APPLICATION OF HUMAN NASH-BASED TRANSCRIPTOME AND METABOLOME PROFILES IN PRECLINICAL MODELS FOR THE TRANSLATIONAL STUDY OF DRUG EFFECTS ON LIVER FIBROSIS

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BACKGROUND

› Recent human studies have identified molecular patterns (metabolomics, transcriptomics) that characterize NASH patients and differentiate between mild and severe pathology.

› Concerns have been raised whether preclinical models sufficiently mimic these molecular disease profiles, bringing into question their translational value in studies of therapeutic interventions in the process of NASH/fibrosis.

› Here, we applied these molecular patterns derived from human NASH in an experimental disease model, to improve the translational value of pre-clinical efficacy studies.

HUMAN NASH-BASED MOLECULAR PROFILES REFLECTED IN HFD-FED LDLR-/-Leiden Mice

Ldlr-/-Leiden serum metabolomic profile was reflected in substantial proportion of NAFLD patients (Human Metabolomics data are described in Alonso et al. Gastroenterology 2017)

Ldlr-/-Leiden mice displayed a hepatic expression profile that differentiates NASH patients from healthy controls (Human gene expression data described in Teufel et al. Gastroenterology 2017, NCBI GEO accession GSE44942)

10-WEEK OCA INTERVENTION ATTENUATES PROGRESSION OF NASH AND LIVER FIBROSIS

OCA reduced steatosis

OCA reduced inflammation

METHODS

› Human NASH-based transcriptomics and metabolomics profiles were compared to corresponding profiles from high-fat-diet (HFD) treated LDLr-/-Leiden mice, a preclinical model with translational characteristics.

› Mice were profiled at the stage of mild (24 weeks HFD) and severe (34 weeks HFD) fibrosis, as well as after OCA intervention to attenuate or resolve fibrosis (treatment from 24 to 34 weeks of HFD; 10 mg/kg).

› Effects of OCA were analyzed histologically, biochemically, by IHC, deuterated water technology (for de novo collagen formation) and the human-based profiles.

OCA TREATMENT NORMALIZES METABOLIC AND INFLAMMATORY GENE EXPRESSION

Treatment with OCA had pronounced anti-inflammatory effects on specific pathways and metabolic regulators, together constituting a balanced therapeutic approach

OCA NORMALIZES METABOLICOMICS AND TRANSCRIPTOMICS SIGNATURES THAT ARE CHARACTERISTIC FOR NASH PATIENTS

CONCLUSIONS

› Ldlr-/-Leiden mice recapitulate specific molecular metabolomics and transcriptomics signatures of NASH patients, which substantiates the translational value of this model.

› Intervention with OCA in developing fibrosis counter-regulates the effects of HFD and normalizes human-based molecular profiles.

› OCA reduces collagen deposition and reticulization 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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