Thrombospondin 1
A Protective “Matri-cellular” Signal in the Stressed Heart

Davy Vanhoutte, Stephane Heymans

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Despite excellent diagnostic and therapeutic strategies, hypertensive heart disease is still an important cause of heart failure. In response to pressure overload, changes occur in the myocardial architecture, including hypertrophic and fibrotic remodeling. Initially, this augments cardiac performance. However, unbalanced remodeling over protracted periods of cardiac stress eventually leads to heart failure through mechanisms that remain poorly understood.

During the last decade, it has become clear that the cardiac extracellular matrix (ECM) not only acts as structural support but also provides a unique environment in which the embedded cells communicate and function. By activating signaling cascades, the ECM transduces extracellular changes into cellular and acellular responses that play central roles during cardiac health and disease. In that respect, we have witnessed increasing interest in a group of nonstructural ECM proteins, known as “matricellular proteins.” Expression of matricellular proteins, including thrombospondins, osteopontin, tenasin, periostin, secreted protein acidic and rich in cysteine, and others, is high during embryogenesis but almost absent during normal postnatal life. Interestingly, they dramatically reappear in response to cardiac injury, stress, or acute remodeling events where they all seem to exhibit critical cardioprotective roles through the regulation of a broad range of ECM and ECM-cell mediated processes. Together, this has made research in this area attractive at the molecular, cellular, and therapeutic levels.

In light of the complexity of these molecular interactions, Xia et al identified thrombospondin 1 (TSP-1) as an essential regulator of the fibroblast phenotype and matrix metabolism, thereby preventing left ventricular dilatation in the pressure-overloaded heart (Figure). Pressure overload attributed to transverse aortic constriction in the mouse heart resulted in a marked overexpression of TSP-1, predominantly localized in the cardiac interstitial and perivascular space. Pressure overload–induced cardiomyocyte injury, hypertrophy, and apoptosis were accentuated in the absence of TSP-1, whereas reduced transforming growth factor (TGF)-β/Smad2 signaling increased matrix metalloproteinase 9 activity and enhanced matrix metalloproteinase 3 expression led to a massive infiltration of functionally impaired fibroblasts that exhibited defective myofibroblast differentiation and disproportional collagen deposition. Intriguingly, the absence of TSP-1 did not affect the inflammatory and angiogenic responses in the pressure-overloaded hearts. These findings are the first to suggest that TSP-1 functions as a protective signal in the pressure-overloaded myocardium. In addition, the study contributes novel insights into the biological actions of TSP-1 that determine the reparative properties of cardiac fibroblasts and preserve the ECM in the pressure-overloaded heart.

TSP-1 is the best-described member of the thrombospondin family, which consists of 5 extracellular calcium-binding proteins (TSP-1 to -5). Because of their ability to bind numerous extracellular proteins and cell surface receptors, all of the TSPs are involved in diverse biological processes. However, despite extensive evidence suggesting a protective role for TSP-1 in response to cardiac injury, a number of important questions still remain. First, studies in humans and experimental models have shown that TSP-1 and its family members TSP-2, -3, and -4 are each induced in the heart in response to hypertrophy or myocardial infarction, and loss of TSP-1 or -2 in gene-targeted mice promoted greater cardiac disease with aging or stress stimulation. Therefore, in addition to their temporal and spatial expression patterns, it will be important to elucidate the exact molecular pathways involved in the re-expression of TSPs in response to cardiac injury. Moreover, identifying the exact cellular sources of TSPs in the diseased heart could unravel whether they function as a paracrine-protective crosstalk between cardiac myocytes and nonmyocytes. It will also be important to more definitively assess how TSP-1 might be linked with other known signaling pathways that mediate the reparative response in the diseased heart. The complex domain structure of TSP-1 allows it to interact with a select number of proteins and cell surface receptors in a synergistic way, thereby regulating wound healing and cardiac remodeling by modulating a variety of cellular functions essential to the reparative response. In this context, TSP-1 has been recognized as a crucial activator of latent TGF-β, mediator of angiostatic signals, inhibitor of inflammation through its CD47 interaction, and modulator of matrix metabolism by direct or indirect matrix metalloproteinase inhibition. Interestingly, TSP-3, -4, and -5 constitute a different structural TSP subfamily and are <50% homologous to TSP-1 and -2, presumably indicating overlapping and divergent—yet unexplored—functions for TSPs in the stressed heart.
Extensive evidence suggests a pivotal role for TSP-1 in activation of TGF-β. However, the results presented by Xia et al.4 seem to indicate a selective and pathology-dependent course of action for TSP-1–mediated TGF-β signaling in the injured heart. Experiments using TSP-1 null mice suggested that, after myocardial infarction, locally deposited TSP-1 in the infarct border zone serves as a “barrier,” limiting expansion of the inflammatory process into the noninfarcted myocardium through its TGF-β–activating effect.6 On the other hand, in the pressure-overloaded heart, where inflammatory response is less prominent, TSP-1 seems to induce the TGF-β/Smad2 signaling axis that stimulates the matrix-preserving fibroblast phenotype and provides mechanical support to the myocardium to prevent chamber dilatation and adverse remodeling (Figure).4 According to these observations, it would indeed be appealing to hypothesize that the differential consequences of TSP-1 loss in cardiac disease are predominantly mediated through the regulation of TGF-β signaling.9 However, TSP-1–deficient mice also exhibit degenerative cardiomyocytes, increased numbers of α-smooth muscle cell actin-positive myofibroblasts, and increased matrix metalloproteinase expression and activity in the pressure-overloaded and/or infarcted heart,4,6 suggesting that TSP-1 also regulates cardiac wound healing—at least in part—through alternative mechanisms.

One limitation of this study, however, is that the translation of these findings into a clinically relevant setting is still lacking. Xia et al.4 suggest that TSP-1 may serve as a protective signal in the pressure-overloaded heart through its critical effects on fibroblast function and matrix metabolism. Nevertheless, one must wonder what a reasonable therapeutic time frame would be to administer such an “agent”? In fact, therapeutic use of TSP-1 could potentially play dual roles in the injured heart, one that is initially beneficial, by delimiting hypertrophic growth and providing the necessary strength in the early stages after hemodynamic overload, and a second role that is maladaptive, by mediating progressive myocardial fibrosis that could lead to increased myocardial stiffness, contractile dysfunction, and increased cardiac arrhythmias.1 In addition, we cautiously need to keep the many other functions of TSP-1 in mind, which could result in undesirable effects on both the cardiovascular system and other organs.3,5 An elegant approach to bypass this potential problem would be to obtain a more detailed and defined structure-function analysis of TSP-1. Mapping the specific biological functions of TSP-1 to a defined structural region will probably allow us to fine-tune novel therapies based on TSP-1 peptide fragments or analogues that either mimic a specific TSP-1–mediated function or act as a dominant negative in the stressed heart, while limiting undesirable adverse effects. Nevertheless, because of the critical involvement of TSP-1 in the regulation of fundamental pathways during cardiac injury, repair, and fibrosis, further in-depth analysis of its endogenous roles will undoubtedly provide novel insights into the mechanistic basis of various cardiac diseases.

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Disclosures

None.

References

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