

News Release

Title

Cardiac myocyte-derived follistatin-like 1 prevents renal injury in a subtotal nephrectomy model

Key Points

- Renal injury increased plasma levels of follistatin-like 1 (Fstl1), which is a heart-derived secreted factor.
- Cardiomyocyte-specific deletion of Fstl1 led to exacerbation of renal injury in a mouse model of chronic renal failure.
- Systemic administration of Fstl1 to mice led to improved renal damage in a model of chronic renal failure.
- Fstl1 could represent a novel therapeutic target for the treatment of chronic kidney disease.

Summary

Satoko Hayakawa (Department of Cardiology), Noriyuki Ouchi (Department of Molecular Cardiology), Toyooki Murohara (Department of Cardiology) and their collaborators in Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, MD, PhD) investigated the role of cardiac follistatin-like 1 (Fstl1) in renal injury in a mouse model of chronic renal failure induced by subtotal nephrectomy. Subtotal nephrectomy increased plasma Fstl1 levels, which was suppressed by cardiomyocyte-specific ablation of Fstl1. Ablation of Fstl1 in a cardiomyocyte-specific manner led to exacerbation of renal injury and inflammatory response after subtotal nephrectomy. Systemic administration of Fstl1 to mice led to improvement of renal damage and inflammation after subtotal nephrectomy. Therefore, cardiac myocyte-derived follistatin-like 1 protects against renal injury following subtotal nephrectomy, suggesting that Fstl1 could represent a novel therapeutic target for the treatment of chronic kidney disease. This work was published online in Journal of the American Society of Nephrology on July 28, 2014.

Research Background

The prevalence and incidence of chronic kidney disease (CKD) have increased in developed countries (e.g. US, Japan). CKD is an independent risk factor of heart diseases. Conversely, heart diseases including chronic heart failure are involved in the development of CKD. Thus, a bidirectional, pathological interaction between heart and kidney can contribute to the progressive dysfunction of both tissues. A number of studies demonstrate that heart tissue produces a variety of secreted proteins which have been termed “cardiokines”. Previously, we reported that follistatin-like 1 (Fstl1) is a cardiokine, which is up-regulated by various heart stresses and that Fstl1 improves cardiac ischemic injury and hypertrophy in an autocrine or paracrine manner. However, the functional role of cardiac Fstl1 in regulating remote organ phenotypes has not been examined previously. Here, we investigated whether cardiac myocyte-derived Fstl1 affects the development of chronic kidney disease in an endocrine manner using a mouse subtotal nephrectomy model.

Research Results

Cardiac specific Fstl1 deficient (cFstl1-KO) mice and control mice were subjected to subtotal (5/6) nephrectomy. Renal injury increased plasma levels of Fstl1, which were suppressed in cFstl1-KO mice. cFstl1-KO mice showed exacerbated albuminuria and renal injury after subtotal nephrectomy, which were accompanied with increased inflammatory cytokines and oxidative stress markers. Systemic administration of Fstl1 to mice led to improvement of albuminuria and renal damage after subtotal nephrectomy, which was accompanied with attenuation of inflammatory response and oxidative stress. Treatment of cultured human mesangial cells with recombinant Fstl1 protein attenuated the inflammatory responses through an AMP-activated protein kinase (AMPK)-dependent manner.

Research Summary and Future Perspective

In summary, we demonstrated that cardiac myocyte-derived Fstl1 protects against renal injury following subtotal nephrectomy by its ability to reduce the inflammatory response through an AMPK-dependent mechanism (Figure 1). Thus, Fstl1 could represent a novel mediator involved in communication between the heart and kidney. Furthermore, Fstl1 could represent a novel therapeutic target for the treatment of chronic kidney disease.

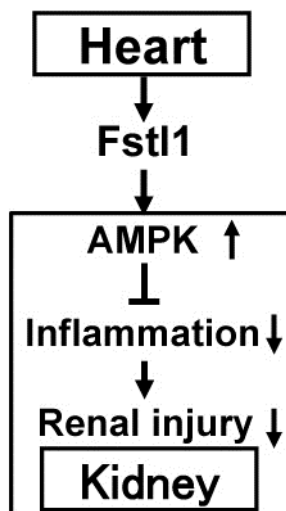


Figure1: Renal protection by Fstl1

Hayakawa S, Ohashi K, Shibata R, Kataoka Y, Miyabe M, Enomoto T, Joki Y, Shimizu Y, Kambara T, Uemura Y, Yuasa D, Ogawa H, Matsuo K, Hiramatsu-Ito M, Van Den Hoff MJ, Walsh K, Murohara T, Ouchi N. Cardiac myocyte-derived follistatin-like 1 prevents renal injury in a subtotal nephrectomy model. *Journal of the American Society of Nephrology* , July 28, 2014

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http://www.med.nagoya-u.ac.jp/medical/dbps_data/_material/_nu_medical/_res/topix/2014/Fstl1_20140728jp.pdf