Janus face of thrombospondin-4: impairs small artery vasodilation but protects against cardiac hypertrophy and aortic aneurysm formation

Venkata N. Sure and Prasad V. G. Katakam
Department of Pharmacology, Tulane University School of Medicine, New Orleans, Louisiana

ADAPTIVE RESPONSES OF TISSUEs to various stressors often involve expression of many proteins that play key role during the developmental phase but become undetectable in adults. Thrombospondins (TSPs) are such a family of matricellular proteins that are overexpressed in response to stress caused by pathological conditions including myocardial infarction, hypertension, chronic inflammation, and metabolic diseases. There are five recognized TSPs, named 1 through 5, that are secreted calcium-binding glycoproteins (9, 10). TSPs structurally contain similar carboxy-terminal domain followed by calcium-binding domain, but the NH2-terminal domains tend to display variation among the family members (1). The ability of TSPs to modulate the cellular function derives from binding with the extracellular matrix components including other matrix proteins (collagens, fibrinogen, and fibronectin), matrix metalloproteases (MMPs), cytokines, growth factors, signaling molecules (intracellular calcium), and cell membrane receptors (CD36, CD47, and integrins) (8). Thus, as matricellular proteins, family members of TSPs interact with multiple cell types and induce diverse effects that often are antagonistic (8). For example, TSP-1 inhibits endothelial tubule formation in vitro and is antiangiogenic. In contrast, TSP-4 knockout mice were found to display diminished angiogenesis, indicating proangiogenic function of TSP-4 (14).

The effects of TSPs in vascular pathologies have been the focus of recent investigations. TSP-1 has been implicated in the progression of ischemia-reperfusion injury in kidney (19) and pulmonary hypertension (2). However, the role of thrombospondins in systemic hypertension has not been investigated. Gene expression and microRNA expression analysis in small arteries of spontaneously hypertensive rats by Palao and coauthors (17) identified marked increase in expression of TSP-4. This novel observation led to the investigation of the role of TSP-4 in angiotensin II (ANG II)-induced hypertension. In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, the study by Palao et al. (16) provides novel insights into the differential effects of TSP-4 on small arteries and aorta in the setting of hypertension. The authors subjected Thbs4 knockout mice and wild-type mice to ANG II-infusion induced the formation of aortic aneurysms in Thbs4 knockout mice were found to display diminished angiogenesis, indicating proangiogenic function of TSP-4 (14).

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One paradoxical observation made by the authors was that despite the preservation of the resistance artery vasodilation and vascular mechanics, ANG II-induced hypertension in both wild-type and Thbs4 knockout mice alike. It is likely that in tissues other than resistance arteries, TSP-4 may promote antihypertensive mechanisms. Thus, further careful examination of angiotensin-sensitive mechanisms mediated by TSP-4 is required to understand the role of TSP-4 in the pathogenesis of hypertension.

Palao and coauthors also made a novel observation that ANG II-infusion induced the formation of aortic aneurysms in Thbs4 knockout mice compared with normal wild-type controls. Thus, it appears that TSP-4 affords protection against hypertension-induced aortic aneurysms. Interestingly, recent evidence showed that Thbs1 knockout mice develop significantly smaller aortic expansion in response to ANG II-induced abdominal aortic aneurysms (AAAs) compared with wild-type mice (13). Thus, TSP-1 and TSP-4 exert diverse effect on the pathogenesis of ANG II-induced aortic aneurysm. Aortic aneurysms exhibit remarkable difference in the etiologies based on the locations with AAAs in humans exhibiting strong positive association with the male sex (11), whereas thoracic aortic aneurysms (TAAs) displaying no such propensity with sex difference (12). Similar sexual dimorphism has been observed in ANG II-induced AAAs (7). Thus, the impact of sex on the TSP-4-allowed protection against ANG II-induced AAA and the key sex-dependent mechanisms underlying the AAA development in Thbs4 knockout mice remain to be studied. Moreover, the effects of TSP-4 on key etiological mechanisms such as inflammation (20) and vascular remodeling (18) for aortic aneurysms need further examination.

The role of TSPs, particularly TSP-4, in cardiac remodeling after myocardial ischemia (15) and pressure overload (4) has been well documented. The Thbs4 knockout mice displayed...
lower levels of mRNA for several inflammatory-associated proteins: intracellular adhesion molecule 1, chemokines, nuclear factor κ-light-chain-enhancer (NF-κB), and CD50 (6). Interestingly, TSP-1 has been shown to be anti-inflammatory in cardiac remodeling (8). Palao et al. (16) made the novel observation that ANG II-induced hypertension in Thbs4 knockout mice selectively promoted cardiac hypertrophy, suggesting that TSP-4 abrogates cardiac hypertrophy.

In conclusion, the novel findings by Palao et al. (16) provide insight into the differential impact of TSP-4 on the heart, aorta, and resistance arteries in hypertension. The questions that remain to be investigated include the exact molecular mechanisms of TSP-4 actions in the aorta, endothelium, heart, kidneys, and possibly autonomic nervous system that regulate blood pressure. Finally, the protective actions of TSP-4 against aortic aneurysm need further examination to identify the role of location of aneurysms, age, sex, and the impact of diabetes. Nevertheless, the novel observations of Palao et al. (16) pave the way for studies that could lead to the identification of the therapeutic targets for the prevention and/or slowing the progress of aortic aneurysms.

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REFERENCES