Human iPS-derived Cardiac Myocyte-Fibroblast 3D Co-Cultures: A Predictive In Vitro Model to Assess Drug-Induced Contractile and Metabolic Liabilities

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Aims

In order to address the need for a predictive and physiologically relevant contractility assay in cardiovascular safety pharmacology, we developed an in vitro model based on a co-culture of cardiomycocytes and cardiac fibroblasts derived from human induced pluripotent stem cells. For this purpose, the innovative "CellDrum" technology was used to quantify the effects of ten different compounds on the mechanical properties of the co-cultures including ion channel modulators, sensitizers and adrenergic agents. Additionally, metabolic drug-response and general cell metabolism were analyzed with the label-free Seahorse AT 96 technology.

CellDrum: Cellular Tension Measurements

CellDrum Technology: The CellDrum developed at the Institute for Bioengineering (Aachen University of Applied Sciences, Germany) consists of a thin, flexible membrane attached to a cylindrical well that is not only capable for supporting 2D and 3D cell cultures under basal load conditions, but also for concurrent measurements of membrane deflection and pressure. Using Laplace's law it is possible to derive cellular tension measurements from the deflection of the myocyte-layered membrane and pressure throughout. Using this load-bearing approach, temporal, biological and drug-induced changes in mechanical tension (i.e., cardiomyocyte contacts) can be easily observed.

Fibroblast Contribution to Cardiac Contractile Tension and Metabolism

Cardiac fibroblasts enhance myocyte amplitude of contraction. A 25% fibroblast : 75% myocyte co-culture produced optimal force.

Pharmacological Characterization

A set of 10 blinded compounds was tested on the previously determined optimal co-culture (25% fibroblasts:75% cardiomyocytes). The results were consistent with the expected pharmacological responses.

Summary

- The CellDrum provides a robust, sensitive multi-well compatible platform to assess cardiomyocyte contractility in a more physiologically-relevant cell culture environment. Reference compounds demonstrated responses in agreement with previously reported responses.
- Co-cultures of hPSC-derived cardiomyocytes and cardiac fibroblasts (25% fibroblasts : 75% myocytes) produced the optimal contractile tension.
- 25% fibroblasts cultures exhibit better respiratory performance than the 10% fibroblasts cultures and may represent the optimal co-culture condition in this system.
- iPSC-derived cardiac fibroblasts help to create a more efficient, physiologically-relevant cardiac system and play a distinct role in electrically-coupled contraction.