Loss-of-function mutations in the co-chaperone protein BAG5 cause dilated cardiomyopathy requiring heart transplantation

Science Translational Medicine. 2022 Jan 19;14(628):eabf3274.

Hideyuki Hakui, Hidetaka Kioka, Yohei Miyashita, Shunsuke Nishimura, Ken Matsuoka, Hisakazu Kato, Osamu Tsukamoto, Yuki Kuramoto, Ayako Takuwa, Yusuke Takahashi, Shigeyoshi Saito, Kunio Ohta, Hiroshi Asanuma, Hai Ying Fu, Haruki Shinomiya, Noriaki Yamada, Tomohito Ohtani, Yoshiki Sawa, Masafumi Kitakaze, Seiji Takashima, Yasushi Sakata, Yoshihiro Asano

Dilated cardiomyopathy (DCM) is a major cause of end-stage heart failure requiring heart transplantation. Here, we identified that homozygous truncating mutations in the gene encoding BAG co-chaperone 5 (*BAG5*) caused inherited DCM in patients among four unrelated families 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 *BAG5* gene could fully ameliorate these DCM phenotypes. 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. Our findings highlight the involvement of JMC protein homeostasis in the pathogenesis of heart failure.