INTERNAL MEDICINE, GASTROENTEROLOGY & HEPATOLOGY
COLLEGE OF MEDICINE

SUMMER RESEARCH OPPORTUNITIES FOR UNDERGRADUATE students

FOR APPLICATION YEAR: 2026

PROJECT TITLE: Identifying the molecular binding partners of alternatively spliced tissue factor in the MASH liver

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Project Description

Due in large part to diet, 1 in 3 Americans have fat accumulation in their liver, a symptom of metabolic dysfunction associated steatotic liver disease. 20% have or will develop a more severe form of disease – metabolic dysfunction associated steatohepatitis (MASH) – during their lifetime. Currently, over 1 million individuals have progressed to cirrhosis, an immense clinical and economic burden resulting in ~11,400 new liver cancer diagnoses and 1,700 new cases of liver transplant per year. Fibrosis is the major determinant of progression to cirrhosis. As scarring accumulates with time, it deprives hepatocytes of oxygen and nutrients.

The Lewis lab studies alternatively spliced tissue factor (asTF), a protein involved in blood vessel development. Hepatocytes are the primary producer of asTF in the liver. In the normal liver, hepatocytes secrete asTF into adjacent biliary canaliculi, likely to maintain patency of the structure. We have discovered asTF becomes dysregulated during the progression from MASH to cirrhosis where it becomes secreted into a new microenvironment: sinusoidal spaces. Here, it can interact with cell types of the liver other than just hepatocytes – these include sinusoidal endothelial cells and stellate cells. To determine if asTF can elicit pathological responses from these cell types, we performed extracellular matrix deposition and endothelial tube formation assays with immortalized human cells of liver sinusoidal endothelial as well as stellate cell origin. We found asTF promotes the enhanced production of extracellular matrix by both cell types pointing to a potential role in fibrosis. We also found asTF elicited tube formation by sinusoidal endothelial cells, pointing to a potential role in endothelial transformation.

To identify the proteins asTF is interacting with on cell surfaces, we have

created asTF fusion proteins linking asTF to biotin-transferase, an enzyme that covalently tags endogenous proteins within a few nanometers when free biotin is available. The fusion protein and biotin will be added to cell culture media and incubated with sinusoidal endothelial cells and stellate cells for short time courses. Biotinylated proteins will be isolated and identified via mass spectroscopy. We will then utilize antibodies and immunoprecipitation to validate these interactions. These findings are likely to identify novel binding partners and reveal the signaling cascades driven by asTF. A student assigned to this project will receive hands-on instruction with the goal of becoming proficient in basic human tissue culture, western blotting, and immunoprecipitation techniques.