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Title of project: Spatiotemporal Deconstruction of Microvascular Decay in NASH

ABSTRACT

The global prevalence of chronic liver disease has reached pandemic proportions. Non-alcoholic steatohepatitis (NASH) alone has an estimated global prevalence of 3-5%. NASH is associated with hepatic steatosis, lobular inflammation and extensive fibrosis. Advanced NASH may lead to liver cirrhosis and hepatocellular carcinoma, and NASH-related, decompensated cirrhosis is the major indication for liver transplants in the United States. Whereas the liver parenchyma holds a remarkable ability to regenerate, defects of the hepatic microvasculature is a common complication of chronic liver disease, which hinders functional restoration of the liver. Importantly, neither the molecular interactions upholding normal sinusoid function nor the events underlying their disruption are well understood. Much better insights of the underlying pathology are urgently needed to identify better diagnostic markers and novel therapeutic targets.
This interdisciplinary project aims at understanding the molecular basis for the microvascular decay in NASH by an explorative application of single-cell and spatial transcriptomics analysis on human and mouse liver. Integrating these techniques, I will study the sinusoidal cell interactions in healthy and NASH livers and acquire high-dimensional information about individual cells. I will be able to map functional interactions between cell populations by combining tissue localization and singlecell transcriptomes. My findings will be validated histologically. To further support my findings, I will investigate a novel genetic mouse model of accelerated sinusoid decay. PlvapHSC; -/- mice with hepatic stellate cell-specific ablation of the gene encoding Plasmalemma Vesicle-Associated Protein PLVAP will be characterized. I expect that the findings in this project will provide important insight into the cellular dynamic underlying microvascular decay in NASH, some of which may point to novel therapeutic targets for effective treatment of the disease.