Modeling Liver Disease Using Human iPSC-derived Hepatocytes

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is quietly becoming a worldwide pandemic. While relatively silent and undetected at first, NAFLD can slowly, but surely progress into a more serious condition called non-alcoholic steatohepatitis (NASH) that leads to hepatocyte damage, inflammation, fibrosis, and liver cancer. Understanding the molecular mechanisms of disease progression from NAFLD to NASH and liver damage is an area of increasing research activity, but one that is hampered by the lack of suitable animal or cellular models of the disease. With the advent of induced pluripotent stem cell (iPSC) technology, there is now access to a renewable source of various types of functional human cells, including hepatocytes. Disease-specific iPSC lines are a valuable tool for studying disease pathobiology at the cellular level. The ability to generate functional iPSC-derived hepatocytes from patients with genetic variants associated with NAFLD is critical for modeling liver disease in vitro. In this poster, we present data supporting the use of iPCell Hepatocytes 2.0 to measure accumulation of lipids (i.e., fatty liver) in a quantitative high content imaging-based assay that can be used to screen for modulators of this phenotype. Furthermore, we have begun to explore co-culture experiments with iPSC-derived macrophages and iPSC-derived mesenchymal stem cells as hepatic Kupffer cells and hepatic stellate cells, respectively. Considerations for constructing these advanced cell culture systems will be presented.

Modeling Fatty Liver Phenotypes Using iCell Hepatocytes 2.0

iCell Hepatocytes 2.0 morphology at 7 days in culture represents typical hepatocyte morphology

- Adherent monolayer
- Cobblestone / polygonal
- Round nucleus
- Distinct nucleoli
- High cytosol : nuclear ratio
- Bi-nucleation (circles)
- Bile canaliculi (arrows)

Thaw & plate cells

Days in Culture

Feed cells

Fatty acid treatment

Assay: Fix or Live

iCell Hepatocytes 2.0 can be induced to exhibit fatty liver-like phenotypes (accumulation of BODIPY positive lipid droplets) by feeding the cells with excess fatty acids. High content imaging assays using fixed or live-cells enables quantification of the accumulated fluorescence from the stained lipid droplets.

Modeling Liver Fibrosis Phenotypes Using Co-culture models (iCell Hepatocytes 2.0 + iCell Mesenchymal Stem Cells)

Adding iCell Mesenchymal Stem Cells to cultures of iCell Hepatocytes 2.0 enables modelling in which fibrotic-like deposition of Collagen I can be studied.

I ncorporation of markers like smooth muscle actin (SMA) also enables detection of cellular phenotypes reminiscent of activated stellate cells with coincident formation of collagenous fibril-like structures.