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A Microfluidic Patterned Model of Non-alcoholic Fatty Liver Disease: Applications to Disease Progression and Zonation

Beyza Bulutoglu[1], Camilo Rey-Bedón[1], Young Bok (Abraham) Kang[1], Safak Mert[1], Martin L. Yarmush[1,2], and O. Berk Usta[1]
[1]Center for Engineering in Medicine, Massachusetts General Hospital, Harvard Medical School and Shriners Hospitals for Children, Boston, USA
[2]Department of Biomedical Engineering, Rutgers University, Piscataway, USA

Abstract:
Non-alcoholic fatty liver disease (NAFLD) and its progressive form non-alcoholic steatohepatitis (NASH) affect 25% of the world population. NAFLD is predicted to soon become the main cause of liver morbidity and transplantation. The disease is characterized by a progressive increase of lipid accumulation in hepatocytes, which eventually induce fibrosis and inflammation, and can ultimately cause cirrhosis and hepatic carcinoma. Here, we created a patterned model of NAFLD on a chip using free fatty acid gradients to recapitulate a spectrum of disease conditions in a single continuous liver tissue. We established the NAFLD progression via quantification of intracellular lipid accumulation and transcriptional levels of fatty acid transporters and NAFLD pathogenesis markers. We then used this platform to create oxygen driven steatosis zonation mimicking the sinusoidal lipid distribution on a single continuous tissue and showed that this fat zonation disappears under progressed steatosis, in agreement with *in vivo* observations and recent computational studies. While we focus on free fatty acids and oxygen as the drivers of NAFLD, the microfluidic platform here is extensible to simultaneous use of other drivers.

Keywords: non-alcoholic fatty liver disease (NAFLD), progressive disease model, metabolic patterning on a chip (MPOC), free fatty acids, microfluidic gradients, primary hepatocytes