News Release

Title

Protein kinase N promotes stress-induced cardiac dysfunction through phosphorylation of myocardin-related transcription factor A and disruption of its interaction with actin.

Key Points

○Despite therapeutic advances in cardiovascular diseases, heart failure is a major clinical health problem with significant mortality and morbidity.

○We found that members of the PKN family plays a role in regulating hypertrophy and fibrosis in the heart by mediating the interaction of MRTFA with actin

○PKN may provide unique targets for therapeutic intervention for heart failure.

Summary

Dr. Teruhiro Sakaguchi, Dr. Mikito Takefuji and Prof. Toyoaki Murohara at Department of Cardiology, Nagoya University Graduate School of Medicine identified a novel pathological signaling pathways of cardiac dysfunction via Protein kinase N (PKN). Heart failure is a syndrome resulting from structural or functional impairment of ventricular filling or ejection of blood. Despite therapeutic advances in cardiovascular diseases, heart failure is a major clinical health problem with significant mortality and morbidity. Protein phosphorylation is a key intracellular regulatory mechanism that mediates various cellular processes in cardiomyocytes in response to extracellular and intracellular signals, and protein kinases are emerging as potential therapeutic targets. The small GTPase RHOA is known for its role in regulating cytoskeletal rearrangements and cell polarity and for its coordination of a wide range of cellular processes. RHOA controls cardiac related genes mediating myocardin-related transcription factor A (MRTFA)/ serum response factor (SRF). Although RHOA-mediated intracellular concentration of G-actin is a well-known factor to mediate MRTFA/SRF activity, RHOA signaling also contributes to MRTFA phosphorylation. The role of MRTFA phosphorylation by RHOA remains largely unclear. They found that MRTFA is a novel substrate of PKN and that PKN mediates the interaction of MRTFA with actin by phosphorylating the actin-binding region of MRTFA. They also show that cardiomyocyte-specific PKN-deficient mice are resistant to pressure overload- and AngII-induced cardiac dysfunction. The data suggested that PKN can be a therapeutic target not for heart failure. This work was published online in Circulation on Sep 30, 2019.

Research Background

Heart failure is a major clinical health problem with significant mortality and morbidity

worldwide. The mechanisms underlying heart failure have been studied to extensively improve its prognosis. However, the mechanisms of cardiac dysfunction and the therapeutic strategy for the patients are not fully established. In recent years, protein kinases are emerging as potential therapeutic targets. Protein phosphorylation is a key intracellular regulatory mechanism that mediates various cellular processes in cardiomyocytes. Protein phosphorylation regulates cardiac pump function by controlling energy metabolism and the contraction and relaxation of cardiomyocytes, however dysregulated phosphorylation often plays key roles in cardiac disease development.

Research Results

The research team sought to clarify the role of PKN in heart failure. They used transverse aortic constriction (TAC) as a model for pressure overload-induced cardiac hypertrophy and showed that TAC-induced phosphorylation of PKN. They used newly generated mice with cardiomyocyte-specific deficiency for PKN and found that PKN knockout mice were resistant to TAC-induced cardiac hypertrophy and fibrosis. In vitro, they also showed PKN mediates the interaction of MRTFA with actin by phosphorylating the actin-binding region of MRTFA. PKN deficiency protects mice from heart failure development by inhibiting MRTFA/SRF-mediated gene expression with chromatin immunoprecipitation assay. These data indicated that PKN inhibits the binding of MRTFA to actin by phosphorylating MRTFA and activates SRF-mediated expression of cardiac hypertrophy- and fibrosis-associated genes.

Research Summary and Future Perspective

PKN-MRTFA-SRF-mediated gene expression provides important novel insight into the pathological signaling pathways of cardiac dysfunction. The PKN family plays a role in regulating hypertrophy and fibrosis in the heart and is a unique target for therapeutic intervention for heart failure.

Publication

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