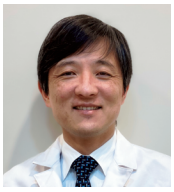
Medicine / Healthcare, Drug development

Generation of human disease model recapitulating inherited cardiomyopathy



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Abstract

Mutations in desmosome genes cause arrhythmogenic cardiomyopathy, mainly in an autosomal dominant manner. Here, we identified a desmoglein-2-deficient cardiomyopathy caused by rare homozygous stop-gain mutation in *DSG2* (R119X) in a patient with severe biventricular heart failure. Induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) generated from the patient recapitulated arrhythmia, tissue fragility and decreased contractile force. These phenotypes were corrected by restored expression of desmoglein-2 mediated by genome editing or gene replacement by adeno-associated virus. The recapitulation and correction of the disease phenotype using isogenic iPSC-CMs provides evidence for precision medicine and the proof of concept for gene replacement therapy.

Background & Results

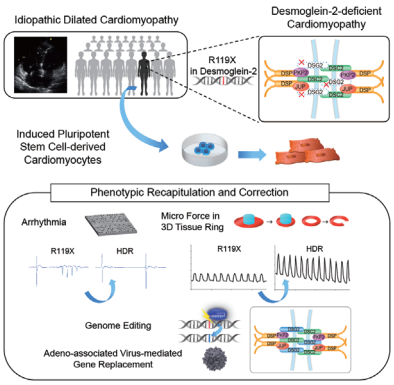
Desmoglein-2, encoded by *DSG2*, maintains the structural integrity of tissues, including heart. Genetic mutations in DSG2 cause arrhythmogenic cardiomyopathy, mainly in an autosomal dominant manner. The purpose of this study was phenotypic recapitulation and correction of desmoglein-2-deficient cardiomyopathy using induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs).

We identified a homozygous stop-gain mutation in *DSG2* (R119X) that led to complete desmoglein-2 deficiency in a patient with severe biventricular heart failure. The patient's ventricular myocardium was analyzed histologically. Phenotype analysis was performed on patient-derived iPSC-CMs with or without restored desmoglein-2 expression mediated by CRISPR/Cas9 genome editing or gene replacement by adeno-associated virus (AAV). Immunohistochemical and electron microscopic analysis revealed abnormal deposition of desmosome proteins, disrupted intercalated disc structures, and aggregated cytoplasmic desmosomes in the patient's left ventricular myocardium. iPSCs were generated from the patient (R119X-iPSC), and R119X mutation was heterozygously corrected to the normal allele via homology-directed repair (HDR-iPSC). Multiple electrode array analysis detected abnormal excitation in R119X-iPSC-CMs but not in HDR-iPSC-CMs. Micro force test detected tissue fragility and weak maximum forces in 3-dimensional self-organized tissue rings (SOTRs) from R119X-iPSC-CMs. Notably, these phenotypes were significantly recovered in SOTRs from HDR-iPSC-CMs. The myocardial fiber structures in R119X-iPSC-CMs were severely aberrant, and electron microscopic analysis revealed disrupted desmosomes in R119X-iPSC-CMs. AAV-mediated replacement of *DSG2* significantly recovered the contraction force in SOTRs generated from R119X-iPSC-CMs.

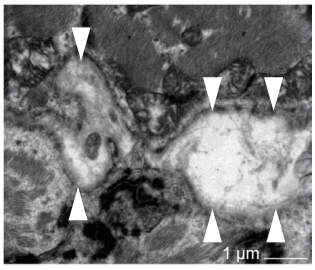
Conclusions: Recapitulation and correction of the disease phenotype of desmoglein-2-deficient cardiomyopathy using iPSC-CMs provides evidence for precision medicine and the proof of concept for gene replacement therapy.

Significance of the research and Future perspective

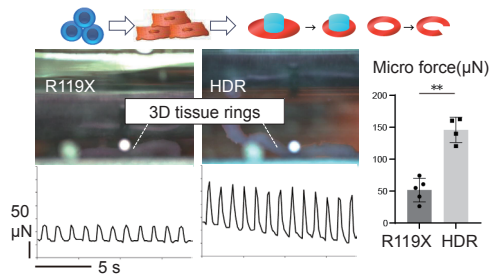
In 2021, more than 900 patients with advanced heart failure are waiting for heart transplantation in Japan. Dilated cardiomyopathy is a major cause of advanced heart failure. Recapitulation and correction of the disease phenotype of desmoglein-2-deficient cardiomyopathy using iPSC-CMs provide evidence for precision medicine and the proof of concept for gene replacement therapy.



Severely disrupted intercalated disc structures in left ventricular myocardium from desmoglein-2-deficient cardiomyopathy



Restoration of desmoglein-2 recovered micro force in 3D tissue rings



Patent Japanese Patent Application No. 2020-44996, PCT/JP2021/10137

Treatise Shiba M, Higo S, Hikoso S, Sakata Y. Phenotypic recapitulation and correction of desmoglein-2-deficient cardiomyopathy using human-induced pluripotent stem cell-derived cardiomyocytes. Hum Mol Genet. 2021 Jul 9; 30(15): 1384-1397. doi: 10.1093/hmg/ddab127.

URL http://www.cardiology.med.osaka-u.ac.jp/?page_id=37187

Keyword dilated cardiomyopathy, desmoglein-2, human induced pluripotent stem cell-derived cardiomyocytes, genome editing, adeno-associated virus