JACC: BASIC TO TRANSLATIONAL SCIENCE
VOL. 1, NO. 4, 2016
ISSN 2452-302X
http://dx.doi.org/10.1016/j.jacbts.2016.04.002

PRE-CLINICAL RESEARCH

Follistatin-Like 1 Regulates Hypertrophy in Heart Failure With Preserved Ejection Fraction

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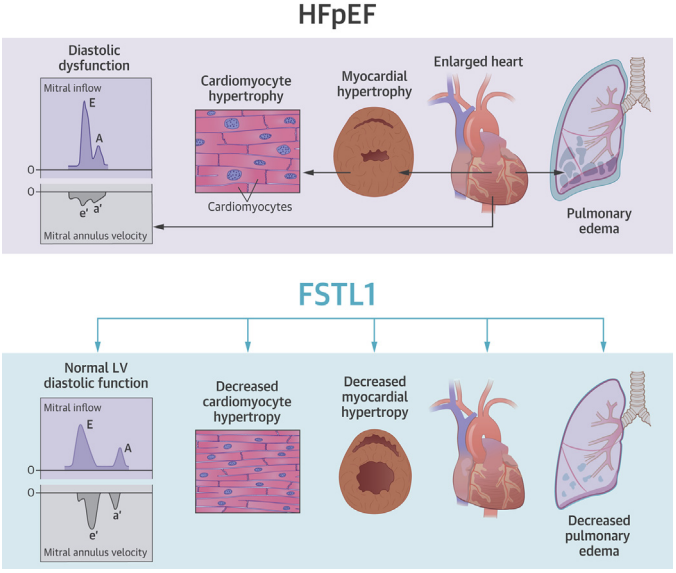
VISUAL ABSTRACT



Tanaka, K. et al. J Am Coll Cardiol Basic Trans Science. 2016;1(4):207–21.

HIGHLIGHTS

- **Fstl1, also known as transforming growth factor-β–stimulated clone 36, is an extracellular glycoprotein implicated in the pathophysiology of cardiac disease.**
- **Fstl1 acts in a noncanonical manner relative to other follistatin family members, but its functions remain poorly understood.**
- **Circulating Flst1 levels are increased in humans with chronic stable HFpEF.**
- **Fstl1 treatment modulates cardiomyocyte hypertrophy in vitro and in vivo.**
- **Cardiac myocyte deletion of Fstl1 worsens the HFpEF phenotype in mice.**
- **These studies indicate that Fstl1 may be therapeutically effective in HFpEF by modulating cardiac hypertrophy and improving parameters of diastolic dysfunction.**

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This work was supported by a grant from the National Institutes of Health (HL117153) to Dr. Sam. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Tanaka and Valero-Muñoz contributed equally to this work.

Manuscript received November 11, 2015; revised manuscript received March 12, 2016, accepted April 6, 2016.

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 1, NO. 4, 2016
JUNE 2016:207–21

SUMMARY

Heart failure with preserved ejection fraction (HFpEF) accounts for ~50% of all clinical presentations of heart failure, (HF) and its prevalence is expected to increase. However, there are no evidence-based therapies for HFpEF; thus, HFpEF represents a major unmet need. Although hypertension is the single most important risk factor for HFpEF, with a prevalence of 60% to 89% from clinical trials and human HF registries, blood pressure therapy alone is insufficient to prevent and treat HFpEF. Follistatin-like 1 (Fstl1), a divergent member of the follistatin family of extracellular glycoproteins, has previously been shown to be elevated in HF with reduced ejection fraction and associated with increased left ventricular mass. In this study, blood levels of Fstl1 were increased in humans with HFpEF. This increase was also evident in mice with hypertension-induced HFpEF and adult rat ventricular myocytes stimulated with aldosterone. Treatment with recombinant Fstl1 abrogated aldosterone-induced cardiac myocyte hypertrophy, suggesting a role for Fstl1 in the regulation of hypertrophy in HFpEF. There was also a reduction in the E/A ratio, a measure of diastolic dysfunction. Furthermore, HFpEF induced in a mouse model that specifically ablates Fstl1 in cardiac myocytes (cardiac myocyte-specific Fstl1 knockout [cFstl1-KO]) showed exacerbation of HFpEF with worsened diastolic dysfunction. In addition, cFstl1-KO-HFpEF mice demonstrated more marked cardiac myocyte hypertrophy with increased molecular markers of atrial natriuretic peptide and brain natriuretic peptide expression. These findings indicate that Fstl1 exerts therapeutic effects by modulating cardiac hypertrophy in HFpEF. (J Am Coll Cardiol Basic Trans Science 2016;1:207–21)

Heart failure with preserved ejection fraction (HFpEF) accounts for up to 50% of all heart failure (HF) presentations (1); yet, in contrast to heart failure with reduced ejection fraction (HFrEF), there are no evidence-based therapies. The numerous negative or neutral HFpEF clinical trials, to date, suggest an incomplete mechanistic understanding about HFpEF and the comorbidities that are ubiquitous in HFpEF (2,3). Therefore, the increasing prevalence of this disease and the failure to identify successful therapies for HFpEF suggest that the identification of novel pathways is a priority.

ABBREVIATIONS AND ACRONYMS

ANP = atrial natriuretic peptide
ARVM = adult rat ventricular myocytes
BNP = brain natriuretic peptide
BP = blood pressure
Fstl1 = follistatin-like 1
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction
HR = heart rate
HTN = hypertension
IVST = interventricular septum wall thickness
LV = left ventricular
LVEDD = left ventricular end-diastolic diameter
LVEF = left ventricular ejection fraction
LVH = left ventricular hypertrophy
LVPWT = left ventricular posterior wall thickness

SEE PAGE 222

Despite associated comorbidities, such as obesity and diabetes mellitus, hypertension (HTN) remains *the* most important risk factor for HFpEF, with a prevalence of 60% to 89% reported in large controlled trials, epidemiological studies, and HF registries (1). The presence of left ventricular hypertrophy (LVH) plays a major pathophysiological role in HFpEF, particularly when associated with HTN (4). Myocardial biopsies obtained from a highly selected, younger patient population with HFpEF demonstrated cardiac myocyte hypertrophy, interstitial fibrosis, and evidence of systemic and myocardial inflammation, and oxidative stress (5,6). Therefore, an improved understanding of the HFpEF phenotype, particularly LVH, may provide insights into the development of new therapies for the treatment of HFpEF (7).

Follistatin-like 1 (Fstl1), also known as transforming growth factor-beta–stimulated clone 36, is an extra-cellular glycoprotein that was originally cloned from a mouse osteoblastic cell line as a transforming growth factor-beta–inducible gene and is highly conserved across species (8). Fstl1 acts in a noncanonical manner relative to other follistatin family members. However, its functions remain poorly understood and are possibly cell-type specific. Transduction of Fstl1 into cancer cell lines suppresses growth and invasion (9). Fstl1 is reported to have both anti-inflammatory (10) and proinflammatory (11) actions. Recent studies also implicate Fstl1 in the pathophysiology of cardiac disease in several murine models. Fstl1 overexpression minimized ischemia-reperfusion injury and diminished apoptosis (12). Similarly, Fstl1 improved endothelial cell function and revascularization in a hind-limb ischemia model (13). Recently, we demonstrated elevated blood levels of Fstl1 in a cohort of humans with chronic, stable HFrEF; where elevated Fstl1 levels were significantly associated with LV mass and circulating brain natriuretic peptide (BNP) levels, suggesting a pathogenic role for Fstl1 in cardiac remodeling and LVH (14). In patients with HFpEF, more often than not, structural changes such as LVH are present, because HTN is a major risk factor for the development of LVH (1).

We previously utilized a murine model of HFpEF, which demonstrates features consistent with HFpEF in humans (15–17). HFpEF mice exhibit exercise