In Vitro Modeling of Cardiac, Neuronal, and Metabolic Disorders with Human iPSC-derived Cell Types

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Abstract

Introduction: To understand the onset and progression of a human disease, an effective model that combines known genetic elements with a predictive phenotypic readout is required. Recent advances in iPSC technology grant access to unique human samples and enable the generation of disease- and patient-specific cell lines. Terminally differentiated cell types – such as cardiomyocytes, neurons, and hepatocytes – derived from iPSC lines are extremely useful for understanding the pathophysiological mechanisms for cardiovascular, neurodegenerative, and metabolic disorders.

Methods: We have used human iPSC-derived, cryopreserved cell types manufactured by CDI to create disease models for Cardiac Hypertrophy, Alzheimer’s Disease (AD), and metabolic diseases. Examples of phenotypic screening (using high content imaging and label-free systems), genetic analysis and modulation, and cell signaling analysis are highlighted.

Results: First, we have developed a suite of hypertrophy assays with iPSC-derived cardiomyocytes that monitor endothelin-1 (ET-1)-induced cardiac hypertrophy, focused primarily on the expression of B-type natriuretic peptide (BNP), re-activation of fetal gene expression, and changes in cell size. Using a phenotypic screening approach, numerous compounds that modulate the hypertrophic response were evaluated. Secondly, using iPSC-derived neurons, we applied beta amyloid (1-42) peptide to mimic the undesired outcomes observed during AD. We measured the neurotoxicity and decrease in neurite outgrowth by cell viability and high content imaging assays. Additionally, we reversed some of the negative effects with reduced expression of fetal genes (e.g., NPPB). Finally, we have utilized iPSC-derived hepatocytes to begin to investigate the impact that insulin and glucagon have on glucose regulation and the associated cell signaling events. This same cell type also serves as a model system for understanding cholesterol homeostasis through LDLR and PCSK9 signal transduction.

Discussion: The use of iPSC-derived cell types for modelling complex diseases is intensifying. Their use in high-throughput screening applications brings more physiologically relevant, human cell models into the drug discovery and development process sooner. Here we present a variety of cell-based approaches to test induced, infected, and inherited disease models with the hope that more efficient and reliable assessment of new chemical entities is possible.

Cardiac Hypertrophy Disease Model

- Cardiac hypertrophy is generally characterized by an increase in cardiomyocyte cell size and is manifested through numerous transcriptional, biochemical, and structural transformations
- Reversion back to the cardiac fetal gene program is a hallmark trait of the disease, and expression of B-type natriuretic peptide (BNP) is one of the most commonly used markers for the hypertropic response.

Neuronal Model for Alzheimer’s Disease

Researchers at GSK used iCell Neurons to establish a cellular model of Alzheimer’s Disease. Neuronal loss was induced by exposure of the cells to an insult of Aβ1-42 aggregates. CDK2 was validated as an important signaling target for rescue of toxicity using known inhibitors and shRNA against CDK2. This model system was further utilized to identify novel modulators of this neurodegenerative disease in a focused drug screen.

- We have verified the Aβ-induced neurotoxicity with this cell model in a cell viability assay and neurite outgrowth assay (data not shown)
- Additionally, iPSC-derived neurons secrete relevant markers and the release can be modulated with small-molecules
- CDK2-specific knockdown or inhibition with GW8510 rescues the neurotoxicity induced by the peptide Aβ (1–42)

Metabolic Diseases

- Using genetically normal iPSC-derived hepatocytes, we have developed cell-based assays to monitor levels of biologically relevant metabolic markers for future use with disease-specific lines

Summary

- Human iPSC-derived cell types from both apparently normal and disease-specific donor backgrounds can be used to develop methods for “disease-in-a-dish” studies, thus enabling researchers to investigate mechanism of action and to evaluate new drug therapies.

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