News Release

Protein kinase N regulates cardiac fibrosis in heart failure. ~ A novel therapeutic target for cardiac fibrosis ~

Key Points

- In an aging society, the number of patients with heart failure is rapidly increasing, and the development of heart failure therapy is an urgent priority.
- The extent of fibrosis is associated with the progression of heart failure, however, a mechanism of cardiac fibrosis remains unclear.
- Cardiac fibrosis and function are regulated by protein kinase N in murine myocardial infarction and heart failure models.
- Protein kinase N controls cardiac fibrosis through cardiac fibroblast-to-myofibroblast differentiation.
- Protein kinase N could be a novel therapeutic target for cardiac fibrosis in heart failure.

Summary

In this study, Satoya Yoshida, Mikito Takefuji and Toyoaki Murohara in Department of Cardiology, Nagoya University Graduate School of Medicine, demonstrat~~ed~~ protein kinase N (PKN) regulates cardiac fibrosis in heart failure.

In an aging society, the number of patients with heart failure is rapidly increasing. The development of heart failure therapy is an urgent priority. In response to injury, the heart develops fibrosis to maintains its structure, but the expansion of fibrosis impairs cardiac function and leads to the development and progression of heart failure. The mechanism of cardiac fibrosis remains unclear. We have found that PKN activation in cardiomyocyte causes cardiac dysfunction (Sakaguchi T *et al.*, *Circulation 2019*). Here, we investigated the role of PKN in cardiac fibroblasts. Fibroblast-specific PKN deficiency reduced cardiac fibrosis and preserved cardiac function in myocardial infarction and heart failure with preserved ejection fraction (HFpEF) models. Moreover, PKN regulated cardiac fibroblast differentiation and fibrosis through p38 MAPK phosphorylation.

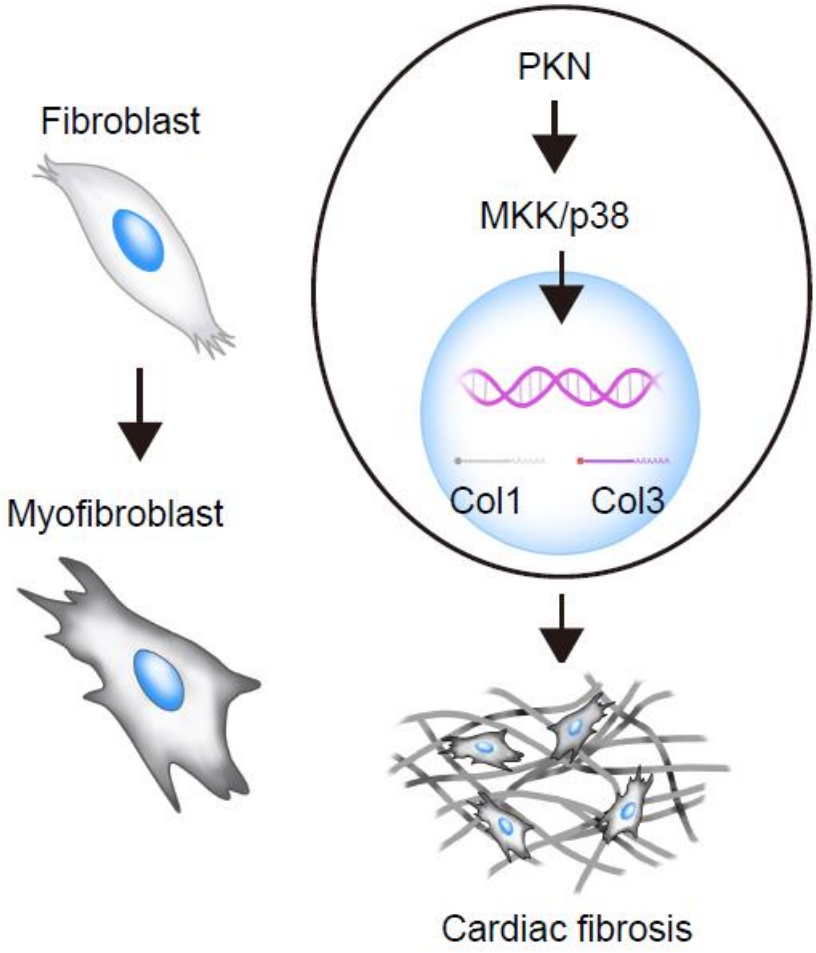
Research Background

Recently, heart failure is a global pandemic with increasing prevalence, and its prognosis remains poor. In response to injury, the heart develops fibrosis to maintains its structure, but the expansion of fibrosis impairs cardiac function

and leads to the development and progression of heart failure. It is known that a cardiac fibroblast contributes to the formation of cardiac fibrosis, however its mechanism remains unclear. Here, we investigated the role of PKN in cardiac fibroblasts.

Research Results

PKN1 and PKN2 were expressed in cardiac fibroblasts and activated by transforming growth factor-b (TGFb) stimulation. Tamoxifen-inducible fibroblast-specific PKN deficiency reduced cardiac fibrosis and preserved cardiac function in murine myocardial infarction and HFpEF models. Although PKN1/2 deletion in cardiac fibroblasts did not significantly affect proliferation and migration, PKN1/2 deletion decreased the TGFb-induced expression of alpha smooth muscle actin as well as collagen I and III. PKN deficiency in cardiac fibroblasts significantly inhibited p38 MAPK phosphorylation, conversely, PKN overexpression promoted p38 MAPK activity.



Research Summary and Future Perspective

PKN controls cardiac fibrosis through fibroblast differentiation, suggesting that PKN could be a novel therapeutic target for cardiac fibrosis in heart failure.

Publication

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