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New Advances in the Knowledge of Autophagy in Cardiac Disease

Kuhn Ch, Menke M, Senger F, Mack C, Dierck F, Hille S, et al. FYCO1 Regulates Cardiomyocyte Autophagy and Prevents Heart Failure Due to Pressure Overload In Vivo. **JACC Basic Transl Sci. 2021;6(4):365-80. https://doi.org/10.1016/j.jacbts.2021.01.001.**

Heart failure is a clinical condition of multiple etiology and pathophysiological complexity that is not yet fully understood. During its evolution, the failing heart suffers myocardial remodeling, characterized by increased myocyte size and extracellular matrix modifications, together with molecular changes leading to diastolic and systolic dysfunction. In the last years, special attention was paid to protein homeostasis as a relevant mechanism in the pathogenesis of heart failure and cardiomyopathies. In this sense, two mechanisms participate in the regulation of cellular protein turnover; one is the ubiquitin-proteasome system, and the other is the autophagic-lysosomal system. Autophagy is a lysosomal-dependent intracellular degradation mechanism allowing the inclusion of cytosolic material -from proteins to defective or dysfunctional organelles- in vesicles called autophagosomes, which fuse with lysosomes for the degradation and recycling process. Thus, autophagy is an important cellular adaptation mechanism to stress. Changes in the normal control mechanisms of protein quality is a common pathway of different diseases that culminate in the failing heart, but the regulatory autophagy mechanisms in these conditions are scarcely understood.

In this work, Kuhn et al. carried out a solid bioinformatic research, identifying a variety of sequences corresponding to FYCO1, a gene which is highly expressed in the heart and has the capacity to directly interact with LC3, Rab7 and phosphatidylinositol 3-phosphate, three key mediators of autophagy. The authors showed that FYCO1 is a potent cardiomyocyte autophagy inducer, promoting both autophagosome formation and autophagic flow in the heart submitted to pressure overload. In addition, in vivo FYCO1 deficiency inhibits the adaptation of the heart to inanition and biomechanical stress due to lack of increased autophagic flow, resulting in contractile dysfunction. Conversely, cardiac overexpression of FYCO1 increases autophagic flow and improves the contractile function in mice hearts with pressure overload due to aortic banding.

Adequate autophagic stimulation is essential to maintain organelle protein balance and activity and, thus, the correct heart function in stressful situations. In pathological conditions, autophagy only activates below physiological levels, as a consequence of inhibitory mechanisms or autophagic machinery depletion. This results in dysfunctional organelle and cellular toxic material accumulation that converge into progressive cardiac impairment. Although recent studies suggest potential interventions to increase cardiac autophagy, limited knowledge prevents a significant progress in this field. Kuhn et al. postulate a new pathway of autophagic induction through the FYCO1 gene as an essential component of the heart autophagic machinery, constituting a favorable action that improves cardiac function in stressful states. The authors not only found that in pathological conditions the decrease in FYCO1 is associated with functional organ impairment, but also that its overexpression is an effective pathway to increase autophagy and improve cardiac function. As a whole, these results position FYCO1 as a potential therapeutic target for heart failure induced by pressure overload. Further studies are necessary to confirm these findings and elucidate their role in other cardiovascular diseases.

Ethical considerations

Not applicable.