This editorial refers to ‘Syndecan-4 is a key determinant of collagen cross-linking and passive myocardial stiffness in the pressure-overloaded heart’ by K.M. Herum et al., pp. 217–226.

Approximately one in 10 deaths in developed countries is attributed to heart failure, and the prevalence of heart failure (HF) is expected to increase 50% by 2030.1 Diastolic dysfunction is central to HF development and is defined as increased stiffness of the left ventricle (LV) resulting in abnormal relaxation, decreased compliance, and impaired filling. On the molecular level, myocardial stiffness can develop as a result of altered sarcomere structure and function and extracellular matrix (ECM) reorganization.2,3

Herum et al.1 investigated the impact of syndecan-4 deletion on myocardial stiffness and LV remodelling in a mouse model of pressure overload induced by aortic banding. Syndecan-4 null mice showed reduced concentric hypertrophic remodelling after banding, resulting in significantly lower passive tension. Passive tension was not affected by altered cardiomyocyte function, as there was no change in the ratio of compliant to stiff titin isoforms. Rather, the passive tension changes were attributed to ECM changes. Previously, the same group has shown that syndecan-4 deletion attenuates collagen deposition 24 h after aortic banding through the calcineurin/nuclear factor of activated T-cells (NFAT) signalling, but that by day 7 the effect was lost.5 This finding suggested that in chronic pressure overload, syndecan-4 properties shift from ECM induction and deposition to ECM cross-linking and reorganization. Indeed, calcineurin stimulation of cardiac fibroblasts induced osteopontin, which is known to enhance lysyl oxidase (LOX) expression and activity.6 Further, osteopontin production in cardiac fibroblasts was inhibited after treatment with an NFAT inhibitor. Syndecan-4 directly promotes LOX expression during all stages of LV remodelling stimulated by aortic banding, as this effect is attenuated in the absence of syndecan-4. Interestingly, the extracellular domain of syndecan-4 was also shown to interact with collagen fibrils and to promote collagen cross-linking by LOX. A mechanistic diagram depicting syndecan-4 regulation of myocardial stiffness is shown in Figure 1.

Syndecan-4 is a transmembrane heparan sulfate proteoglycan expressed by multiple cell types, including macrophages, fibroblasts, smooth muscle cells, and cardiomyocytes.7,8 Syndecan-4 interacts with a range of ECM components such as laminin and fibronectin and is implicated in focal adhesion assembly with integrins αVβ3, α5β1, and α6β4.9–11 In particular, syndecan-4 links cytoskeleton to ECM and functions as a receptor for fibroblast growth factor-1 and -2.12,13 In addition to aortic banding, increased syndecan-4 expression has also been reported in diabetes, myocardial infarction, and heart failure.13–15 Syndecan-4 is up-regulated by the inflammatory mediators tumour necrosis factor-α and interleukin-1β.5

LV remodelling in the pressure overload myocardium involves the increased expression of a variety of ECM enzymes, including matrix metalloproteinase (MMP)-2, -9, and -13. All three of these MMPs interact or proteolytically process syndecan-4.16–18 While syndecan-4 deletion did not affect MMP expression or activity, proteolytic cleavage of syndecan-4 by MMPs regulates cell adhesion and migration.19,20 Further investigation into the effects of cleaved syndecan-4 products in the setting of pressure overload is needed, and proteomics experiments to reveal cleavage sites coupled with examination of the syndecan-4 matricryptins generated would better define these connections.

In addition to direct regulation of ECM, syndecan-4 indirectly regulates ECM by controlling macrophage function. Transglutaminase 2 interacts with syndecan-4 and CD44 at the macrophage surface to promote phagocytic removal of apoptotic cells.21 Boyanovsky et al. reported that syndecan-4 null mice have reduced uptake of V secretory phospholipase A2-modified low-density lipoprotein by macrophages in the atherosclerotic plaque, indicating a direct role for syndecan-4 in mediating endocytosis and microphagocytosis functions.22 Additional studies examining how syndecan-4 regulates macrophage function in late stages of pressure overload setting may reveal additional mechanisms of action.23

Cardiac fibroblasts are the major cell type that contribute to ECM reorganization and increased LV stiffening through increased collagen deposition. Collagen deposition is increased with age, in pressure-overload hypertrophy, and after myocardial infarction.24–26 However, it is not only the amount of collagen that determines diastolic ventricular compliance, but also the qualitative characteristics of the collagen. For example, the type of collagen produced (e.g. collagen I or III), amount and type of post-translational modification (e.g. glycation and cross-linking), and location (e.g. in perimysial or endomysial fibres) combine to determine net influence of collagen on LV stiffness.27
Among the enzymes that contribute to collagen cross-linking, LOX occupies an important role; however, little is known about LOX mechanisms regulating LV remodelling.  In summary, Herum et al. identify Syndecan-4 roles in collagen cross-linking and passive LV stiffness in the setting of the pressure-overloaded myocardium. The findings of this study are novel and suggest important multi-step roles for syndecan-4 along the continuum of heart failure progression. Their results highlight the importance of collagen cross-linking, which may be a potential therapeutic target for diastolic dysfunction.

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**References**


