A comparison of histological and transcriptional markers of non-alcoholic steatohepatitis (NASH) in man and mouse

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INTRODUCTION AND AIM

Animal models of non-alcoholic steatohepatitis (NASH) are important tools in preclinical drug discovery and biomarker research. One of such models is the Gubra Amfy NASH (GAN) diet-induced obese (DIO) and biopsy-confirmed mouse [1]. Our aim was to compare the histopathological and transcriptional profile in liver biopsies from NASH and lean mice with NASH patients and lean individuals.

METHODS

Liver biopsies were obtained from patients with histology-proven NASH (n=16; BMI=33.9±6.2 kg/m2) and healthy lean individuals (n=14; BMI=23.1±1.6 kg/m2). Mouse liver biopsies were obtained from C57BL/6 mice fed the GAN diet (40 kcal% fat, 22% fructose, 10% sucrose, 2% cholesterol; DO1100310, Research Diets) for 38 weeks and chow-fed lean control mice. Histopathological assessment of NASH-Lipid Activity Score and Fibrosis Stage was compared between human and mouse cohorts, and quantitative histological analyses were performed for assessment of steatosis (H&E staining), inflammation (galectin-3 immunohistochemistry) and fibrosis (Pico-Sirius red staining). Liver transcription analysis was performed by next generation RNA sequencing.

RESULTS

Comparative histopathological hallmarks

Figure 4 | Top panel | Comparison of histopathological hallmarks in representative liver biopsy sample from NASH patient (top panels) and GAN DIO-NASH mouse (lower panels). Arrows indicate inflammatory foci and ballooning hepatocytes, respectively.

Corresponding disease-associated gene expression profiles

Figure 5 | Histomorphometric assessment of steatosis, inflammation and fibrosis in human and GAN DIO-NASH mouse liver biopsies. *p<0.05, **p<0.01, ***p<0.001 vs. corresponding control group.

Conclusions

- A head-to-head comparison of NASH patients and the GAN-DIO NASH mouse demonstrated good clinical transiliability with respect to the physiological and histopathological aspects of fibrosing NASH.
- The GAN-DIO NASH mouse was in concordance with the liver transcriptome signature of human disease.
- Hence, these findings highlight the GAN-DIO NASH mouse model as relevant model for human NASH suitable for identifying therapeutic targets and characterizing novel drug therapies for NASH.

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