

The role of the vasculature in the progression of nonalcoholic fatty liver disease to hepatocellular carcinoma

Liver cancer deaths are significantly increasing worldwide. Hepatocellular carcinoma (HCC) accounts for the majority of primary liver cancers, and despite progress in therapeutics, its prognosis remains unfavorable. Amongst the risk factors, nonalcoholic fatty liver disease (NAFLD) and the more advanced form of disease nonalcoholic steatohepatitis (NASH), are emerging as leading etiologies of HCC. While the risk factors for NAFLD/NASH are well known, the precise mechanism of how simple fatty liver progresses to chronic inflammation, liver fibrosis, and HCC is not known.

The aim of this project is to explore the role of the hepatic vasculature in the progression of NAFLD/NASH to HCC. By combining state-of-the-art approaches with omics technologies and *in vivo* mouse models, we will investigate the functional role of liver sinusoidal endothelial cells (LSEC) as key players in the development of liver injury and HCC from fatty liver disease. We will assess LSEC immunomodulatory and homeostatic properties in the progressive phases of NAFLD pathophysiology and characterize the intercellular communication of LSEC and other liver cells. By dissecting this interplay at molecular level, we expect to identify novel mechanisms that support the detrimental role of LSEC during disease progression. We will select a subset of newly identified targets for *in vivo* validation using pharmacological strategies.

The fundamental insights that will be generated with this project will contribute to identify novel pathogenic mechanisms that can be targeted to prevent NAFLD/NASH to HCC progression.

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