HHS Public Access

Author manuscript

Circulation. Author manuscript; available in PMC 2018 November 21.

Published in final edited form as:

Circulation. 2017 November 21; 136(21): 2094–2095. doi:10.1161/CIRCULATIONAHA.117.030421.

Response by Du et al to Letter Regarding Article "Cardiac Fibroblast-Specific Activating Transcription Factor 3 Protects Against Heart Failure by Suppressing MAP2K3-p38 Signaling"

Jie Du, PhD[1,*], **Xin-liang Ma, MD PhD**[2,*], **Yulin Li, PhD**[1], and **Boya Chen**[1]

[1]Beijing Anzhen Hospital of Capital Medical University and Beijing Institute of Heart Lung and Blood Vessel Diseases

[2]Department of Emergency Medicine, Thomas Jefferson University

In response

We thank Dr. Li and colleagues for their comments and interest on our article[1], in which we demonstrated a cell type specific ATF3-medicated transcriptional mechanism against hypertensive remodeling. They agreed with us that ATF3's cardioprotective effects are cardiac fibroblast-dependent through antagonize Map2K3-p38-TGFβ signaling. However, they raised two questions. First what is the importance of cell-specific role of ATF3 in cardiac fibrosis? Second, does the ATF3 dependent mechanism have a general impact on cardiac fibrosis associated with different diseases (such as myocardium infarction, aging et al)? We appreciate their comments and agree that these are important as understanding the role of ATF3 will certainly lead to potential treatment of cardiac fibrosis and heart failure associated with various diseases.

Regarding the role of ATF3 in cardiac fibrosis, it had been uncertain due to conflicting phenotypes. Global ATF3 deficiency promotes pressure overload-induced heart failure, whereas cardiomyocyte-specific transgenic overexpression of ATF3 promotes cardiac hypertrophy. We demonstrated that the function of ATF3 in cardiac fibroblasts is a primary driver of remodeling in hypertension. We believe that this observation is important as it provided the first scientific explanation for the discrepancies of cardiac phenotype in ATF3 manipulated animals. Additionally, we believe our observation is clinically important as it suggests a cell-specific therapy may achieve the best protective effect against cardiac injury. In this connection, we have established a strategy combining miRNA-aided cardiac fibroblast-selective system[1] and hypertensive heart-target agent to achieve cell-specific gene manipulation[2]. Li et al also raised a question of whether neutrophils are involved in hypertensive fibrosis. Our previous study demonstrated that neutrophils play a critical role in arterial hypertension and cardiac fibrosis. $CXCR2^{+}$ neutrophils promote vascular superoxide

[*]**Address for Correspondence:** Jie Du, PhD, Beijing Institute of Heart, Lung, and Blood Vessel Diseases, Beijing Anzhen Hospital, Capital Medical University, 2 Anzhen Avenue, Beijing, China, Tel: 0086-010-64456030, Fax: 0086-010-64456095, jdu@bcm.edu; Xin-Liang Ma, MD, PhD, Department of Emergency Medicine, Thomas Jefferson University, 1025 Walnut Street, Pennsylvania, Philadelphia, USA, **Tel: 215** 955 4994, Fax: 215 503 4458, xin.ma@jefferson.edu.

Disclosures None.

formation, and inhibition of CXCR2 prevents and reverses aortic fibrosis[3]. Moreover, neutrophil-generated S100a8/a9 proteins initiate Ang II-induced cardiac inflammation and fibrosis by activating nuclear factor-κB in cardiac fibroblasts[4]. Cardiac fibroblast is a vital cell type involved in each phase of cardiac remodeling in response to cardiac injury, including inflammatory, proliferative and transdifferentiation. Consistent with our finding, a recent report demonstrates that transgenic mice with fibroblast-specific activation of MKK6-p38 developed interstitial and perivascular fibrosis in the heart, lung and kidney[5].

Regarding the question whether the ATF3 dependent mechanism have a general impact on cardiac fibrosis associated with different diseases, we have recently determined the role of ATF3 dependent fibroblast function utilizing an acute myocardium infarction model. We observed that cardiac fibroblast-specific ATF3 overexpression inhibits cardiac scar formation and heart failure. Taken together, we showed that upregulation of ATF3 in cardiac fibroblasts is a self-compensatory protective mechanism against ventricular remodeling associated with heart failure.

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