

EDITORIAL COMMENT

Follistatin-Like 1

Growing Evidence for Its Beneficial Role in Heart Failure*

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Heat failure with preserved ejection fraction (HFpEF) is associated with debilitating symptoms, recurrent hospitalizations, and a poor prognosis similar to that in heart failure with reduced ejection fraction (HFrEF). Major clinical trials have failed to identify specific drug therapies for HFpEF. These disappointing results have been attributed in part to an incomplete understanding of HFpEF pathophysiology (1).

Follistatin-like 1 (FSTL1) is a secreted glycoprotein that was originally cloned as a transforming growth factor β -inducible gene (2). FSTL1 shares a structural motif, the follistatin domain, with follistatin, follistatin-like 3, and members of the secreted protein acidic and cysteine rich (SPARC) protein family. Overall, FSTL1 displays a low degree of amino acid sequence similarity with these other proteins, suggesting that it has evolved distinct functions. FSTL1 is weakly expressed in the normal myocardium but strongly induced in mice with HFrEF after transverse aortic constriction (3). Hypertrophied cardiac myocytes have emerged as the main producers of FSTL1 in this setting. Notably, genetic deletion of FSTL1 in cardiomyocytes exacerbated cardiac (myocyte) hypertrophy and systolic dysfunction in the HFrEF model (3). Outside the heart, FSTL1 has been shown to promote inflammation and fibrosis (4,5).

Comorbidities such as arterial hypertension and diabetes have been proposed to drive microvascular inflammation, fibrosis, and cardiomyocyte hypertrophy in HFpEF (6), disease pathways that may all be influenced by FSTL1 (3-5). In this issue of *JACC: Basic*

to Translational Science, Tanaka et al. (7), therefore, postulated that FSTL1 plays a role in HFpEF. In their study, mice were subjected to unilateral nephrectomy followed by intraperitoneal infusion of aldosterone and addition of NaCl to the drinking water for 4 weeks. The animals developed arterial hypertension with concentric left ventricular hypertrophy, interstitial fibrosis, and diastolic dysfunction on Doppler echocardiography. Left ventricular ejection fraction was preserved, and wet lung weight was (slightly) increased, indicating that the animals had developed HFpEF with pulmonary congestion. Considering the

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challenges of using Doppler echocardiography to assess diastolic function in mice (8), pressure-volume loop analyses would have strengthened the data. Genetic deletion of FSTL1 in cardiomyocytes did not affect arterial blood pressure, but worsened cardiac (myocyte) hypertrophy, diastolic dysfunction, and pulmonary congestion (7). These data support the idea that FSTL1 provides an autocrine feedback loop to protect from maladaptive cardiac hypertrophy in HFrEF and now also HFpEF (3,7). Notably, mice lacking FSTL1 in cardiomyocytes developed enhanced cardiac fibrosis in the HFrEF model, but not the HFpEF model, indicating that FSTL1 may also exert anti-fibrotic effects under specific experimental conditions (3,7). Inflammatory cells and endothelial cells participate in the regulation of cardiac hypertrophy, fibrosis, and remodeling during pressure-overload (9), but the impact of FSTL1 on these non-myocyte cell types in HFrEF or HFpEF currently remains unknown.

To start exploring the clinical ramifications of their study, Tanaka et al. (7) measured serum FSTL1 concentrations in 32 patients with HFpEF using a commercially available immunoassay. Patients had higher circulating FSTL1 levels (mean 167 ng/ml) than 8 apparently healthy individuals (96 ng/ml) (7). At first sight, this observation confirms a previous

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report from the same group documenting elevated FSTL1 levels in patients with HF_{rEF} (10). However, the concentrations measured in the present study are surprisingly high (7). In a previous study, FSTL1 concentrations in 120 apparently healthy individuals ranged from 1 to 18 ng/ml (11). Other investigators have measured similar FSTL1 concentrations in apparently healthy individuals (12,13). The very high FSTL1 concentrations reported in the present study (7), and by others (14), remain unexplained. In the HF_{rEF} patients, serum FSTL1 was measured by SDS-PAGE and immunoblotting, and protein standards were used to ascertain the appropriate size of the FSTL1 band (10); concentrations in the HF_{rEF} study were reported as arbitrary units, thus precluding a direct comparison with the HF_{pEF} data (10). The specificity of an immunoassay also needs to be established, especially in a complex matrix such as serum or plasma. For example, size-exclusion chromatography can be used to confirm that an immunoassay detects a single analyte with the correct size (~50,000 kDa in the case of human FSTL1) (11). Such an analysis was not performed in the current report (7), and this critical information is also not provided by the vendor of the immunoassay.

In any case, the beneficial effects of endogenous FSTL1 in HF_{rEF} and HF_{pEF} models, suggest that augmentation of FSTL1 signaling could be a therapeutic approach in heart failure. In fact, transgenic

overexpression of FSTL1 mitigated left ventricular hypertrophy, fibrosis, and systolic dysfunction in the murine HF_{rEF} model (3). Likewise, adenoviral transfer of FSTL1 attenuated cardiac hypertrophy and diastolic dysfunction in the HF_{pEF} model (7). Translation of these findings into clinical practice may be challenging if long-term FSTL1 gene overexpression or protein delivery is required in patients with heart failure. Potential extracardiac side effects also need to be considered (4,5). Acute conditions may represent more feasible indications for FSTL1 therapies. Indeed, capitalizing on the antiapoptotic effects of FSTL1 in cardiac myocytes (15), a brief intracoronary infusion of FSTL1 has been shown to reduce infarct size in pigs with acute myocardial infarction (16). A recent study indicated that application of FSTL1 via an epicardial patch enhances cardiomyocyte proliferation and systolic function after acute myocardial infarction (17), further heightening interest in FSTL1 as a therapeutic agent (18). Ultimately, new therapies may emerge from a better understanding of the mechanisms whereby FSTL1 exerts its multifaceted effects in acute and chronic heart diseases.

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