EFFECTS OF FIBRILLIN MUTATIONS ON THE BEHAVIOUR OF HEART MUSCLE CELLS IN MARFAN SYNDROME

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Marfan syndrome (MFS) is a systemic disorder of connective tissue caused by pathogenic variants in the FBN1 gene. Myocardial dysfunction has been demonstrated in MFS patients and mouse models but little is known about the intrinsic effect of the mutations on the heart muscle cells, the cardiomyocytes. Cardiomyocytes were obtained by differentiating isogenic human induced pluripotent stem cells: one harboring a FBN1 mutation, and one corrected with CRISPR-CAS9. Cardiomyocytes were functionally characterized using several techniques. Atomic force microscopy revealed that MFS cardiomyocytes were stiffer compared to corrected cardiomyocytes. The contraction amplitude of MFS cardiomyocytes was lower compared to corrected cardiomyocytes. MFS cardiomyocytes showed a lower beat-to-beat variability compared to corrected cardiomyocytes on multi electrode array measurements. Addition of increasing isoproterenol concentrations increased the beat-to-beat variability only in the MFS cardiomyocytes. After chronic isoproterenol treatment, the fibronectin network provided additional support in corrected cardiomyocytes, which was lacking in the MFS culture. Stretching the cells using Flexcell resulted in diminished cell to cell interactions of the MFS cardiomyocytes. Functional abnormalities of cardiomyocytes were revealed in the established human in vitro MFS system. These results show that an impaired matrix plays a key role in the improper functioning of cardiomyocytes in MFS.