Medical & healthcare, Drug development

Elucidation of pathological mechanism and therapeutic development using human disease model recapitulating inherited cardiomyopathy

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Researchmap https://researchmap.jp/s.higo?lang=en

Abstract

Dilated cardiomyopathy (DCM), a heart disease exhibiting dilated left ventricle and reduced contractile function is the primary cause of severe heart failure that requires heart transplantation. Although Becker muscular dystrophy (BMD) is one of the causative diseases of DCM, early-onset advanced heart failure in female BMD carriers is extremely rare. We encountered a female BMD carrier with advanced heart failure carrying Δ45-48 dystrophin and identified a stop-gain variant in *PLOD3* as a potential second-hit variant. Isogenic induced pluripotent stem cells (iPSCs) with dominant expression of WT-*DMD*, Δ45-48-*DMD*, or Δ45-48-*DMD* with corrected *PLOD3* variant were established. Microforce testing using 3-dimensional self-organized tissue rings (SOTRs) generated from iPSC-derived cardiomyocytes (iPSC-CMs) demonstrated that correction of the heterozygous *PLOD3* variant significantly recovered the reduced stiffness in Δ45-48-DMD SOTRs. Correction of the *PLOD3* variant restored collagen synthesis in iPSC-CMs. Our findings revealed the pathogenesis underlying advanced heart failure in a female BMD carrier.

Background & Results

Becker muscular dystrophy (BMD) is an X-linked genetic disorder caused by variants in the *DMD* gene, which encodes the dystrophin protein and is required for structural stability of the sarcolemma. Dilated cardiomyopathy (DCM), a heart disease exhibiting dilated left ventricle and reduced contractile function is the primary cause of severe heart failure that requires heart transplantation. Although BMD is one of the causative diseases of DCM, early onset advanced heart failure in female BMD carriers is extremely rare. We encountered a female BMD carrier with advanced heart failure carrying Δ45-48 dystrophin. Immunohistochemical analysis of serial sections obtained from the patient's LV myocardium demonstrated the mosaic expression of wild type and Δ45-48 dystrophin. From the genetic analysis, we further identified a stop-gain variant in *PLOD3* as a potential second-hit variant. Isogenic induced pluripotent stem cells (iPSCs) with dominant expression of WT-*DMD*, Δ45-48-*DMD*, or Δ45-48-*DMD* with corrected *PLOD3* variant were established. Microforce testing using 3-dimensional self-organized tissue rings (SOTRs) generated from iPSC-derived cardiomyocytes (iPSC-CMs) demonstrated that correction of the heterozygous *PLOD3* variant significantly recovered the reduced stiffness in Δ45-48-DMD SOTRs. Correction of the *PLOD3* variant restored collagen synthesis in iPSC-CMs. Our findings revealed the pathogenesis underlying advanced heart failure in a female BMD carrier.

Significance of the research and Future perspective

DCM is the primary cause of advanced heart failure requiring heart transplantation. While DCM is uniformly diagnosed as a disease exhibiting dilated left ventricle and reduced contractile function, recent advances in genetic analysis have revealed the wide-ranging mechanisms underlying the disease progression. To overcome DCM, it is crucial to understand each patient's clinical course, genetic background, and histopathological findings, and to investigate the individual upstream molecular mechanisms through basic research.

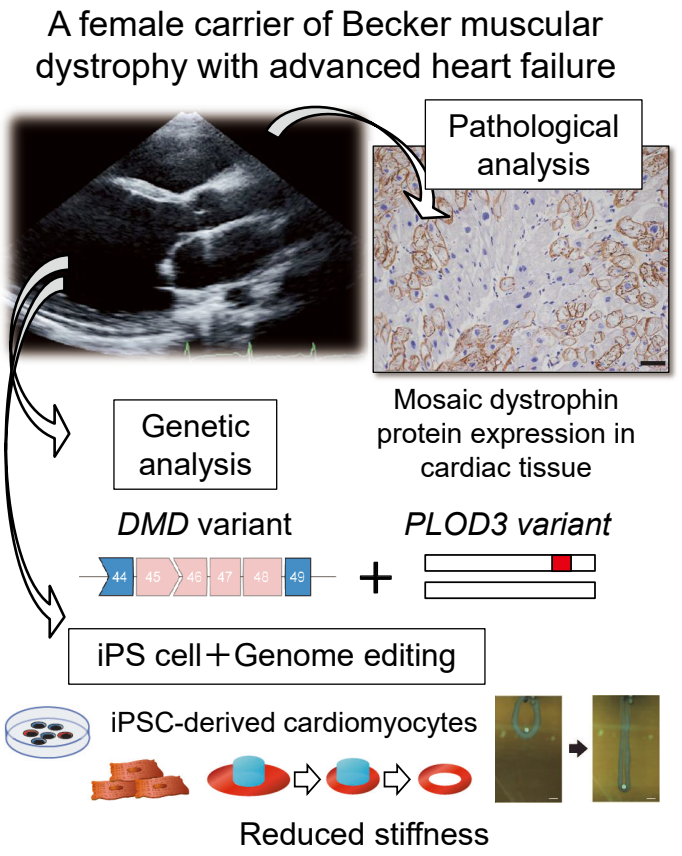

Figure 1

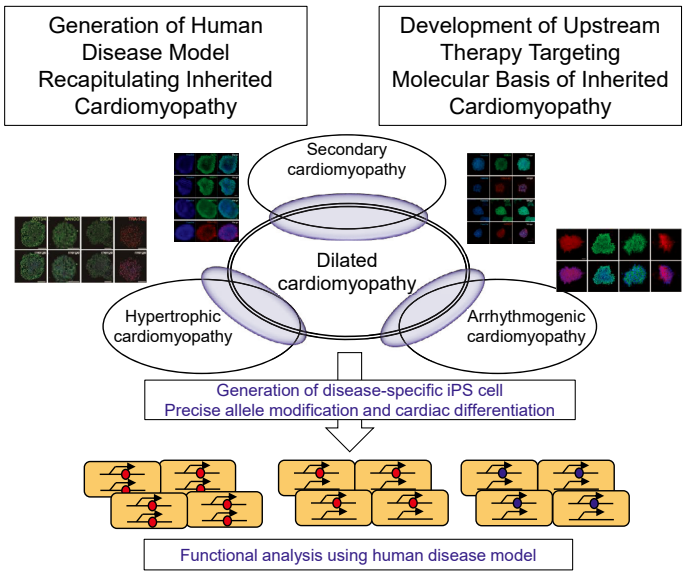

Figure 2

Patent

Treatise Kameda, Satoshi; Higo, Shuichiro; Sakata, Yasushi et al. Modeling reduced contractility and stiffness using iPSC-derived cardiomyocytes generated from female Becker muscular dystrophy carrier. JACC Basic Transl Sci. 2023, 8(6), 599-613. doi: 10.1016/j.jacbts.2022.11.007

URL

Keyword Becker muscular dystrophy, female carrier, advanced heart failure, iPS cell-derived cardiomyocyte