Cell and Myofibril Contractile Properties of hiPSC-Derived Cardiomyocytes from a Patient with a MYH7 Mutation Associated with Familial Cardiomyopathy

Myosin heavy chain 7 (MYH7) mutations are associated with familial cardiomyopathies (FCM) and result in a high rate of sudden cardiac death. Human induced pluripotent stem cells derived cardiomyocytes (hiPSC-CMs) have recently shown promise as a model for studying FCM. We identified a cohort with familial cardiomyopathy (FCM) associated with a MYH7 mutation (E848G) and middle-age onset of systolic dysfunction and arrhythmias. hiPSC-CMs from patient affected (FCM-CMs) and non-affected (WT-CMs) individuals were generated from skin fibroblasts. Here we report, for the first time, contractile properties of isolated myofibrils from these cultured hiPSC-CMs for comparison using cultured cells and 3D engineered cardiac tissue (3D-ECT) constructs. Isolated myofibrils were obtained from differentiation day 20 hiPSC-CMs that were replated onto fibronectin-coated nanopatterned cover slides and matured in culture for an additional 60 days to obtain elongated and aligned myofibrils. This procedure produced hiPSC-CMs that were usually > 100+ μm in length. hiPSC- FCM-CMs and WT-CMs were harvested and skinned in a rigor solution containing 1% Triton and contractile properties of single or small bundles of myofibrils were measured in a custom built apparatus with rapid solution switching capabilities. During maximal calcium activation FCM-CM myofibrils produced approximately half the amount of force of WT-CM myofibrils, but preliminary data suggests no differences in the kinetics of force development or relaxation. This compares well with 50 day cardiomyocytes plated on nano-patterned surfaces or seeded into 3D-ECT constructs, where shortening and force (respectively) of FCM-CMs was much less than for WT-CMs, with no difference in calcium transient amplitudes. We speculate this early stage contractile deficit may contribute to disease development and conclude hiPSC-FCM-CMs can be a viable model for mechanical studies of cardiomyopathies in vitro.

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