Hepatic Deconstruction: The Genes Driving Liver Disease

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Main Research Areas

In the Ravnskjaer group we use advanced functional genomics tools to identify and target molecular mechanisms underlying the development of chronic liver disease.

IMPORTANCE: Obesity, diabetes, cardiovascular disease and chronic liver disease are growing health challenges worldwide. A severe complication in obesity is non-alcoholic steatohepatitis (**NASH**), which develops over years and is now the most frequent cause of deadly liver cirrhosis and liver cancer. NASH results from lipid deposition in the liver and is associated with hepatic inflammation and widespread fibrosis. Hepatic fibrosis is the uncontrolled formation of scar tissue throughout the liver caused by overproduction of extracellular matrix. An estimated 5% of the global population suffer from NASH.

CHALLENGE: The mammalian liver is composed of multiple cell types in constant interaction. These interactions are responsible for both normal liver functions and NASH development, but the complexity has until now prevented scientists from studying the roles individual cell types *in vivo*.

STRATEGY: To overcome this challenge, we use single-cell and spatial transcriptomics on patient liver biopsies and advanced mouse models to dissect molecular disease mechanisms in the liver one cell at the time. By combining single-cell studies of human biopsies and mouse liver with high-definition imaging we can study transcriptional programs, cellular interactions and signaling pathways during NASH progression and resolution.

TOOLS: We work with human biopsies and mouse models of diabetes, NASH and hepatic fibrosis; isolation and culture of primary cells; analyses of RNA, protein and chromatin; next-generation sequencing including single-cell mRNA sequencing; spatial transcriptomics; histopathology; advanced bioimaging.

Are you interested in our projects, please contact Kim Ravnskjaer:
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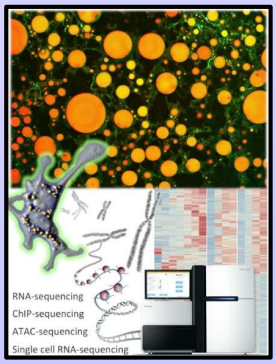
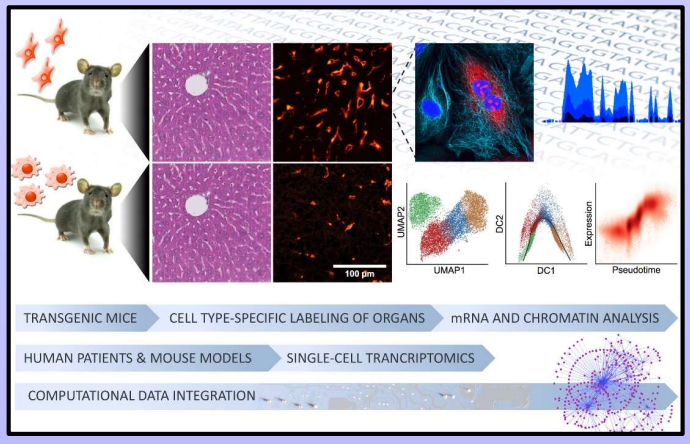
Functional Genomics & Metabolism

ATLAS
CENTER FOR FUNCTIONAL GENOMICS AND TISSUE PLASTICITY





Projects	Description
Single-cell and spatial analyses of cell populations during liver disease development and resolution	Single-cell transcriptomics has reshaped our view and understanding complex biological systems. We use single-cell RNA sequencing to study the development and resolution of NASH in obese human patients as well as mouse models. Through bioinformatics analysis and machine learning algorithms we seek to capture the extensive tissue plasticity of the liver, delineate cellular trajectories of the affected cell populations, and determine the often-transient transcriptional networks driving these cellular transitions. **TOOLS:** Patient biopsies, mouse models of type-2-diabetes and NASH, single-cell transcriptomics, RNA-sequencing, spatial transcriptomics, histopathology, flow cytometry, confocal microscopy, bioinformatics.
Functional analyses of hepatic stellate cells and their precursors in health and disease	Hepatic Stellate Cells (HSCs) are deeply implicated in the development of NASH and liver fibrosis but also play fundamental roles in normal liver function. Generation of new HSCs from stem cells is therefore essential to uphold homeostasis. We use knock-out mice, single-cell transcriptomics, and advanced bioimaging to study HSCs function in the healthy liver, in NASH and during resolution. Focus is on transcriptional regulation of HSC function and G protein-coupled receptor signaling with other liver cell types to identify novel anti-fibrotic drug targets. **TOOLS:** Knock-out mice, cell isolation, single-cell transcriptomics, spatial transcriptomics, RNA-sequencing, ATAC-sequencing, tissue clearing, confocal microscopy, bioinformatics.
Cellular memory in chronic liver disease	Cellular identity, plasticity and memory are central concepts in chronic disease development. In healthy tissues, cells undergo transitions during periods of stress and later revert to their original identity. During prolonged stress and repeated insults, as seen in obesity and NASH, cellular changes may become irreversible. In this project, we study the plasticity and memory of HSCs responsible for liver fibrosis (scaring) in NASH. HSC inactivation is a promising treatment strategy. But do they fully revert, or do they hold epigenetic memory of prior activation? **TOOLS:** Patient biopsies, transgenic mouse lines, single-cell transcriptomics, spatial transcriptomics, ATAC-sequencing, histopathology, confocal microscopy, bioinformatics.