APPLICATION OF HUMAN NASH-BASED TRANSCRIPTOME AND METABOLOME PROFILES IN PRECLINICAL MODELS

TRANSLATIONAL STUDY OF DRUG EFFECTS ON LIVER FIBROSIS

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NASH patients are characterized by complex metabolic disturbances in liver
- chronic inflammation drives disease progression towards fibrosis

Recent studies have comprehensively profiled these metabolic and inflammatory disturbances
- Liver transcriptomics
- Serum metabolomics

Identified molecular patterns:
- That characterize NASH patients
- That can differentiate between mild and severe pathology

**INTRODUCTION**


Gene profile that associates with severe NASH
Concerns whether preclinical models sufficiently mimic molecular disease processes of patients

translational value in studies of therapeutic interventions for NASH/fibrosis?

Aim of this study:

Representation of human-based disease profiles in Ldlr-/-Leiden mice

Obeticholic acid (OCA) as prototype intervention

Comparison of Gene Expression Patterns Between Mouse Models of Nonalcoholic Fatty Liver Disease and Liver Tissues From Patients

Aim of this study:

Representation of human-based disease profiles in Ldlr-/-Leiden mice

Obeticholic acid (OCA) as prototype intervention
LDLR-/- . LEIDEN MICE

▶ Energy-dense high-fat diet (HFD) without added cholesterol

▶ **Phenotypical** and **histopathological** characteristics of NASH patients
  ◀ Obesity, insulin resistance, hyperlipidaemia
  ◀ Macro- and micro-vesicular steatosis, lobular inflammation, and pronounced fibrosis

Do they also recapitulate molecular disease signatures observed in patients?
STUDY OUTLINE

Ldlr-/-Leiden

0w 24w 34w

HFD

HFD

HFD + OCA

NASH + Early fibrosis

NASH + Fibrosis

Serum Mx Liver Tx

Serum Mx Liver Tx

NASH fibrosis
HUMAN NASH SIGNATURES RECAPITULATED IN LDLR-/-LEIDEN MOUSE

Serum metabolome

Liver transcriptome

Non-Ldlr-/-Leiden subtype  Ldlr-/-Leiden subtype

Ldlr-/-Leiden metabolome reflected in substantial proportion of NAFLD/NASH patients

(human cohort described in Alonso et al. Gastroenterology 2016)

Gene profile that characterizes NASH patients

(human dataset described in Teufel et al. Gastroenterology 2016)

Gene profile that distinguishes between mild and severe NASH patients

(gene-set described by Moylan et al. Hepatology 2014)
OCA ATTENUATES PROGRESSION OF LIVER FIBROSIS

Effect on *de novo* collagen formation?

- Incorporation of deuterium from heavy water ($^{2}$H$_{2}$O) into newly synthesized collagen
- Measures collagen newly synthesized during labeling period (14 days)

**Data are mean ± SD**
OCA REDUCED COLLAGEN AREA AND RETICULATION

Multi-photon imaging and Second harmonic generation imaging

- diameter of collagen fibrils: effect on thin or aggregated fibers?
- Reticulation of collagen fibers: complexity/cross-linkage of collagen network

Data are mean ± SD

THIN FIBRES

AGGREGATED FIBRES
OCA COUNTER-REGULATES HUMAN-BASED OMICS SIGNATURES

Serum metabolome

OCA reversed HFD-induced alterations in metabolome

Liver transcriptome

Gene profile that characterizes NASH patients

(human dataset described in Teufel et al. Gastroenterology 2016)

Gene profile that distinguishes between mild and severe NASH patients

(gene-set described by Moylan et al. Hepatology 2014)
Ldlr-/- Leiden mice recapitulate specific molecular metabolomics and transcriptomics signatures of NASH patients.

Intervention with OCA in developing fibrosis counter-regulates the effects of HFD and normalizes transcriptomics and metabolomics profiles.

OCA reduces collagen deposition and de novo synthesis but does not resolve already manifest fibrosis in the period studied (10 weeks).

Human molecular signatures may be used to estimate the translational value of preclinical models for NASH.
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