COMPARISON OF HEPATIC PATHOLOGY SIGNATURE IN RODENT MODELS OF NAFLD TO THAT OBSERVED IN HUMAN NASH PATIENTS WITH MODERATE-TO-SEVERE DISEASE

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the number one cause of chronic liver disease in the Western world, with more than one-third of the population affected [1]. Although usually benign, fatty liver may result in serious injury with inflammation and hepatocellular death. Ablated non-alcoholic steephepatitis (NASH), which may progress to fibrosis and cirrhosis and lead to hepatocellular carcinoma [2], currently has no approved therapy for NASH.

Academic research and drug discovery dedicated to NASH treatment have a need for models that represent human pathology and especially the severe forms of the disease. The histological signature of human NASH is well characterized using a systematic transcriptomic analysis [3–4]. These studies revealed that a profile of 200 NASH-like rodent models were also used in this study to put the signature of the advanced disease in perspective.

AIM

This study aimed to identify a transgenic signature of NASH patients with moderate-to-severe disease.

STUDY DESIGN

Transcriptomic signature of pathological liver tissue, as compared to healthy liver tissue, was established in human samples, for 3 different NAFL models and for 3 different NASH models.

CHARACTERIZATION OF THE HUMAN NASH DATASET

A list of 20 functional hyperpathways identified by metascape approach in the human moderate-to-severe NASH dataset.

CHARACTERIZATION OF THE TRANSCRIPTOMIC DATASETS IN ROdent MODEls

A list of 20 functional hyperpathways identified in moderate-to-severe NASH patients (NAS≥5 & fibrosis ≥1) with that of moderate-to-severe NASH patients with NAS≤4 and (ii) patients with NAS ≥ 5 and no histological fibrosis were compared to healthy liver tissue. The pathways that were not well clustered in the human NASH dataset or those that did not significantly overlap were also used for this analysis.

CONCORDANCE BETWEEN THE PATHWAYS IN SIGNATURES OF HUMAN NAFLD AND RODENT NASH MODELS

The Concordead pathway analysis identified 3 major pathways that were significantly enriched across all NASH models with higher and lower significance than the human NASH dataset.

REFERENCES