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New Pathophysiological Mechanisms in Heart Failure with Preserved Ejection Fraction

Schiattarella GG, Altamirano F, Kim SY, Tong D, Ferdous A, Piristine H, et al. Xbp1s-FoxO1 axis governs lipid accumulation and contractile performance in heart failure with preserved ejection fraction. Nat Commun. 2021; 12 (1): 1684**. doi: 10.1038 / s41467-021-21931-9.**

Heart failure with preserved ejection fraction (HFpEF) is currently the most prevalent form of heart failure and its diagnosis is constantly increasing. More than two-thirds of heart failure patients over 65 years of age suffer from HFpEF. Nevertheless, there is still no effective specific therapy, and the management of this large number of patients is based on symptomatic treatment and correction of risk factors. HFpEF is a multicausal syndrome with a complex pathophysiology that is still difficult to understand. However, it is known that most of these patients have obesity and metabolic syndrome, with cardiac functional impairment that is independent of the increased risk of suffering from myocardial ischemia. Myocyte steatosis in failing hearts and the causal relationship between lipid accumulation and systolic and diastolic dysfunction have been well documented. At present, HFpEF can be considered the most frequent clinical manifestation of lipotoxic cardiomyopathy, although the molecular mechanisms by which metabolic alterations with functional repercussions in the myocardium occur are very poorly understood.

In this work, Schiattarella et al. used isolated rat myocytes and an in vivo model of HFpEF in mice overfed with a high-fat diet plus the administration of L-NAME, a non-specific inhibitor of nitric oxide synthase, to study the role of Xbp1s (X-box binding protein 1) and FoxO1 (Forkhead box protein O1) in the pathogenesis mechanisms of HFpEF of cardiometabolic origin. Using transgenic mice, they observed that Xbp1s promotes the degradation of FoxO1, and, in turn, stimulates the accumulation of lipids in the myocyte. Interestingly, the specific overexpression of Xbp1s or the depletion of FoxO1 in cardiomyocytes decreases the HFpEF phenotype and cardiac steatosis. Finally, they also observed a decrease in STdUB1 expression, a direct transcriptional target of Xbp1s that participates in maintaining the stability of FoxO1 in cardiac muscle cells.

Previous studies demonstrated a cardioprotective effect of Xbp1s activation and that its inhibition could participate in the functional impairment of HFpEF. The Xbp1s-FoxO1 pathway is found downstream of a mechanism activated by transmembrane sensors of the endoplasmic reticulum in response to cellular stress, and which is known as unfolded protein response (UPR). In a stressful situation, UPR seeks to recover normal cell functioning or, failing that, it induces its programmed death.

HFpEF is a highly heterogeneous syndrome in which patients may have different predisposing factors. Lack of knowledge on its pathophysiological mechanisms limits progress in the study of new therapeutic opportunities. In this study, Schiattarella et al. made a significant contribution to the knowledge of this syndrome using a clinically relevant cardiometabolic model, simulating the most prevalent forms of HFpEF presentation. They identified the biological Xbp1s-STUB1-FoxO1 axis as a key element in the regulation of cardiac steatosis in HFpEF, opening a new study path by placing metabolic disorders in a central role in the pathogenesis of these patients suffering from a complex syndrome and not just an isolated diastolic dysfunction.

Ethical considerations

Not applicable.