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Characterizing Molecular and Functional Differences between Adherent and Suspended iPSC-CMs

The need to engineer an assay for assessment of proarrhythmic potential of new drugs, which does not only depend on hERG assays has sparked an interest in using iPSC-derived cardiomyocytes as an alternative to hERG-only cell lines. hERG, also known as delayed rectifier K⁺ current (IKr) is important for cardiac repolarization and its inhibition causes acquired long QT syndrome, which can lead to cardiac arrhythmia.

In vitro-derived iPSC-CMs can be used for electrophysiology studies using patch-clamping to evaluate the effect of drugs on different ion channels. Nonetheless, variations in measured electrical properties between the labor-intensive manual patch-clamp and high-throughput automated patch clamp (APC) pose challenges. Particularly concerning is the absence of hERG current in iPSC-CMs, rendering the use of APC impractical for hERG assays.

The focus of this study is to determine what causes the absence of hERG in iPSC-CMs and explore potential resolutions. A notable difference between the two techniques is the nature of the sample: iPSC-CMs for manual patch-clamp are attached to a matrigel-coated culture dish whereas APC requires suspended cells. Hence, the detachment of cells from the extracellular matrix (ECM) proteins may deactivate or alter the localization of hERG channels. Additionally, cell dissociation enzymes employed during detachment may compromise the integrity of this ion channel.

To address these issues, two iPSC cell lines have been differentiated into cardiomyocytes to investigate the molecular and cellular differences between cells in suspended and ECM-adherent states. The findings are poised to provide insights into the challenges identified above and enhance patch-clamping procedures with the APC.