Cardiac myocyte follistatin-like 1 functions to attenuate hypertrophy following pressure overload

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AUTHOR SUMMARY

Factors secreted by the heart are required for maintaining homeostasis and controlling stress-induced cardiac remodeling. These heart-secreted proteins, referred to as “cardiokines,” are candidate targets for therapeutic treatments. One recently identified cardiokine is follistatin-like 1 (Fstl1), a glycoprotein that shows limited similarity to other follistatin family members. Previous studies have shown that the Fstl1 RNA transcript is expressed in explanted human failing heart and that Fstl1 protein levels in the bloodstream are increased in patients with acute coronary syndrome or heart failure (1–3). Therefore Fstl1 appears to be a clinically relevant secreted protein that participates in the responses to cardiovascular stress. To understand the role of Fstl1 in the heart, we sought to identify the cell types that produce and respond to this factor and to characterize the response of the heart to stress when Fstl1 levels are manipulated genetically. We found that Fstl1 is a stress-induced cardiokine produced in large part by cardiac myocytes (muscle cells) and that it negatively regulates cardiac hypertrophy, which is characterized by a decrease in the size of the heart chambers, and protects the heart from systolic dysfunction, a failure of the heart to contract properly.

Here, we constructed and characterized mouse lines that ablate Fstl1 expression in cardiac myocytes (Fstl1-KO mice) and mice that transgenically overproduce Fstl1 (Fstl1-TG mice), leading to higher circulating levels of this factor in the bloodstream. In normal mice, Fstl1 levels in the heart increase in response to cardiac pressure overload. This induction of Fstl1 expression in response to cardiac stress induced by pressure overload was reduced markedly in the Fstl1-KO mice (Fig. P1A), indicating that the myocytes are a major source of Fstl1 in the heart. The Fstl1-KO and Fstl1-TG mice were not different from normal mice in unstimulated conditions, but Fstl1 ablation in myocytes led to greater cardiac hypertrophy and promoted the transition to cardiac failure when the heart was subjected to pressure overload (Fig. P1 B–D). Conversely, overexpression of Fstl1 in the Fstl1-KO mice inhibited cardiac hypertrophy and protected against cardiac dysfunction under these conditions. Moreover, the specific deletion of Fstl1 in myocytes impaired the activation of AMP kinase (AMPK) signaling, a protective signaling pathway in the heart, under pressure-overload conditions, whereas mice overexpressing Fstl1 showed increased activation of AMPK signaling under these same conditions. In cardiac myocytes maintained in a cell culture, Fstl1 protein caused activation of AMPK signaling that was dependent on the level of Fstl1 and on the duration of exposure to it. In addition, AMPK signaling was required for the antihypertrophic actions of Fstl1 in the cell culture.

We conclude that Fstl1 is a stress-induced cardiokine that is produced largely by cardiac myocytes and functions as an autocrine/paracrine signaling molecule (i.e., signaling within the same cell or to an adjacent cell) to negatively regulate cardiac hypertrophy and to protect the heart from systolic dysfunction. Thus, further studies of Fstl1 regulation and function in the heart may lead...
to a better understanding of how to diagnose and treat cardiac disease.

