Transcriptomic Alterations in an in vitro Model of Nonalcoholic Fatty Liver Disease

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Non-alcoholic fatty liver disease (NAFLD), has become a major health problem worldwide and is predicted to become the leading cause of liver transplantation in the United States. In vitro models that accurately recapitulate NAFLD pathogenesis have been used for preclinical drug development and testing; however, there is a great need for efficient and reliable "human" in vitro models to study the development of NAFLD and identification of molecular targets for the treatment and prevention of NAFLD. Thus, the goal of the project was to establish an in vitro model to study the molecular mechanisms of NAFL development using primary human hepatocytes (PHH) mono- and nonparenchymal cells (NPCs) co-culture model to identify potential biomarkers and molecular targets for therapy. Both PHH and PHH-NPCs treated with free fatty acid (FFA) showed significant increases in intracellular lipid accumulation. In PHH-NPC co-culture model treated with FFA and verbascoside (VB), a herbal hepatoprotectant, lipid accumulation notably decreased. Pathway enrichment analysis of the differentially expressed genes in PHH and PHH-NPC cells treated with VB, FFAs, and FFA/VB combination for 7 days revealed extensive changes in NAFL-specific pathways, such as synthesis of D-glucose, proliferation of liver cells, quantity and synthesis of carbohydrates, fatty acid metabolism, and cell death of hepatocytes. The results of this study demonstrate that both PHH mono-culture and PHH-NPC co-culture models treated with FFAs were able to recapitulate NAFL-specific alterations similar to human NAFLD, and PHH-NPC co-culture model presents an useful tool to identify potential molecular targets, develop mechanism-based drug candidates, and test their efficiency for NAFLD treatment in preclinical settings.

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