Using induced pluripotent stem cell derived cardiomyocytes to screen for multichannel pharmacology and proarrhythmic risk in acquired long QT syndrome

A.P. Hill, M.D. Perry, W. Lee and J.I. Vandenberg, Molecular Cardiology and Biophysics Division, Victor Chang Cardiac Research Institute, 405 Liverpool Street, Darlinghurst, NSW 2010, Australia.

Acquired, or drug-induced, long QT syndrome (aLQTS) occurs as a result of pharmacological block of hERG potassium channels in the heart. Reduced hERG function prolongs the QT interval on the surface electrocardiogram and increases the risk of the potentially fatal cardiac arrhythmia torsades des pointes (Roden, 2004). As a result of these side effects, it is mandated that all drugs must be screened for hERG block and action potential prolongation in preclinical tests before coming to market (Food and Drug Administration HHS, 2005). However, while current tests are very effective in identifying dangerous drugs, there is growing concern that they are not sufficiently specific, meaning potentially safe drugs are having their development prematurely terminated (Sager *et al.*, 2014). A major factor that confounds assays based solely on hERG block is the multichannel pharmacology of many compounds, whereby block other ion channels in addition to hERG can modify the risk profile of a drug.

One way to avoid this issue is to screen compounds in assays using human cardiomyocytes, so the effect on disruption of repolarization is evaluated in the context of all the different ion channels and signalling processes that contribute to normal cardiac electrophysiology. While using isolated human cardiomyocytes in screening is not a feasible approach, induced pluripotent stem cell derived cardiomyocytes (iPSC-CM) provide readily available source of cells by which this approach can be explored. In this study we have used multielectrode arrays to measure electrical parameters from 2D syncytia of iPSC-CMs and show how drugs with diverse pharmacology and risk profile affect depolarization, repolarization, beat period and emergence of proarrhythmic markers in these cardiac cells. Specifically, we tested dofetilide (a pure hERG blocker), ranolazine (blocks hERG and late sodium current, I_{NaL}), quinidine (blocks hERG and fast sodium current, I_{Na}) and nifedipine (blocks calcium current, I_{CaL}). Our data show a correlation between proarrhythmic risk and prolongation of field potential duration at therapeutic concentrations while emergence of proarrhythmic markers such as early after-depolarizations was only observed for dofetilide, a known high risk drug. Effects on depolarization parameters measured from MEAs such as spike amplitude and slope, were observed at concentrations corresponding to the IC_{50} for block of hERG (a repolarizing current) not of the depolarizing currents (I_{CaL} or I_{Na}). We propose this counterintuitive observation occurs as a result of the relative electrical immaturity of iPSC-CMs. These results suggest a promising role for iPSC-CM electrophysiological assays in screening for proarrhythmic risk in drug development, but show that ongoing work in achieving a greater degree of phenotypic maturity may be necessary to reach this goal.

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