VALIDATION OF NASH TRANSLATIONAL MODELS

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Non-alcoholic fatty liver disease (NAFLD) is a chronic, progressive liver disease. The onset of the disease is highly associated with obesity, insulin resistance and dyslipidemia. Without intervention, the disease can progress to non-alcoholic steatohepatitis (NASH), and via fibrosis and cirrhosis, to end-stage liver disease and hepatocellular carcinoma (HCC). New technologies and more research efforts are needed to develop crucial stage-specific diagnosis, effective treatment decisions and translational models.
In this study, we used GENEVESTIGATOR® for NASH mouse model characterization and biomarker validation. GENEVESTIGATOR® is an analysis tool and database, containing high quality curated gene expression data. It allows the user to mine the data of thousands of experiments simultaneously, to identify genes having a very specific profile or indications associated with the transcriptional activity of selected genes.

INTRODUCTION

The increasing incidence of NAFLD worldwide and extensive efforts to elucidate its pathogenesis have led to an increased development of dietary animal models. Despite the strong effect of dietary habits on NAFLD development, no diet-based animal model of NAFLD fully captures the complex nature of metabolic and histological features of the disease. The selection of an ideal animal model is a crucial step for translational research in NAFLD and NASH. Novel -omics approaches may therefore help identifying models optimal for disease investigation or for drug discovery and validation.

RESULTS AND DISCUSSION

Gene regulation in diet-dependent NASH mouse models

We used a transcriptomic approach to define differences between two main dietary mouse models of NAFLD/NASH fed a high-cholesterol diet (MM-00464, GSE51432) and a methionine- and choline-deficient (MCD) diet (MM-00463, GSE35961). To avoid mouse strain bias, experiments using animals with a similar genetic background were selected (C57BL6/C57BL6J). The effect of diet composition on liver gene expression was investigated using the Gene Search tools of GENEVESTIGATOR® (Hruz et al., 2008). The results showed that mice fed a high cholesterol diet differ in liver gene expression from mice fed MCD (Figure 1A). 25 down-regulated and 25 up-regulated genes were selected for further analysis in the Signature tool of GENEVESTIGATOR® to identify other correlated studies. A similar gene expression pattern could be identified in several diet studies and NASH

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mouse model studies accross different transcriptomic technology platforms (Figure 1B and 1C). This confirms the importance of characterizing animal models for NASH research and verifying the translatability of findings.

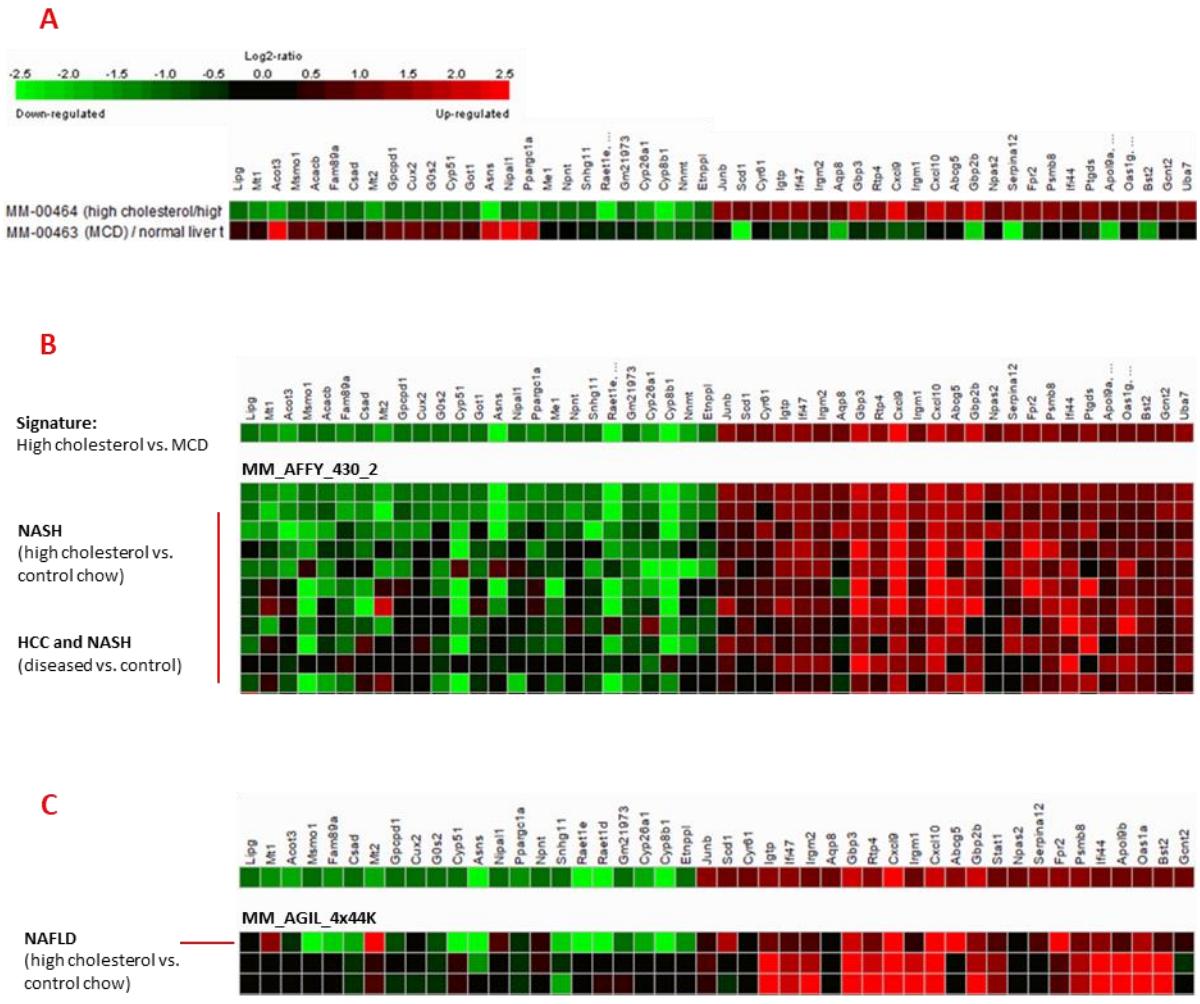

Fig1: The effect of diet composition on liver gene expression in dietary NASH mouse models. **A**: Gene regulation upon high cholesterol, and methionine- choline deficient diet (MCD) was assessed using the Gene Search tool for Perturbations in GENEVESTIGATOR®. **B:** Perturbations giving expression results most similar with the high cholesterol vs. MCD gene signature. **C:** The specifity of the signature was confirmed on the MM_AGIL_4x44K platform, identifying high cholesterol diet induced NAFLD as the most correlated perturbation.

Biomarker validation: 2-gene plot over multiple samples collections

When studying biomarkers, the validation of co-localization and co-expression provides valuable insights. By choosing two genes from the high cholesterol diet vs. MCD signature, a clear distinction between these models can be confirmed (Figure 2).

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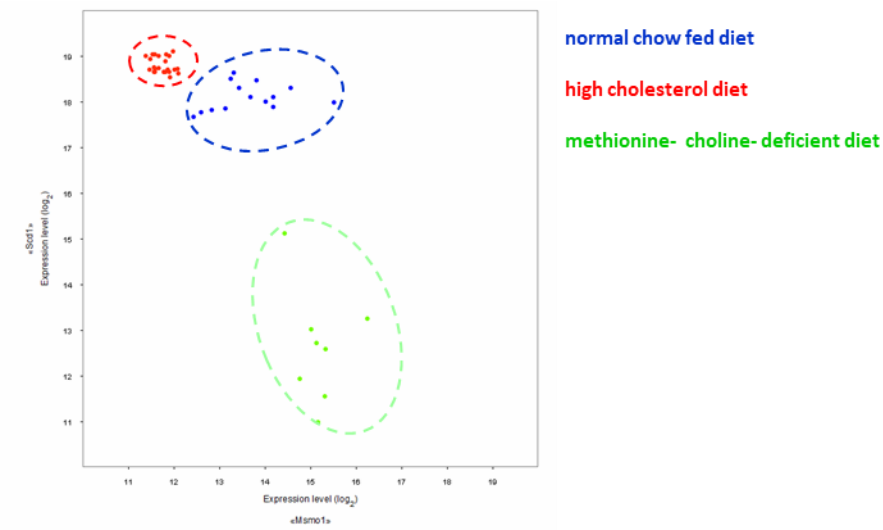

Fig2: The 2-Gene Plot tool in GENEVESTIGATOR® was used to plot the expression of mouse genes Scd1 and Msmo1, highlighting the sample separation of induced NASH by high cholesterol and methionine- and choline-deficient high fat diet.

Smart integrated systems with high quality curated data empower scientists to perform compendium-wide searches and analyses, advancing their research and accelerating novel scientific discoveries. The described case study shows how GENEVESTIGATOR® effectively takes advantage of the world's high-quality expression data to help identifying new biomarkers and characterize expression patterns across diseases.

SELECTED DATA AND SETTINGS FOR GENEVESTIGATOR®

Gene Search *Perturbations* tool: Data selection: MM-00463, MM-00464 Settings: Min. target |Log ratio|: 1
Signature tool: Data selection: MM_AFFY_430_2 (full platform), MM_AGIL_4x44K (full platform)
2-Gene Plot: Data selection: MM-00463, MM-00464, MM-01162 Gene selection: Scd1, Msmo1

REFERENCES

Hruz T, Laule O, Szabo G, Wessendorp F, Bleuler S, Oertle L, Widmayer P, Gruissem W and P Zimmermann (2008) **Genevestigator V3: a reference expression database for the meta-analysis of transcriptomes.** Advances in Bioinformatics 2008, 420747 [Full Text]

CONTACT INFORMATION

For any questions or to learn more about GENEVESTIGATOR®, please write to info@nebion.com or visit genevestigator.com.

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