Fibrosis, the development of excess fibrous connective tissue, plays a major role in the process of heart injury or stress resulting in heart failure and is categorized into two types - replacement fibrosis and reactive fibrosis. The former involves the replacement of necrotic cardiomyocytes, and the latter is suggested to be involved in undesirable conditions leading to functional deterioration and remodeling. In reactive fibrosis, fibroblast activation subsequently leads to the accumulation of a high amount of extracellular matrix (ECM) in the interstitial space. Developmentally, residual fibroblasts originate from the epicardium (most abundant), endothelial cells, and neural crest. In pathological situations, cells from other sources (e.g., endothelial-to-mesenchymal transition and hematopoietic cells) were also reported to be mobilized and to contribute substantially to fibrosis. The cellular sources of ECM that promote cardiac fibrosis have been a matter of controversy because of the lack of robust fibroblast markers. However, a recent study using strict lineage tracing in combination with highly specific fibroblast markers showed that only residual fibroblasts contribute to fibrosis under pressure overload. Under various kinds of stress or injury imposed on myocardium, the activated and mobilized inflammatory cells (monocytes/macrophages, neutrophils, lymphocytes, dendritic cells, and mast cells), vascular cells, cardiomyocytes, and activated fibroblasts themselves produce several profibrotic cytokines and chemokines. In addition, fibroblasts also activate inflammatory cells, resulting in mutual communication. When activated by profibrotic stimuli, fibroblasts proliferate and differentiate into a secretory phenotype, called "myofibroblast". Myofibroblasts are hyper-reactive to chemical signals, thereby provoking exaggerated production of ECM, mainly collagen type I (Col1) and type III (Col3). An excess of such collagen production compared with its degradation results in substantial fibrosis and destruction of cardiac architecture and function (Figure).

The factors known to activate fibroblasts include renin-angiotensin-aldosterone system (RAS)-related hormones, growth factors (e.g., TGF-β, PDGF, CTGF), inflammatory cytokines (e.g., IL-6), and protease secreted from mast cells. Cardiac fibroblast proliferation and migration is also affected in part by the NADPH oxidase (Nox)/ROS activity produced due to mitochondrial dysfunction. Factors related to collagen processing include LOX, matricellular protein, and metalloproteinase (MMP), and they are involved in both collagen production and degradation. For pathological accumulation of collagen, in addition to the above factors, several other factors have been reported, and recently, cardiotrophin-1 (CT-1), galectin-3 (Gal-3), neutrophil gelatinase-associated lipocalin (NGAL), and microRNAs were reported as new candidates in pre-clinical and clinical studies. Among these factors, angiotensin II (Ang II) plays a major role in cardiac fibrosis, and circulatory as well as local Ang II has been reported to stimulate fibroblast proliferation, and collagen production via fibrotic signaling pathways such as activation of the TGF-β signaling pathway, or Nox/ROS activation.

The mitochondrial single-stranded DNA-binding protein 1 (SSBP1), known to be involved in mitochondrial DNA replication, recombination, and repair was shown to have preventive effects on breast cancer metastasis. Further, its downregulation increases the radiosensitivity of lung cancer cells. In addition, SSBP1 downregulates TGF-β/SMAD-3 expression in Hela cells, and knocking out its expression increases N-cadherin or fibronectin production. However, its role in cardiac fibrosis has not been reported.

In their report, Tian, et al stated that SSBP1 expression levels decreased during Ang II-induced fibrosis in mouse hearts, and this decrease was attenuated by the addition of valsartan, an Ang II receptor blocker. They further showed that in vitro, both in adult primary fibroblasts and embryonic mouse fibroblast clone cells, namely, NIH 3T3 cells, the SSBP1 expression level was decreased under Ang II and the decrease was attenuated by valsartan. Ang II increased the proliferation of both types of fibroblasts, and consequently increased ColI and 3 protein expression levels. Under Ang II exposure, SSBP1 overex-

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pression inhibited cell proliferation and the expression of collagen-related proteins. In contrast, a decrease in SSBP1 level stimulated fibroblast proliferation and collagen production. These effects were also observed without addition of Ang II.

To determine the pathway downstream to SSBP1, the authors examined the relationship between SSBP1 and Nox/ROS. In the above-mentioned two types of fibroblasts, SSBP1 over- and underexpression had no effects on Nox1 and Nox3 expression levels. Therefore, the authors scrutinized the relationship between p53 and SSBP1 expression levels. The p53 protein plays a role in cardiac fibroblast cell senescence, survival, and collagen expression and is reported to affect cardiac fibrosis through modification of several pathways including TGF-β. They showed that SSBP1 overexpression increases the p53 level whereas underexpression decreases the level, in presence and absence of Ang II. These results show that SSBP1 is related to cardiac fibrosis, at least in part, via the effect of p53 expression level.

A growing body of evidence suggests that cardiac fibrosis may play an important role in the pathogenesis of heart failure. In their study, Tian, et al showed that SSBP1 negatively regulates cardiac fibroblast proliferation, and consequently collagen production via p53 modulation. This finding may offer multiple potential targets for antifibrotic drugs, although several points need to be elucidated for further advancement. First, although the authors showed that SSBP1 does not transcriptionally regulate p53 mRNA levels, the elucidation of the potential mechanisms through which SSBP-1 regulates p53 is crucial. Second, because SSBP-1 was shown to be downregulated in the presence of Ang II, factors regulating the SSBP-1 expression are intriguing to investigate. Third, SSBP-1 may affect a wider range of fibrotic processes such as myofibroblast transformation and collagen processing and degradation. In a previous study using breast cancer cells, knockdown of SSBP1 induced c-Rel/p50 nuclear localization and activated TGF-β promoter activity. SSBP1 may modulate cytokine and chemokine networks in inflammatory cells, vessel cells, or cardiomyocytes. In addition, MMPs include members that not only affect collagen processing but also affect fibroblast proliferation and transformation, partly by coordinating with cytokines such as TGF-β. Currently, antifibrotic drugs have been approved for idiopathic pulmonary fibrosis, while no specific antifibrotic pharmacological therapy exists for cardiac fibrosis. This report sheds new light on the mecha-
nisms of cardiac fibrosis, and can lead to new therapeutic targets based on SSBP1-related fibrosis inhibition.

Disclosures
Conflicts of interest: None.

References