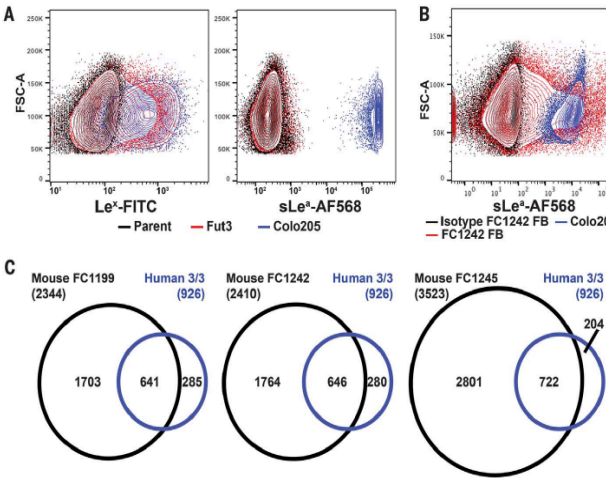
CA19-9 promotes pancreatitis and pancreatic cancer

The glycan CA19-9 promotes pancreatitis and pancreatic cancer in mice

Focus: Dr. Engle's lab focuses on pancreatic cancer and basically every stage of disease that leads to pancreatic cancer. The lab has devised powerful new mouse models of pancreatitis and pancreatic cancer that improve on existing models by incorporating carbohydrate CA19-9, which is a fundamental aspect of human, but not mouse, pancreatic biology. The presence of CA19-9 can indicate pancreatic cancer. However, because it is also present in pancreatitis, it can result in false positive diagnoses of cancer. Using an organoid culture platform, the lab has established new and improved ways to evaluate CA19-9 that make it possible to distinguish between pancreatitis and pancreatic cancer. The Engle lab started this project by creating CA 19-9-sugar mouse models so that they could look for biomarkers. At the same time, the lab developed a new culture technology called organoids. This in itself is very revolutionary because the lab can grow normal proliferating epithelial cells that are very similar to what you see in an inflammatory process as well as each stage of cancer.

By making organoids from autopsy samples, as well as from biopsies and surgical resections of patient tumors, the lab has shown that they are able to grow organoids from many different stages of diseases that were previously inaccessible. As a result, Dr. Engle and her lab has really opened up the field to studying the entire gamut of pancreatic cancer progression in patients in a way that wasn't really previously possible.

Summary of the related manuscript:



Glycosylation alterations are indicative of tissue inflammation and neoplasia, but whether these alterations contribute to disease pathogenesis is largely unknown. To study the role of glycan changes in pancreatic disease, we inducibly expressed human fucosyltransferase 3 and b1,3-galactosyltransferase 5 in mice, reconstituting the glycan sialyl-Lewisa, also known as carbohydrate antigen 19-9 (CA19-9). Notably, CA19-9 expression in mice resulted in rapid and severe pancreatitis with hyperactivation of epidermal growth factor receptor (EGFR) signaling. Mechanistically,CA19-9 modification of the matricellular protein fibulin-3 increased its interaction with EGFR, and blockade of fibulin-3, EGFR ligands, or CA19-9 prevented EGFR hyperactivation in organoids. CA19-9–mediated pancreatitis was reversible and could be suppressed with CA19-9 antibodies. CA19-9 also cooperated with the KrasG12D oncogene to produce aggressive pancreatic cancer. These findings implicate CA19-9 in the etiology of pancreatitis and pancreatic cancer and nominate CA19-9 as a therapeutic target.

APPLICATIONS:

*Developing and testing putative therapies and treatment strategies in pancreatitis and pancreatic cancer organoids and mouse models
*Biomarker discovery and testing pipeline in mice with every stage of pancreatic disease progression
*Discovery of novel drug targets
*Interrogation of mechanism(s) of action and resistance
*Investigating CA19-9 as a drug target to prevent progression from pancreatitis to cancer

ADVANTAGES

*The mouse and organoid models are a renewable resource
*Patient-derived organoid models predict patient response
*Organoid models can be generated from normal pancreas as well as from pancreatitis, pre-malignant lesions, and invasive and metastatic pancreatic cancer

BACKGROUND: Pancreatitis, or inflammation of the pancreas, is a painful, recurrent, and occasionally lethal medical disorder with limited treatment options. The incidence of acute and chronic pancreatitis is rising. Pancreatitis accounts for more than 275,000 hospitalizations in the United States per year, and the number of hospital admissions has increased by 20% over the past decade. The causes of pancreatitis include blockage of the pancreatic duct by gallstones, alcohol and certain drugs that cause acinar cell damage, medical procedures or trauma that damage pancreatic tissue, and autoimmune diseases. In approximately one third of cases, the underlying etiology of the pancreatitis is unknown (idiopathic). Most acute pancreatitis cases will resolve with supportive care; however, up to 20% of patients will develop severe tissue damage and will either on proteins and other molecules, culminating in the a1,4 linkage of fucose toN-acetylglucosamine. Fucosyltransferase 3 (FUT3) is the only enzyme with the ability to add fucose moieties through an a1,4 linkage and generate CA19-9. Mice lack this enzyme because Fut3 is a pseudogene in rodents. To facilitate the discovery of PDAC biomarker candidates, we sought to create a mouse model of PDAC that recapitulated the elevation of CA19-9 observed in human patients. This model would enable prioritization of biomarkers that outperform CA19-9.

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