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073

In vitro cardiac safety evaluation for repurposed COVID-19 drugs by using human iPS cell-derived cardiomyocyte with gelatin fiber scaffold

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Repurposing of approved drugs that are expected to be effective with low adverse effects is one of reasonable strategies for emergent requirement of COVID-19 treatment. Chloroquine (CQ) or hydroxychloroquine (HCQ) alone or combined with azithromycin (AZM) for COVID-19 have attracted global attention and have been widely used in early clinical trials. Although CQ and HCQ are supposed to have risk of QT prolongation clinically, cardiac safety risks (QT prolongation and contraction impairment) of combination AZM with CQ or HCQ have not been fully characterized preclinically. We aimed to evaluate the risk of QT prolongation and contraction impairment by the drugs used for COVID-19 treatment by a novel of human induced pluripotent stem cell derived-cardiomyocytes (hiPSC-CMs) and gelatin hydrogel fibrous nonwoven (GHFN) as a scaffold. Because the GHFN model is expected to detect the risk of both QT prolongation and contraction change we used iCell cardiomyocytes^2 (FUJIFILM Cellular Dynamics, Inc.). The iPSC-CMs were seeded on fibronectin-coated GHFN. After cultured for 6 to 9 days, CQ, HCQ, AZM or these combinations were added cumulatively to achieve the target concentrations. To evaluate the risks for QT prolongation and arrhythmia, calcium sensitive dye (EarlyTox, Molecular Devices) was used. Calcium fluorescence images were captured with confocal imaging system CQ1 (Yokogawa Electric Co.) and analyzed by CellPathfinder (Yokogawa Electric corp.). The contraction of hiPSC-CMs was analyzed from bright field images by MUSCLEMOTION (Sala et al, Circ. Res., 2018, 122). Dynamic beating of hiPSC-CM with GHFN was observed after 6 days culture before drug administration. In proarrhythmic risk evaluation, both CQ or HCQ alone, and combination of AZM prolonged calcium signal and caused arrhythmia, while AZM caused shorting of calcium signal. On the other hand, in contraction evaluation, combination of CQ or HCQ with AZM caused arrest at lower concentration than that of CQ and HCQ alone or AZM alone. We succeeded in evaluating cardiac safety for COVID-19 potential drugs by using iPSC-CM and GHFN. GHFN enabled to detect both risk of proarrhythmia and contraction impairment. Our results suggest that combination use of AZM enhances the risk of cardiac safety.

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074

Improvement of contractile function of human iPS cell-derived cardiac cell sheets by electric stimulation for several days

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Drug-induced cardiotoxicity is a major cause of attrition of drug candidates during drug development. Assessments of cardiotoxicity risk like cardiac contractility are mostly conducted during the late phase of preclinical development using in vivo animal models. Although it would be preferable to use a human cell-based assay to predict clinical effects on cardiac contractility earlier in development, translatability of drug induced responses of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) to clinical outcomes has been limited by their immaturity. Because stimulation with electrical pacing is known to promote maturation of hiPSC-CMs, we evaluated the contractile function of hiPSC-CMs with and without electrical stimulation. hiPSC-CM sheets were prepared by transferring hiPSC-CMs cultured in temperature-sensitive culture dishes to fibrin gels. We utilized the system for direct measurement of the cardiac contractile force with a cardiac cell-tissue sheet model using hiPSC-CMs. Force- frequency relationship (FFR) at pacing rates of 0.5 to 3.5 Hz was measured before and after continuous stimulation at 2 Hz for 48-72 h. The action of positive inotropic drugs (isoproterenol, dobutamine, milrinone, digoxin, levosimendan, omecamtiv mecarbil, and Bay K-8644) with and without electrical stimulation was examined under spontaneous beat. The sheet before electrical stimulation showed negative FFR but changed to positive FFR after pacing. Positive inotropic drugs did not elicit a positive inotropic response without the electrical stimulation but did with electrical stimulation. Thus, we developed a biologically similar model to human cardiac contractile function that showed drug responses like human cardiac muscle. This model can be a useful tool for early cardiotoxicity evaluation.

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075

Automated cardiac tissue assay system with perfusion for monitoring contractility

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As part of an effort to better identify and characterize drugs for safety and efficacy with respect to the heart, screening platforms that directly measure contractility of cardiac tissue constructs have potential for improved predictivity of inotropic drug effects. We have developed a biomimetic in vitro model composed of human pluripotent stem cell-derived ventricular cardiomyocytes self-organized into tissue resembling a human cardiac muscle fiber. As with most tissue assays in development, screening throughput is a potential limitation when screening multiple independent factors that may affect contractility. Therefore, there is a need to develop hardware platforms to automate the screening process to probe drug effects more efficiently. Here we describe a novel cardiac tissue assay system that integrates multiple features, including: drug perfusion, biphasic electrical stimulation, force measurements through real-time optical tracking (up to 50Hz), protocol automation, signal processing, and data analysis. The integrated temperature-controlled (±0.1 °C) perfusion system permits flow (0.03–10 mL/min) of up to 8 different solutions, permitting studies on force-concentration response, drug-drug interactions, or chronic effects. To validate the system, the effects of digoxin on the cardiac tissue strips (10^6 human pluripotent stem cell-derived cardiomyocytes, 10^5 human fibroblasts) were evaluated under electrical stimulation (0.5 Hz).