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Ion Channel Dysfunctions in Dilated Cardiomyopathy in Limb-Girdle Muscular Dystrophy.

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Abstract

BACKGROUND: Limb-Girdle muscular dystrophies (LGMD) are a heritable group of genetically determined disorders with a primary involvement of the pelvic or shoulder girdle musculature with partially cardiac manifestation, such as dilated cardiomyopathy (DCM) and life-threatening tachyarrhythmia. We report here that human induced pluripotent stem cell (hiPSC)-derived cardiomyocytes from a patient with LGMD2I and DCM associated with recurrent ventricular tachycardia displayed ion channel dysfunction and abnormality of calcium homeostasis.

METHODS: Dermal fibroblasts obtained from a patient with LGMD2I harboring a fukutin-related protein gene mutation (826C>A; Leu276Ile) and 3 healthy donors were reprogrammed to hiPSCs. The hiPSCs were differentiated into cardiomyocytes and used for biological and electrophysiological studies.

RESULTS: Compared with hiPSC cardiomyocytes from the healthy donors, the hiPSC cardiomyocytes from the patient exhibited abnormal action potentials characterized by reduced amplitude and upstroke velocity. The peak and late Na channel currents (I_{Na}) as well as the peak L-type calcium channel currents were significantly reduced. The expression of SCN5A and CACNA1C was reduced in DCM cardiomyocytes, consistent with reduction of I_{Na} and L-type calcium channel currents. In addition, the rapidly activating delayed rectifier potassium current (I_{Kr}) was reduced, whereas the transient outward current (I_{to}) and slowly activating delayed rectifier potassium current (I_{Ks}) were similar in DCM and control cardiomyocytes. Finally, a significant reduction of systolic and diastolic intracellular Ca^{2+} concentrations was detected in DCM cardiomyocytes.

CONCLUSIONS: This study demonstrates that patient-specific hiPSC cardiomyocytes can

recapitulate some phenotypic properties of LGMD2I with DCM and provide a platform for studies on the cardiac events in LGMD.

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KEYWORDS: action potentials; calcium channels, L-type; cardiomyopathy, dilated; induced pluripotent stem cells; muscular dystrophies, Limb-Girdle

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