Identification of a causative gene for dilated cardiomyopathy and future precision medicine

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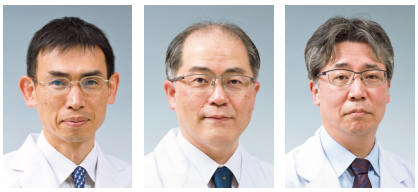

Abstract

Dilated cardiomyopathy (DCM) is a major cause of heart failure, characterized by ventricular dilatation and systolic dysfunction. We identified that homozygous truncating mutations in the gene encoding BAG co-chaperone 5 (BAG5) caused inherited DCM in unrelated multiple patients with complete penetrance. BAG5 acts as a nucleotide exchange factor for heat shock cognate 71 kDa protein (HSC70), promoting ADP release and activating HSC70-mediated protein folding. Bag5 mutant knock-in mice exhibited ventricular dilatation, arrhythmogenicity, and poor prognosis under catecholamine stimulation, recapitulating the human DCM phenotype, and administration of an adeno-associated virus 9 vector carrying the wild-type BAG5 gene could fully ameliorate these DCM phenotypes.

Background & Results

Heart failure is an increasingly serious public health issue, affecting more than 37.7 million individuals worldwide. The prognosis of patients with heart failure is still poor, with 5-year survival rates of 45.5%, regardless of advanced medical therapy. DCM, characterized by ventricular dilatation and systolic dysfunction, is one of the major causes of end-stage heart failure requiring heart transplantation. Inherited DCM can be caused by mutations in genes encoding the sarcomere, cytoskeleton, nuclear membrane, desmosome, and calcium-handling proteins. However, the underlying genetic causes of approximately 60%–80% of familial DCM cases remain unknown. Identifying the further genetic causes of DCM could improve the utility of genetic testing and might lead to new insights into the pathogenesis of heart failure. Molecular chaperones are essential for maintaining protein homeostasis (proteostasis) under physiological and stress conditions. Impaired proteostasis has been implicated in various diseases, including Alzheimer's disease and Parkinson's disease, diabetes mellitus, cancer, myopathy, and cardiovascular diseases. We revealed that the BAG co-chaperone 5 (BAG5) is a causative gene for juvenile-onset DCM with complete penetrance. Immunocytochemical analysis revealed that BAG5 localized to junctional membrane complexes (JMCs), critical microdomains for calcium handling. Bag5-mutant mouse cardiomyocytes exhibited decreased abundance of functional JMC proteins under catecholamine stimulation, disrupted JMC structure, and calcium handling abnormalities. After demonstrating that BAG5 mutations led to loss of functional BAG5 protein, we also showed that administration of an AAV9-BAG5 vector in a murine model could restore cardiac function.

Significance of the research and Future perspective

Our study suggests that BAG5 may be a target for genetic testing in cases of DCM, and that gene therapy may potentially be a treatment for this disease. In addition, our study demonstrated that maintaining proteostasis is essential for cardiomyocyte. Further study focusing on proteostasis network in cardiomyocytes would shed light on the development of novel therapy for cardiomyopathy and heart failure.

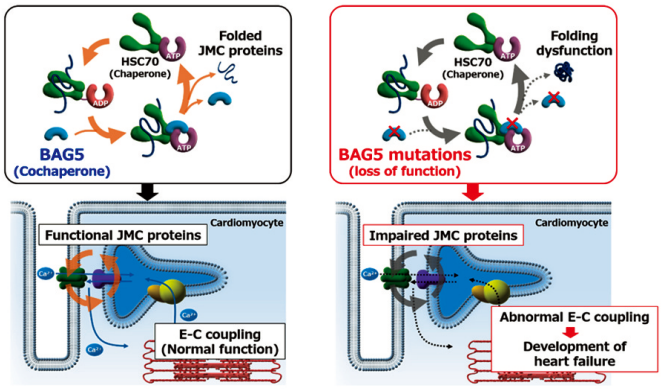

Fig.1 Loss of function mutations in the cochaperone protein BAG5 can lead to dilated cardiomyopathy and ultimately heart failure through an impaired quality control of junctional membrane complex (JMC) proteins.
E-C coupling: Excitation-Contraction coupling

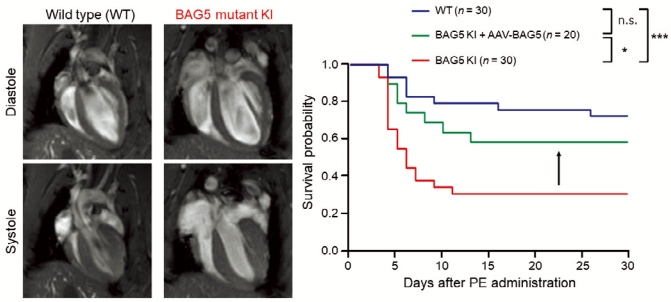

Fig.2 A. Cardiac MRI. B. Survival after phenylephrine administration.

Patent PCT/JP2020/042283

Treatise Hakui, Hideyuki et al. Loss-of-function mutations in the co-chaperone protein BAG5 cause dilated cardiomyopathy requiring heart transplantation. Sci Transl Med. 2022, 14(628): eabf3274. doi: 10.1126/scitranslmed.abf3274
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Keyword cardiomyopathy, gene therapy, precision medicine, proteostasis