Dynamic chromatin organization and gene transcription controlled by the cellular microenvironment and metabolism

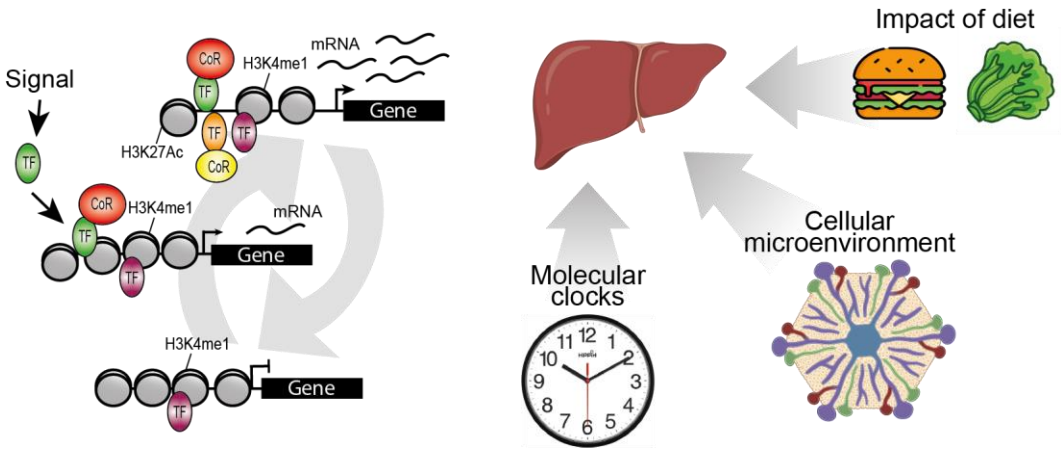
ATLAS
CENTER FOR FUNCTIONAL GENOMICS AND TISSUE PLASTICITY

Forskningsleder Lars Grøntved

Kerneforskningsområder

Many tissues possess striking transcriptional plasticity in response to metabolic changes. This includes response to day/night rhythmic (circadian) reprogramming of metabolism, diet intervention and the cellular microenvironments in the tissues. This ability to adapt to the environment cues is essential for the organism; however adaptation is often linked to pathophysiology of disease such as obesity and diabetes. ***We aim to understand the underlying mechanisms controlling gene expression when cells respond to external cues/signals***.

We are specifically interested in identification of gene regulatory regions (genome-wide) and understand the molecular mechanisms that control their activity. We use ***mouse liver as a model system together with advanced functional genomics technology (e.g. RNAseq, ChIPseq, ATACseq and CRISPR)*** to understand genome-wide chromatin organization and gene transcription in response to various environmental signals.



Examples of biological questions:

a) What mechanisms control feeding regulated gene expression and how are these connected to the circadian rhythm (molecular clocks) of the animal?
b) What gene regulatory networks are dynamically regulated in the diseased liver at single cell resolution?
c) How is hepatocyte gene expression controlled by the cellular microenvironment of the liver?

Er du interesseret i at skrive projekt i gruppen, så kontakt larsgr@bmb.sdu.dk

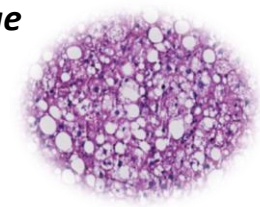
Beskæftigelse af tidligere stud.

Stine Præstholm, Postdoc, Karolinska Institutet, Stockholm
Nicolaj Toft, PhD studerende, SDU
Mathilde Jørgensen, DB Lab, Odense
Dilan Ardik, Pentabase, Odense
Helene Jørgensen, Novo Nordisk, Kalundborg

Teknikker og metoder

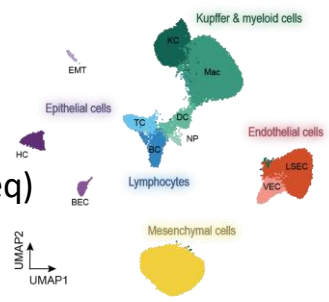
Preclinical disease models and genetic models
- Diet induced fatty liver disease
- CRISPR Cas9 gene disruption
- CRE/LoxP gene disruption
- Primary hepatocyte cell cultures

Evaluate cellular composition of tissue
- H&E staining
- Immunofluorescence



Quantify gene expression
- RT-qPCR, western blotting
- RNAseq and single cell RNAseq

Study chromatin organization
- Chromatin accessibility (ATACseq)
- Single cell ATACseq
- Chromatin IP



Eksempler på projekter

Transcriptional Signaling Networks Regulating Circadian Gene Expression	Hepatic transcriptional oscillation such as circadian rhythm is tightly coupled to the temporal feeding pattern and diet composition. Whereas the diurnal genome-wide changes in hepatic chromatin structure have been studied extensively little is known about dynamic regulation of chromatin accessibility during a circadian rhythm. This project seeks to characterize structural changes to chromatin structure during a circadian rhythm and study the impact of the chromatin remodeling complex SWI/SNF. We use a genetic mouse model to disrupt SWI/SNF function in hepatocytes and genomics technology such as ATACseq and ChIPseq to understand impact on chromatin accessibility at specific regions of the genome.
Identification of Novel Mechanisms Controlling Gene Expression in the Different Cell Types of the Liver	The liver is composed of many different cell types including hepatocytes, kupffer cells, stellate cells, endothelial cells, cholangiocytes and various immune cells. This projects seeks to understand molecular mechanisms controlling differential gene expression in these individual cell populations as a result of acute feeding and in the progression and regression of NAFLD. We use single nuclei RNAseq and ATACseq to uncover gene regulatory networks at single cell resolution, which can be used to reveal signaling crosstalk between the different cell types of the liver. CRISPR Cas9 gene disruption is used to functionally evaluate how specific transcription factors control hepatocyte function in the healthy and disease liver.