Abstract: P527

Modeling DCM due to Lamin A/C gene mutation using hiPSC-CM

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Dilated cardiomyopathy (DCM) is a leading cause of heart failure and heart transplantation. A part of familial  
DCM is due to mutations in the genes encoding the nuclear envelope proteins Lamina A and C. People with this  
mutation have a poor survival outcome. The current study models this disease using induced pluripotent stem  
cell derived cardiomyocyte (hiPSC-CM) to understand the pathophysiology of the mutation in cardiomyocytes.  
Based on previous studies it was hypothesized that the model would present patient-specific phenotype electrophysiologically and the effect of stress compared to controls. It is hypothesized that disorganized nuclear lamina would lead to calcium leak from the nucleus leading to increased arrhythmia under stress. hiPSC-CMs derived from skin biopsies from one healthy control and from two DCM patients were used. Structure of nuclear lamina and sarcomeres were studied using confocal microscopy. Electrophysiology and calcium handling was studied using micro electrode array (MEA) and calcium imaging at basal conditions and under adrenergic and hypoxic stress. Morphologically, confocal imaging revealed that the DCM hiPSC-CMs displayed more nucleoplasmic Lamin A compared to the control. The fluorescence intensities ratios of the lamina to nucleoplasm significantly more in Control compared to DCM. Electrophysiologically, the DCM model displayed bradycardia and increased arrhythmias at multi cellular level by MEA and at single cell level by calcium imaging both at baseline and under adrenaline. Calcium imaging revealed significantly altered calcium decay characteristics in the DCM model. Induction of stress on cardiac aggregates using hypoxic conditions displayed an exaggerated effect on the DCM. In conclusion, our model recapitulated major phenotype characteristics as observed in DCM patients and is a proof of concept that this model can be used to study the disease mechanisms further and can serve as a platform for drug screening.