News Release

Title

Identification of a mechanism that regulates cardiac fibrosis and the development of heart failure with diastolic dysfunction

Key Points

- Heart failure is the leading cause of morbidity and mortality worldwide
- Myofibroblasts participate in the progression of cardiac fibrosis that is the main cause of heart failure.
- Meflin plays an inhibitory role in myofibroblast activation and the development of diastolic heart failure.

Summary

Dr. Akitoshi Hara at Department of Cardiology, Nagoya University Graduate School of Medicine, Prof. Masahide Takahashi and Assoc. Prof. Atsushi Enomoto at Department of Pathology, Nagoya University Graduate School of Medicine, Prof. Toyoaki Murohara at Department of Cardiology, Nagoya University Graduate School of Medicine, Prof. Takahiro Higuchi at Department of Biomedical Imaging, National Cardiovascular and Cerebral Research Center, and their collaborators identified a mechanism that controls cardiac fibrosis. They demonstrated that meflin, a membrane protein that is expressed in cardiac fibroblasts, has an inhibitory role in myofibroblast (MF) activation and prevents fibrosis. In addition, the identified that the deregulation of meflin expression is involved in the development of heart failure (HF) with diastolic dysfunction, which is called “HF with preserved ejection fraction (HFpEF)” by cardiologist.

We all know that the heart works to pump blood to the organs and tissues of our body and provide them with oxygen and nutrients. The HF condition means that the heart has lost its capacity to pump blood as it should normally do. The failed heart cannot supply our body with enough amount of blood, which causes dyspnea, edema and fatigue. There are two types of HF --- 1) systolic HF and 2) diastolic HF. The systolic HF, which is characterized by a defect in the contraction of the left ventricle. has been well recognized by cardiologist, and its mechanisms have been extensively studied in the past decades. Accordingly, the treatments and therapies for the systolic HF have been dramatically improved. On the other hand, the molecular mechanisms of the diastolic HF, which is defined by a defect in relaxation of the left ventricle, have remained obscure even though its prevalence has been found to be increasing recently, Thus the development of strategies for the treatments of diastolic HF has long been needed.

It has been suggested that one of the bases for the development of diastolic HF is cardiac fibrosis which is a pathological process characterized by excessive deposition of the extracellular matrix (ECM). In the process, MFs produce abundant ECM proteins and contribute to progressive fibrosis, which results in an increase in the stiffness of tissues and cardiac dysfunction. It is noted that fibrosis is involved in the pathology of the both types HF.

Here, the research group examined the role of meflin in the development of HF. Meflin knockout (KO) mice exhibited HF with diastolic dysfunction. They found that meflin has an inhibitory role in MF activation. they showed that meflin interacts with bone morphogenetic protein 7 (BMP7), an anti-fibrotic factor, and promotes BMP7 signaling. The data suggested that meflin can be a therapeutic target not only for H but other fibrotic diseases.

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Research Background

Hear failure (HF)is the leading cause of morbidity and mortality worldwide. HF has been described as a condition with the impairment of the pump function. Patients with HF suffer from dyspnea, edema and fatigue. A defect in the systolic function of the heart is the major pathogenic basis of HF and has been extensively studied. The decline in cardiomyocyte contractile function is a major underlying mechanism for the development of systolic dysfunction, which, however, does not fully explain the etiology of all HF patients.

Recently, defects in the diastolic function of the heart have also been increasingly recognized as another major cause of HF. This diseased condition has been termed HF with diastolic dysfunction, the prevalence of which has been found to be higher than previously thought. Previous studies have revealed that the major structural alterations observed in the heart tissues of patients with diastolic HF are cardiac fibrosis and stiffening, which are driven by aging, hypertension, coronary artery diseases, cardiomyopathy, inflammation, and metabolic diseases such as diabetes mellitus. However, the mechanisms of the diastolic dysfunction and the therapeutic strategy for the patients are not fully established.

Fibrosis has been described as an excessive accumulation of fibrillar and collagen-rich extracellular matrix (ECM) that replaces functional tissues, which causes organ stiffening and dysfunction. A major player in fibrosis and tissue repair is myofibroblasts (MFs) that produce and degrade ECM proteins and secrete many types of growth factors and cytokines, such as transforming growth factor (TGF)-β to coordinate inflammation. Previous studies showed that cardiac MFs differentiate from resident fibroblasts that exist in the heart.

Research Results

The research team focused on meflin, which is specifically expressed in a mesenchymal stromal cell (MSC). MSC is known to be a source of MF. They found that meflin inhibited MF differentiation of MSCs. Meflin expression was downregulated by the stimulation with TGF-β, substrate stiffness, aging, and hypoxia in MSCs. When they induced HF in meflin knock-out (KO) mice by a surgical procedure, the failing hearts of meflin KO mice developed stiffer hearts with diastolic dysfunction than those of wild-type mice. Mechanistically, they found that meflin interacts with bone morphogenetic protein 7 (BMP7) and promotes its intracellular signaling. These findings indicate that meflin has an inhibitory role of MF activation, and its deficiency is involved in the development of diastolic HF.

Research Summary and Future Perspective

The important achievement of this research is that they have identified the pathophysiological mechanisms of diastolic HF for which there is no specific medicine. For the next step, we should establish the evidence that the augmentation of meflin expression ameliorates the HF condition using animal models. Meflin can represent a novel therapeutic target for the prevention or treatment not only for HF but other fibrotic diseases.

Publication

Hara A, Kobayashi H, Asai N, Saito Shi, Higuchi T, Kato K, Okumura T, Bando-Kureishi Y, Takefuji M, Mizutani Y, Miyai Y, Saito Sho, Maruyama S, Maeda K, Ouchi N, Nagasaka A, Miyata T, Mii S, Kioka N, Worthley DL, Murohara T, Takahashi M, Enomoto A. [1]Department of Pathology, [2]Cardiology, [4]Division of Molecular Pathology, Center for Neurological Disease and Cancer, [6]Gastroenterology, [7]Nephrology, and [9]Anatomy and Cell Biology, Nagoya University Graduate School of Medicine, Nagoya, Japan,[3]School of Medicine, University of Adelaide and South Australian Health and Medical Research Institute,Adelaide, South Australia, Australia,[5]Department of Biomedical Imaging, National Cardiovascular and Cerebral Research Center, Suita, Osaka,Japan,[8]Division of Anatomy, Department of Human Development and Fostering, Meikai University School of Dentistry, Saitama, Japan,[10]Division of Applied Life Sciences, Graduate School of Agriculture, Kyoto University, Sakyo, Kyoto, Japan,[11]These authors contributed equally. Roles of the mesenchymal stromal/stem cell marker meflin in cardiac tissue repair and the development of diastolic dysfunction. *Circulation Research*. 2019; June:22. doi: 10.1161/CIRCRESAHA.119.314806

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