Fibrosis or hypertrophy: let TIMPs decide

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This editorial refers to ‘Differential role of TIMP2 and TIMP3 in cardiac hypertrophy, fibrosis, and diastolic dysfunction’ by D. Fan et al., pp. 268–280, this issue.

Heart failure with preserved ejection fraction (HFPEF) is a major cause of morbidity and mortality and constitutes a significant portion of medical care costs. Being as deadly as systolic HF, it completely lacks effective therapy beside the management of its metabolic risk factors including diabetes, obesity and hyperlipidaemia, and hypertension. Typical medication that helps systolic HF (HF with reduced EF, HFREF) patients, such as beta-blockade and angiotensin-converting enzyme inhibitors, are not successful in HFPEF patients.¹

HFPEF is characterized by cardiomyocyte hypertrophy and increased interstitial fibrosis, both leading to enhanced cardiac stiffness and dysfunction.² Therapeutic strategies targeting the fundamental underpinnings of hypertrophy and fibrosis remain an unmet medical need and hence represent an important area for research and development.

The present paper by Fan et al.³ reveals paradoxical roles for tissue inhibitors of MMPs (TIMPs) in Angiotensin-II (AngII)-induced cardiac fibrosis. Whereas the absence of TIMP2 enhanced hypertrophy without affecting fibrosis, lacking TIMP3 increased cardiac fibroses along with enhanced cardiac inflammation. These findings first of all underline the anti-inflammatory and parallel anti-fibrotic properties of TIMP3, also observed in other organs. Its absence enhanced immune activation and fibrosis in mouse models of bleomycine-induced pulmonary disease,⁴ nephritis,⁵ and auto-immune hepatitis.⁶

Matrix metalloproteinases (MMPs) and their physiological inhibitors (TIMPs) are key regulators of interstitial fibrosis, matrix remodelling, and overall cardiac structure and function. Whereas activation of MMPs may favour collagen degradation, myocyte slippage, cardiac dilatation and systolic dysfunction,⁷ activation of their physiological inhibitors (TIMPs) may counter-act the MMPs, and enhance cardiac interstitial fibrosis.⁸–¹² In addition to the classical function of the MMP–TIMP family in cardiac fibrosis, the propagation and the termination of immune responses also depend on this MMP–TIMP axis. This new concept linking MMP–TIMP complex more demanding, since changes in inflammation will also have an impact on fibrosis, independent of matrix shedding by MMPs. With TIMPs blocking these immunomodulating function of different MMPs, it becomes a puzzle difficult to solve.

Which are the pathways by which TIMP3 may decrease cardiac immune activation and fibrosis? First of all, TIMP3 is the only TIMP able to bind and inhibit the activity of TNF-α-converting enzyme (TACE), also called the disintegrin metalloenzyme 17 (ADAM17). Increased TACE/ADAM17 sheddase activity in the absence of TIMP3 will result in an increased bioavailability and/or activity of pro-inflammatory factors, including TNFα, interleukin-6 and its receptor, and epidermal growth factor (EGF) receptor ligands such as TGF-α, amphiregulin, and heparin-binding EGF-like growth factor (HBEGF; reviewed in Giannandrea and Parks¹³; Figure 1). In addition, TIMP3 deficiency also may increase the expression of the immune-modulatory and pro-fibrotic TGF-β. Overall, TIMP3 may have a protective function against fibrosis by suppressing cytokines involved in immune and myofibroblast activation. Therefore, follow-up studies should address the TACE/ADAM17 activity and the bioavailability and activity of the pro-inflammatory cytokines in the hypertensive hearts of TIMP3-deficient mice. Is the inhibition of TACE activity able to rescue the exaggerated cardiac inflammatory and fibrotic response in the absence of TIMP3?

In the present study, the authors make a link between the TIMPs and matricellular proteins as a possible explanation for increased fibrosis. The absence of TIMP3 was accompanied by enhanced SPARC and osteopontin protein expression, both known to stimulate collagen cross-linking.¹⁴,¹⁵ Yet, it remains unclear whether the increased expression of these matricellular proteins in the absence of TIMP3 is purely correlative as a result of enhanced inflammation, and cytokine-mediated activation of myofibroblasts. The mechanisms by which TIMP3 may affect the expression of SPARC or osteopontin in AngII-mediated hypertrophy were not addressed. This will require follow-up studies, which should start with cell culture in vitro work to enable us to understand the exact mechanisms.

What about the TIMP2 data, where AngII infusion in the absence of TIMP2 resulted in less cardiac inflammation and fibrosis without affecting hypertrophy, compared with WT. TIMP2 is the main inhibitor of MMP2, and enhanced MMP2-mediated breakdown of inflammatory and pro-fibrotic cytokines¹⁶ may explain the lack of fibrosis in the absence of TIMP2, in line with proven anti-fibrotic properties of MMP2 in the liver and kidneys (reviewed in Giannandrea and Parks¹³; Figure 2). When TIMP2’s negative feedback is missing, this anti-inflammatory property by MMP2 might be indirectly enhanced, driving fibrosis. Whether the lack of fibrosis in the absence of TIMP2 is explained by increased MMP2 activity and inactivation of chemokines involved in inflammation and fibrosis, should be addressed in further studies.

Still, the TIMP2 data are contradicting previous work in aortic banding-induced pressure overload in TIMP2-deficient animals, where
dilatation in two independent studies. This stresses the lack of aortic banding resulted in enhanced hypertrophy, fibrosis, and cardiac dilatation in two independent studies. This stresses the lack of aortic stenosis and high AngII blood levels for 4 weeks do not really reflect any clinical human disease situation.

In general, rescue experiments in all these models where TIMP2 and TIMP3 are overexpressed or inhibited at different time points may allow learning more about their specific role in modulating fibrosis and hypertrophy. What are the exact mechanisms in play: direct effects of TIMP3 on TACE and cytokines such as TNF-α, IL-1, or TGF, or TIMP2-mediated blocking of MMP2 leading to cytokine breakdown? While this was definitely out of the scope of this paper, future research needs to address these important points. Taken together with this, developing animal models with a more direct clinical relevance for the human situation remain a major defy and are required if we want to improve the outcome not only in mice.

Figure 1 A decrease in TIMP3 will increase the activity of TACE, also called the disintegrin metalloenzyme 17 (ADAM17), resulting in an increased bioavailability and/or activity of pro-inflammatory factors including TNF-α, interleukin-6 and its receptor, and EGF receptor ligands such as TGF-α, amphiregulin, and HBEFG. TIMP3 deficiency also may increase the expression of the immune-modulatory and pro-fibrotic TGF-β. TIMP3 deficiency also resulted in enhanced SPARC and osteopontin, both involved in increasing fibrosis and collagen cross-linking. Signalling pathways by which TIMP3 affects TACE are p38, ERK1/2 dependent. The pathways for TGF-β, SPARC, or osteopontin are currently unknown.

Figure 2 TIMP2 deficiency will increase the MMP2 activity, involved in cleavage of pro-inflammatory/fibrotic cytokines, resulting in less inflammation and fibrosis.

References