Liver-Chip: A Model for Understanding Diet-Induced Liver Disease and Drug Efficacy Assessment

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Abstract

Background and Aim: Nonalcoholic fatty liver disease (NAFLD) is a progressive condition initially characterized by increased lipid accumulation in the liver (steatosis) and can develop into nonalcoholic steatohepatitis (NASH). There is an unmet need for a human-relevant in vitro model to enable successful development of therapies. Methods: To address this unmet need, we utilized our human Liver-Chip, which retains key characteristics of native liver function over long-term cultures. To induce steatosis, chips were treated with saturated fatty acids (palmitate) or unsaturated fatty acids (stearate), alone or in combination. TGF-beta was used as a positive control for hepatocellular injury and stellate cell activation. To assess therapeutic efficacy against steatosis, chips were treated for two days after initiating steatosis (therapeutic), or co-treated (prophylactic) with a liver-targeted analogue of fibrostatin, a known inhibitor of αvβ3 integrin (ACC)-I. Morphological evaluation of the hepatocytes and adipocytes was carried out to evaluate steatosis. Quantification of triglycerides released in the media was used to evaluate lipid removal, and alpha-SMA staining was used to assess stellate cell activation. Results: We demonstrated induction of steatosis in hepatocytes in a concentration-dependent manner following continuous exposure to palmitate, or in combination, with a fourfold decrease in fatty acids as well as levels of triglycerides released in a relevant human in vivo model. Administration of TGF-beta resulted in increased stellate cell activation, hepatocellular injury, and lipid accumulation compared to the vehicle controls. Chips treated with the ACC-I demonstrated a concentration-dependent reduction in lipid accumulation in both the therapeutic and prophylactic paradigms when compared to steatosis-induced controls. Conclusions: In this study, we provide preliminary data supporting the potential application of the Liver-Chip for modeling NAFLD-like phenotypes and conducting human-relevant, mechanistic, efficacys, and safety assessments in vitro.

Combining Design, Engineering, and Biology

Recreating the Cellular Microenvironment in Our Chips

Liver-Chip

- Extracellular matrix and cell interactions
- Tissue-tissue interactions
- Hepatocyte and cytoarchitecture
- Mechanical forces
- Dynamic system – flow
- Resident or circulating immune cells

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Results

Fatty Acid Treatment Schematic

Triglyceride Export in Liver-Chip

Hepatic Stellate Cell Activation in Liver-Chip

Compound Efficacy Assessment in Liver-Chip

Conclusions

In this study, we provide preliminary data supporting the potential application of the Liver-Chip for modeling NAFLD-like phenotypes and conducting human-relevant, mechanistic, efficacy, and safety assessments in vitro.

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