populations exhibit elevated risk for developing pancreatic cancer. Patients with chronic pancreatitis are at 3.5-fold higher risk than the general population and patients with hereditary pancreatitis have a 40- 55% lifetime risk of developing PDA. However, the underlying cause of this increased risk is largely unknown. To develop prevention approached for this at-risk patient population, we need a better understanding of why they have increased susceptibility to cancer. Therefore, we will use the models we generate from pancreatitis patients to uncover the source of pancreatic cancer risk.