Metabolic Disease Deconstructed

RAVNSKJAER LAB

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Functional Genomics & Metabolism

ATLAS CENTER FOR FUNCTIONAL GENOMICS AND TISSUE PLASTICITY

Main Research Interests

YOU ARE AS HEALTHY AS YOUR BLOOD VESSELS

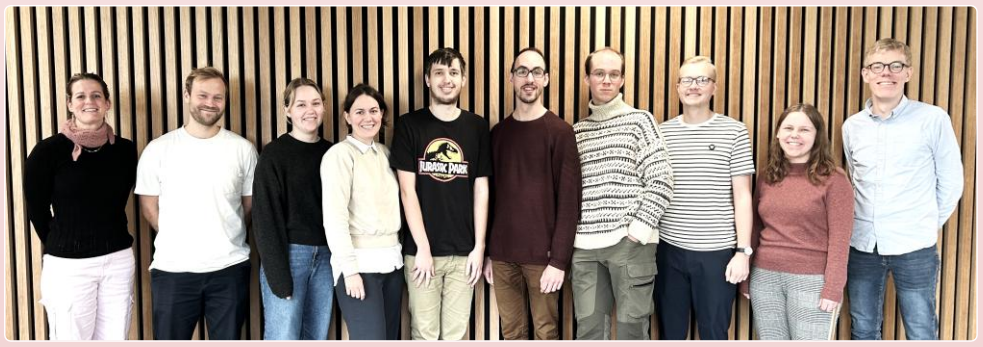
PASSION: In the Ravnskjaer lab we are passionate about micro-vascular function in the liver and other tissues of our body. We use advanced functional genomics and bioimaging to study molecular changes underlying microvascular dysfunction in the cardiometabolic diseases such as diabetes, liver and chronic kidney 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 deterioration of microvascular functions essential for tissue homeostasis and repair. Micro-vascular changes affect metabolism, inflammatory status, and tissue crosstalk across organs. An example is the breakdown of the liver microvasculature in metabolic dysfunction-associated steatohepatitis (**MASH**), which develops over years and is the main cause of end-stage liver disease and liver cancer. Due to proinflammatory and fibrogenic activities of dysfunctional cells in microvasculature, functional liver regeneration is obstructed.

CHALLENGE: Microvascular *niches* are complex and dynamic. They consist of endothelial cells, pericytes, fibroblasts, and local immune cells. These cells constantly communicate with each other and the surrounding tissues and receive signals from the blood and neurons. Deeply fascinating but difficult to study.

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

We combine clinical analyses with experimental studies and computational modelling.



Also excited about our projects? Please talk to Kim Ravnskjaer ⇧

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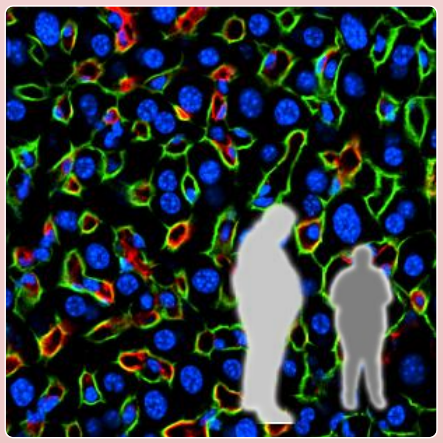
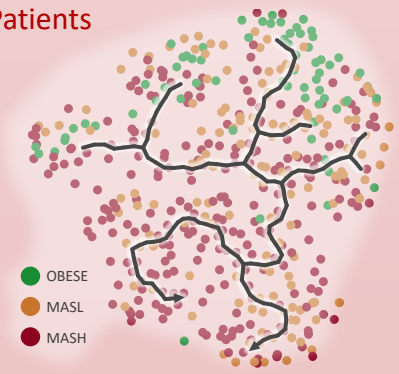
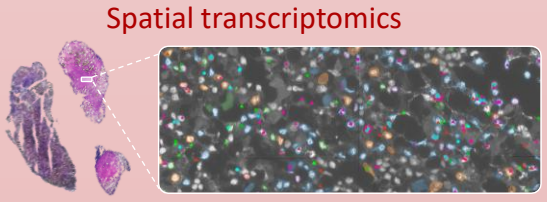
Bioimaging



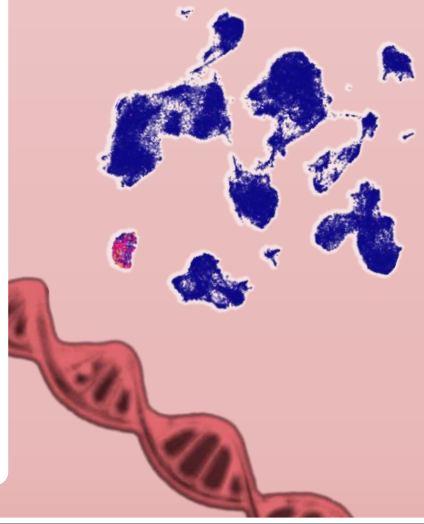
Patients

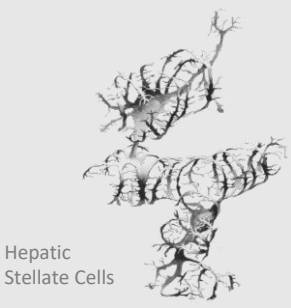


Spatial transcriptomics



Single cell transcriptomics



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 patients. Through bioinformatics analyses and machine learning algorithms we resolve the transcriptional plasticity of liver cells and use this to capture, investigate and target the transient cellular interactions that drive progression and regression of disease. **TOOLS:** Patient biopsies, bulk transcriptomics, single-cell transcriptomics, spatial transcriptomics, histopathology, flow cytometry, light-sheet & confocal microscopy, mouse models, bioinformatics.
Microvascular control of tissue metabolism, signal transduction and gene expression	Hepatic Stellate Cells are deeply implicated in the development of MASH and liver fibrosis but as microvascular pericytes they also play fundamental roles in normal liver function. We study how stellate cells and other pericytes in corporation with endothelial cells regulate metabolism, responses to signaling, and gene expression. **TOOLS:** Knockout mice, CRISPR/Cas9, 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 constant 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 receptors, and the dynamic expression of most of them across cell types is unknown. We use single-cell and spatial transcriptomics to explore the *GPCRome* of the microvasculature in the liver and other organs and try to understand receptor function. GPCRs are good drug targets and half of all approved drugs work by targeting GPCRs. The identification of *new* GPCRs associated with tissue health or disease could therefore enable novel ways to treat cardiometabolic diseases. **TOOLS:** Patient biopsies, transgenic mouse lines, single-cell transcriptomics, spatial transcriptomics, histopathology, light-sheet & confocal microscopy, culture of cells and tissue slices, bioinformatics.