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Systems-level organization of non-alcoholic fatty liver disease progression network

K. Shubham, L. Vinay and P.K. Vinod*

Centre for Computational Natural Sciences and Bioinformatics, International Institute of Information Technology, Hyderabad 500032, INDIA

Presenting author: shubham.kumar@research.iiit.ac.in

Abstract

Non-Alcoholic Fatty Liver Disease (NAFLD) is a hepatic metabolic disorder that is commonly associated with sedentary lifestyle and high fat diets. NAFLD is prevalent in individuals with obesity, insulin resistance and Type 2 Diabetes (T2D). The clinical spectrum of NAFLD ranges from simple steatosis to Non-Alcoholic Steatohepatitis (NASH) with fibrosis, which can progress to cirrhosis and hepatocellular carcinoma. The pathogenesis of NAFLD is complex, involving crosstalk between multiple organs, cell-types, and environmental and genetic factors. Dysfunction of White Adipose Tissue (WAT) plays a central role in the development of NAFLD and other metabolic disorders. WAT is an active endocrine organ that regulates whole-body energy homeostasis, lipid metabolism, insulin sensitivity and food intake by secreting biologically active molecules (lipokines, adipokines and cytokines). WAT dynamically reacts to nutrient excess or deprivation by remodelling the number (called hyperplasia) and/or size (called hypertrophy) of adipocytes to store fat or supply nutrients to other tissues by lipolysis, respectively. Adipose tissue remodelling is also accompanied by changes in the composition or function of stromal vascular cells and ECM. The major objective of our study was to identify and characterize the metabolic and signaling modules associated with the progression of NAFLD in the VAT. We performed Weighted Gene Co-expression Network Analysis (WGCNA) to organize microarray data obtained from the VAT of patients at different stages of NAFLD into functional modules. In order to obtain insights into the metabolism and its regulation at the genome scale, a co-expression network of metabolic genes in the Human Metabolic Network (HMR2) was constructed and compared with the co-expression network constructed based on all the varying genes. We also used the prior network information on adipocyte metabolism (GEM) to verify and extract reporter metabolites. Our analysis revealed the coordination of metabolism and inflammation in NAFLD patients. We found that genes of arachidonic acid, sphingolipid and glycosphingolipid metabolism were upregulated and co-expressed with genes of proinflammatory signaling pathways and hypoxia in NASH/NASH with fibrosis. These metabolic alterations might play a role in sustaining VAT inflammation. Further, the inflammation related genes were also co-expressed with genes involved in the ECM degradation. We interlink these cellular processes to obtain a systems-level understanding of NAFLD.

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