SYSTEMS BIOLOGY APPROACH TO IDENTIFY PROCESSES AND EARLY MARKERS FOR FIBROSIS IN HIGH FAT DIET-INDUCED NASH IN MICE

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Background

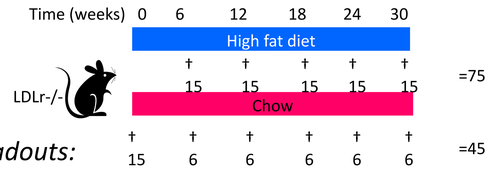
The LDLr-/-.Leiden mouse is a translational, diet-induced model for non-alcoholic steatohepatitis (NASH) with associated fibrosis, displaying many clinically relevant features of NASH. Our goal is to identify processes and pathways involved in the onset and progression of NASH and fibrosis over time with specific emphasis on early detection of fibrosis. After identification of these processes, we aim to study whether these processes can be modulated by pharmacological interventions.

Aim

- Generate insight in the main processes involved in NASH and fibrosis in a time resolved manner
- Define a molecular signature for early detection of liver fibrosis
- Study the effect of interventions on NASH and fibrosis and molecular signature

Methods

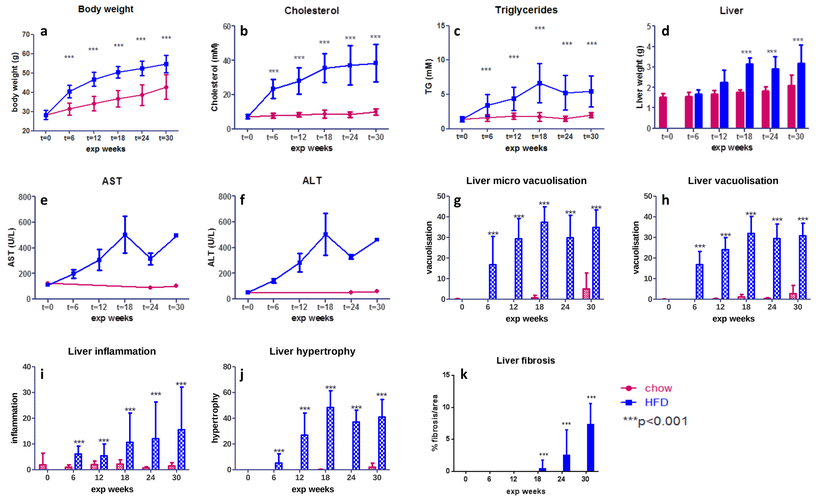
Experiment 1:



Readouts:
Plasma: cholesterol, triglycerides
Liver: AST, ALT
Histopathology: NASH score: vacuolation, inflammation, hypertrophy and fibrosis.

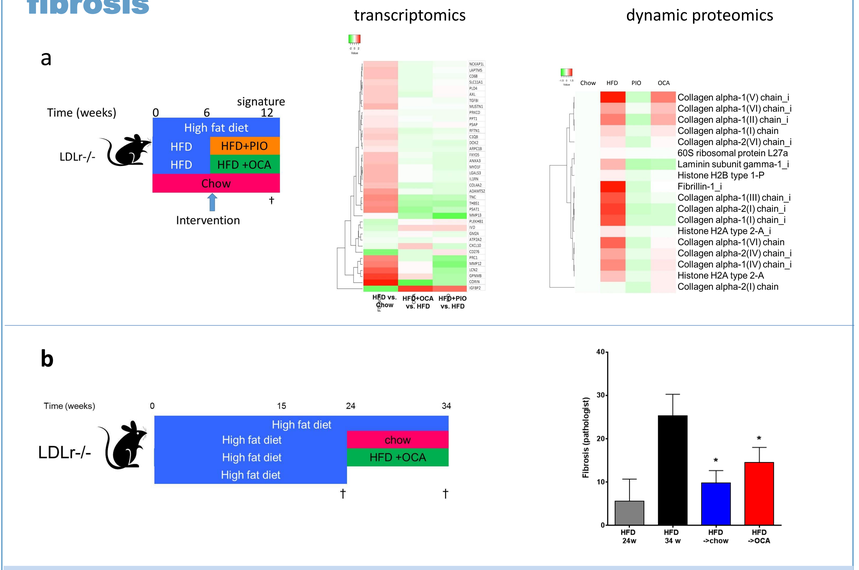
Experiment 2:
HFD was supplemented with obeticholic acid (OCA; 30 mg/kg/day) or pioglitazone (PIO; 10 mg/kg/day) for 6 weeks.

High fat diet induced NASH



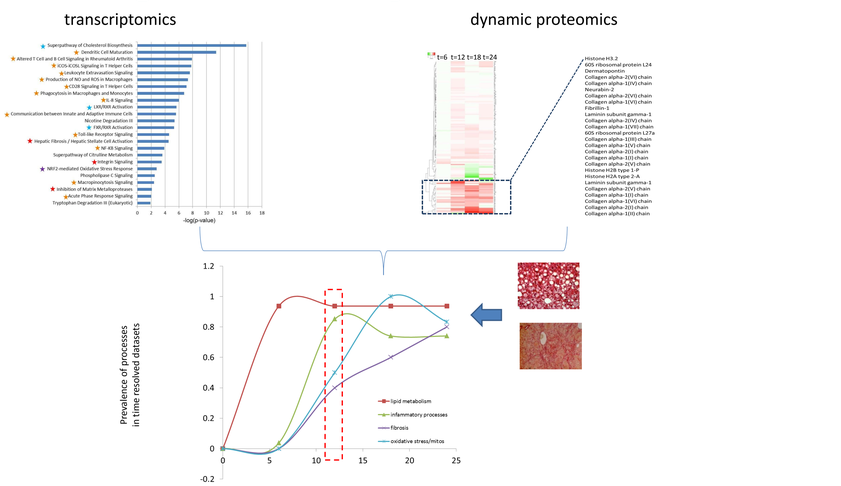
High fat feeding resulted in development of obesity (a), increased plasma cholesterol (b) and triglycerides (c). Liver weight (d), AST (e) and ALT (f) stabilized after week 18. Histopathological scoring revealed increase in micro (g) and macro (h) vacuolation, inflammation (i), cellular hypertrophy (j) and fibrosis (k). Data are means ± SD.

Effect of interventions on early signature and fibrosis



Intervention by both PIO and OCA changed expression of transcriptomics and dynamic proteomics of the early predictive liver fibrosis signature (a). On long term OCA was able to reduce induction of fibrosis (b) by affecting expression of the genes from the early predictive liver fibrosis signature (data not shown).

Molecular signature for early detection of liver fibrosis



Data integration of Tx and dynamic proteomics revealed matrix-related processes. Time-resolved visualisation of processes involved in NASH and fibrosis showed that fibrotic processes can be detected on molecular level already at 12 weeks preceding histological detection.

Conclusions

- We identified processes which contribute to the development of NASH/fibrosis in a time-resolved manner.
- We identified a liver specific molecular signature representing the onset of fibrosis several weeks preceding histological detection.
- Pharmacological interventions were able to modulate this early fibrosis molecular signature and reduced induction of fibrosis.
- These results will help to identify biomarkers for onset of fibrosis and shorten the time frame of (pre)clinical experiments.

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