Cardiometabolic Disease Deconstructed

RAVNSKJAER LAB

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Functional Genomics & Metabolism

ATLAS CENTER FOR FUNCTIONAL GENOMICS AND TISSUE PLASTICITY

Main Research Interests

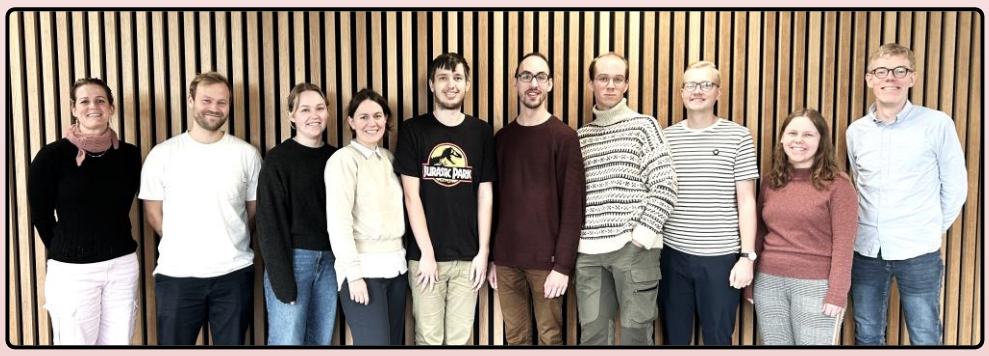
PASSION: In the Ravnskjaer lab we are passionate about micro-vascular function in the liver and other solid organs of our body. We use advanced functional genomics and bioimaging to study molecular changes underlying microvascular dysfunction in the cardiometabolic diseases such as diabetes, chronic kidney and liver diseases, atherosclerosis, aorta aneurysms, and stroke.

IMPORTANCE: Despite weight-loss medicines, cardiometabolic diseases are a growing health care challenge worldwide. A common theme is the early and irreversible deterioration of microvascular functions essential for tissue homeostasis and repair. Microvascular changes affect metabolism, inflammatory status, and crosstalk with other organs. An example is the microvascular breakdown in metabolic dysfunction-associated steatohepatitis (**MASH**), which develops over years and is now the most frequent cause of end-stage liver disease and liver cancer. Hepatocytes are very good at regenerating, but due to proinflammatory and fibrogenic activities of the microvascular cells, functional liver regeneration is extremely ineffective.

CHALLENGE: Microvascular niches are complex and dynamic. They consist of endothelial cells, pericytes, fibroblasts, and local immune cells, which constantly communicate with each other and the surrounding blood and tissue. As such they are highly sensitive to their microenvironment and very difficult to study.

STRATEGY: To overcome this challenge, we apply single-cell and spatial transcriptomics to patient biopsies and advanced mouse models to dissect molecular disease mechanisms one cell at the time. We can hereby study outcomes of signaling pathways and transcriptional networks and validate findings by microscopy and by pharmacological or genetic perturbation in mice.

We combine clinical collaborations with wet-lab studies and computational analysis.



Are you also excited about our projects? Please contact Kim Ravnskjaer

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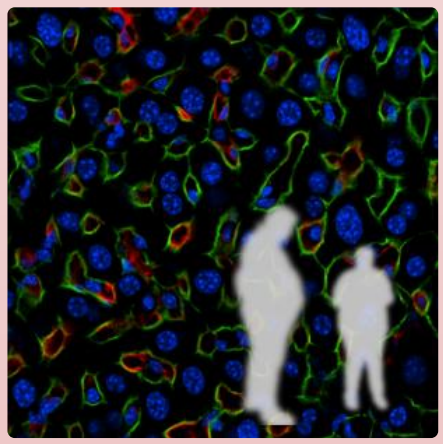
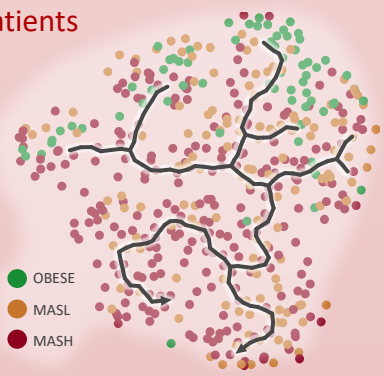
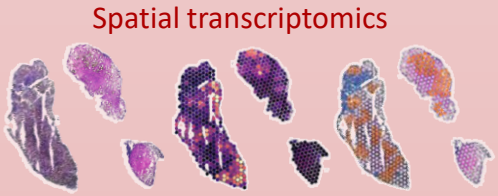
Bioimaging



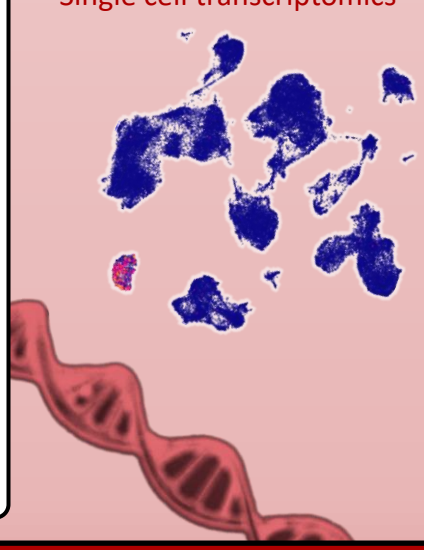
Patients

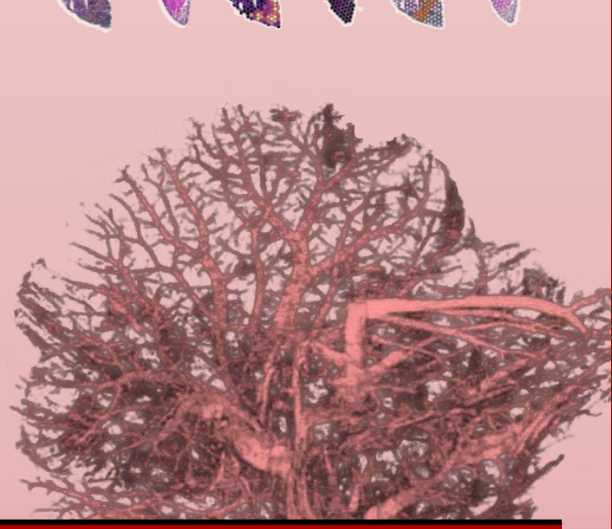


Spatial transcriptomics



Single cell transcriptomics





Project Examples | Description

Project Examples	Description
Single-cell and spatial analyses of cell populations during MASH development and resolution	We use single-cell RNA sequencing and spatial transcriptomics to study the development and resolution of MASH in obese human patients. Through bioinformatics analyses and machine learning algorithms we resolve the profound transcriptional plasticity of liver cells and use this to capture and investigate the often transient cellular interactions that drive progression and regression of disease. **TOOLS:** Patient biopsies, bulk transcriptomics, single-cell transcriptomics, spatial transcriptomics, histopathology, flow cytometry, lightsheet & confocal microscopy, mouse models, bioinformatics.
Microvascular control of tissue perfusion, cellular metabolism, and signal transduction.	Hepatic Stellate Cells are deeply implicated in the development of MASH and liver fibrosis but as micro-vascular pericytes they also play fundamental roles in normal liver function. We study how stellate cells in corporation with microvascular endothelial regulate liver metabolism, responses to signaling, and metabolic gene expression. **TOOLS:** Knockout mice, liver cell isolation, bulk transcriptomics, single-cell transcriptomics, spatial transcriptomics, ELISA, tissue clearing, confocal microscopy, bioinformatics.
Microvascular G-Protein-Coupled Receptor profiling and targeting  Hepatic Stellate Cells	Cellular identity, plasticity and decision-making are important for homeostasis and disease development. In healthy tissues, cells undergo reversible transitions adapting to their environment. These changes become larger and more permanent in disease. G-protein-coupled receptors (GPCRs) is a main way by which microvascular cells in the liver, the heart, and elsewhere sense their environment. The family of GPCRs counts 826 members, and the dynamic expression of most of them across cell types is not known. We use single-cell and spatial transcriptomics to explore the *GPCRome* of the microvasculature in the liver and other organs and try to understand their function. Half of all approved drugs work by targeting GPCRs. The identification of *new* GPCRs associated with tissue health or disease could therefore represent novel ways to treat cardiometabolic diseases. **TOOLS:** Patient biopsies, transgenic mouse lines, single-cell transcriptomics, spatial transcriptomics, histopathology, lightsheet & confocal microscopy, culture of cells and tissue slices, bioinformatics.