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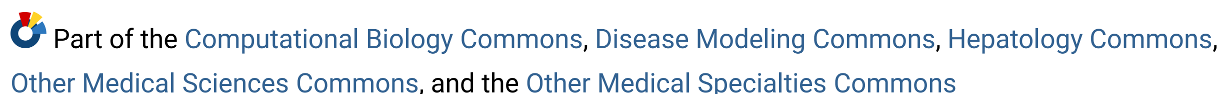
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Patient-Specific Genome-Scale Metabolic Models for Individualized Predictions of Liver Disease*

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Abstract: The prevalence of liver disease is steadily increasing, coupled with the limited availability of therapeutic treatments. Recent literature points to metabolic reprogramming as a key feature of liver failure. Hence, we sought to uncover the metabolic pathways and mechanisms associated with liver disease and acute liver failure. We generated patient-specific genome scale metabolic models by integrating RNA-seq data from patient liver samples with a generalized human metabolic model. Flux balance analysis simulations showed a distinct separation of non-alcohol associated and alcohol-associated disease states. Our analysis suggests that the alcohol associated liver has an increased flux through nucleotide and glycerophospholipid metabolic pathways. By contrast, non-alcohol associated liver has an increased flux through fatty acid oxidation, the carnitine shuttle, and bile acid recycling pathways. Importantly, there was significant variation of metabolic fluxes between patients within the same clinical category of disease stage, pointing to the necessity and opportunity for personalized medicine in treating liver disease. We conclude that the metabolic reprogramming occurring in alcohol-associated liver disease is likely distinct from the adaptations in non-alcohol associated liver disease, potentially requiring alternative therapeutic approaches.

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Keywords: liver disease, genome scale metabolic modeling, RNA-seq, flux balance analysis

1. INTRODUCTION

Alcohol and non-alcohol associated liver failure is a major public health concern with very limited therapeutic approaches. Emerging translational research is pointing towards metabolic reprogramming in liver disease as a key feature of acute on chronic liver failure (Argemi et al., 2019). Genome scale metabolic models have started to inform us of the mechanisms associated with such metabolic reprogramming events in the context of liver and cancer. In the present study, we seek to bring the technologies and methods of genome-scale metabolic modeling to analyze the metabolic adaptations underlying the liver disease and failure.

2. MATERIALS AND METHODS

2.1 Sample Acquisition

Bulk transcriptomic data was obtained from a recent study (Argemi et al., 2019). The dataset consists of RNA-seq analysis of 89 liver tissue samples from patients with the following disease states: explant alcoholic hepatitis (AH, N = 10 patients), severe AH (N = 18), non-severe AH (N = 11), early alcoholic steatohepatitis (ASH, N = 12), healthy control (N = 10), compensated cirrhosis (N = 9), hepatitis C virus (HCV, N = 10), and non-alcoholic steatohepatitis (NASH, N = 9).

2.2 Constructing genome scale metabolic models

Disease-specific metabolic models were constructed by integrating the bulk RNA-seq data with a generalized human genome scale metabolic model (Human1 GEM) using the tINIT algorithm (Robinson et al., 2020; Agren et al., 2012). Briefly, the algorithm determines if a reaction and its associated metabolites are to be included in the model for a specific sample by analyzing the respective gene rule for each reaction. Each gene rule contains one or more genes separated by AND or OR. AND denotes a reaction metabolized by a complex enzyme whereas OR denotes a reaction metabolized by isozymes. Each reaction and its associated metabolites are included in the model only if the corresponding reaction score reaches the specified tINIT threshold of 1.

2.3 Flux Balance Analysis

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Flux balance analysis was performed by first finding a suitable objective function using the SPOT algorithm, which maximizes the correlation between the flux vector and gene expression data, and then minimizing the solution space using the Eflux2 algorithm (Kim et al., 2016). We compared the distribution of the model-predicted reaction fluxes across the spectrum of ALD disease states to determine differential metabolic activity between each patient of the same disease state as well as across patients with differing disease states (Fig. 1).

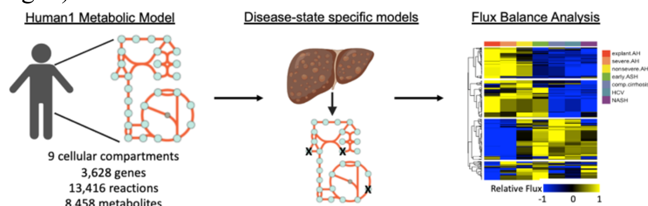

Fig. 1. Workflow for the construction of disease-specific genome scale metabolic models and downstream flux balance analysis.

3. RESULTS

We developed individualized genome scale metabolic models to analyse the metabolic reprogramming events occurring at various stages of liver disease progression. Dimensionality reduction-based analysis suggests distinct grouping when using transcriptomic data versus the model-predicted metabolic flux data (Fig. 2).

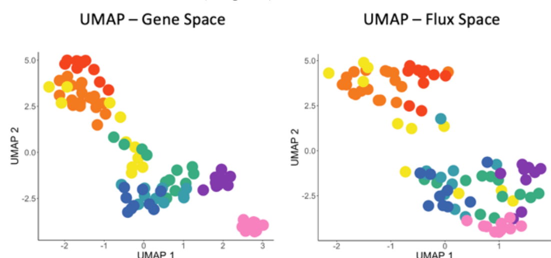

Fig. 2. Distribution of individual patient liver samples coloured by disease state using only transcriptomic data (Gene Space) vs. only predicted flux values (Flux Space).

Our model-based analysis indicates that several metabolic pathways including sphingolipid metabolism, oxidative phosphorylation, fatty acid oxidation, the carnitine shuttle, etc. show significant flux differences between patients within the same diagnosed liver disease state as well as in comparison to other liver disease states and healthy control livers (Fig. 3). Specifically, alcohol associated and non-alcohol associated liver showed differing patterns of metabolic fluxes. While the alcohol associated liver showed an increase in flux through reactions in nucleotide and glycerophospholipid metabolic pathways, non-alcohol associated liver showed increased flux through fatty acid oxidation, the carnitine shuttle, and bile acid recycling pathways (Fig. 4). Hierarchical clustering of samples indicated a high degree of variation in model-predicted metabolic fluxes between patients within same clinical category of liver disease state. Despite this level of variation, most non-alcohol associated, alcohol associated, and healthy livers clustered together in respective groups.

4. CONCLUSIONS

Our integrative transcriptomic and metabolic modelling results have highlighted multiple metabolic pathways and their stage-specific differential activity in liver disease. These results support novel opportunities for therapeutic studies, such as through in silico clinical trials to alleviate or reverse the liver disease characteristics. We illustrate the utility of genome scale metabolic flux-based analysis to provide an alternative window into the liver disease state to complement the conventional differential gene expression analysis.

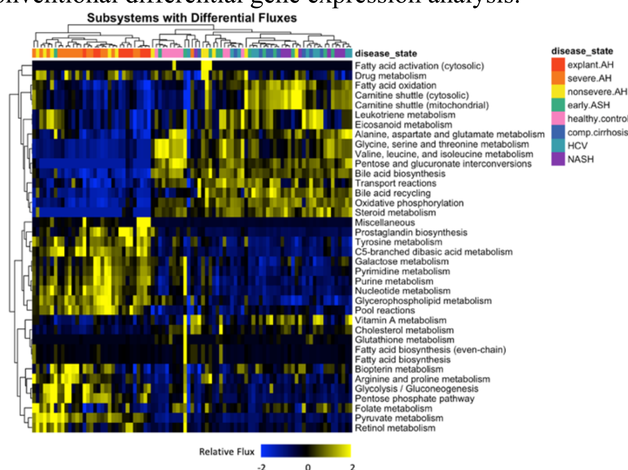

Fig. 3. Heatmap showing metabolic subsystems with significant differences across disease states as computed by the Kruskal Wallis test ($p < 0.05$). Samples (columns) and relative fluxes (rows) are hierarchically clustered to show variation across patients and subsystems.

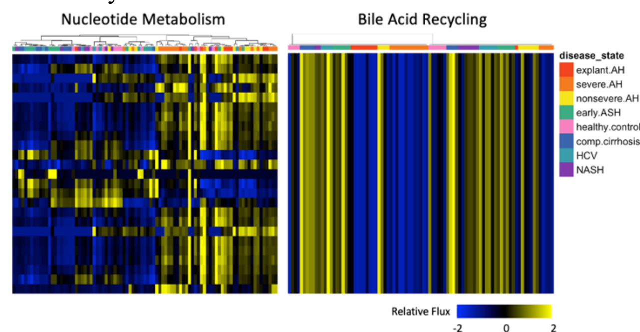

Fig. 4. Heatmaps showing fluxes for reactions within the nucleotide metabolism and bile acid recycling pathways.

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