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ASIA EDITION

Japan explores muscular dystrophy associated cardiomyopathy

14 February 2020 | News

Data show that cardiac dysfunction in muscular dystrophy-associated cardiomyopathy occurs at the cellular cardiomyocyte level

In a study recently published in *Nature Communications,* scientists at Japan based Okayama University describe the detailed molecular pathogenesis of muscular dystrophy-associated cardiomyopathy in mice lacking the fukutin gene (*Fktn*), the causative gene for Fukuyama muscular dystrophy.

Heart failure is the major cause of death for muscular dystrophy patients; however little is known for the molecular mechanism of muscular dystrophy-associated cardiomyopathy. In this study, a research team spearheaded by Senior Lecturer KATANOSAKA Yuki at Okayama University demonstrate for the first time the cellular and molecular pathomechanisms of muscular dystrophy-associated cardiomyopathy using mouse models of Fukuyama muscular dystrophy with a deficiency for the fukutin gene (*Fktn*), which encodes a Golgi-based ribitol-phosphate transferase that catalyzes the biosynthesis of tandem ribitol-phosphate structure on ?-dystroglycans (DG). As DG and proteins of the dystrophin–glycoprotein complex provide structural support for the sarcolemma in muscle tissue, a loss of membrane fragility was thought to be a cause for cardiac dysfunction in these diseases collectively known as ?-DGpathies. However, their data show that cardiac dysfunction in muscular dystrophy-associated cardiomyopathy occurs at the cellular cardiomyocyte level.

In this study, although cardiac *Fktn* elimination markedly reduced ?-DG glycosylation and dystrophin-glycoprotein complex proteins in sarcolemma at all developmental stages, cardiac dysfunction was observed only in later adulthood, suggesting that membrane fragility is not the sole etiology of cardiac dysfunction. Younger *Fktn*-deficient mice show a vulnerability to hemodynamic stress conditions via impaired compensative hypertrophic response of cardiomyocytes. Adult *Fktn*-deficient mice exhibit altered cardiac morphology and dysfunction, suggesting that FKTN is critical for maintaining contractile function of individual cardiomyocytes.

In addition, the team shows that acute *Fktn*-elimination causes the disordered Golgi-microtubule network in myocytes. Finally, the team shows that treatment with colchicine (an FDA-approved drug for the treatment of familial Mediterranean fever) improved cardiac dysfunction of *Fktn*-deficient hearts via the recovery of myocyte shortening, which may open a new avenue for therapeutic strategies.