Counterbalancing Forces
What Is Thrombospondin-1 Doing in Atherosclerotic Lesions?

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Since the discovery of thrombospondin (TSP-1) thirty years ago,1 this matricellular (regulating cell–matrix interaction) protein has been a focal point for attention of cardiovascular biologists. Initial studies of TSP-1 emphasized its role as a major constituent of platelet α-granules and its involvement in platelet aggregation and thrombosis. However, it soon became clear that other cell types, eg, endothelial (ECs),2 leukocytes, fibroblasts, and vascular smooth muscle cells (SMCs),3–5 also produce and secrete TSP-1. This broad distribution triggered extensive studies of the influence of TSP-1 on cellular functions and documented numerous effects on blood and vascular cell responses. The breadth of its effects on cells results from the multidomain structure of TSP-1. The domains fold and often function independently, leading to cell type–specific effects that depend on the expression and combination of multiple receptors for TSP-1 on the cell surface and/or its multiple binding partners in the extracellular matrix. A major function of TSP-1 has emerged from among the myriad of its activities: TSP-1 is among the most potent antiangiogenic proteins and is a regulator of angiogenesis in tumors,6 thereby influencing tumor progression and aggressiveness. This effect of TSP-1 is ascribed to its induction of EC apoptosis mediated through interaction with CD36,7,8 inhibition of EC migration,9 and the CD36-independent cycle arrest.10

The effects of TSP-1 on ECs could also be proatherogenic because of EC dysfunction and its consequences on blood cell recruitment at both initial and advanced stages of plaque development. Proatherogenic effect of TSP-1 also could arise from its effects on SMCs. TSP-1 interacts with integrin αβ, on SMCs to stimulate proliferation and migration with a potency comparable to platelet-derived growth factor effect.11,12 This effect on SMCs is evident in animal models of restenosis: TSP-1 is highly expressed within hours after the injury,13–15 and antibody to TSP-1 reduces neointimal formation.16 In addition to TSP-1 interactions with the surface receptors, it also binds to and modulates the activities of proteins implicated in atherogenesis, including platelet-derived growth factor,17 transforming growth factor (TGF)β,18 vascular endothelial growth factor,19,20 and matrix metalloproteinases.21–23

In this issue of Circulation Research, Moura et al24 seek to unravel the role of TSP-1 in atherosclerosis by comparing the progression of plaque development in ApoE−/− and Tsp1−/−/ApoE−/− mice on a normocholesterolemic diet. The level of TSP-1 in plasma of ApoE−/− mice was unchanged during the progression of atherogenesis, and it was concluded that the role of TSP-1 is vascular rather than systemic. Indeed, TSP-1 was detected in adventitia and neointima of affected vessels: SMCs in the fibrous cap of the plaque, inflammatory cells, and foam cells of the plaque all stained with anti–TSP-1 antibody in both 6- and 9-month-old mice, and the necrotic core of the plaque also contained high levels of TSP-1 in 9-month-old mice. This extensive expression of TSP-1 in lesions contrasts with the absence of easily detectable TSP-1 in the healthy undamaged vascular wall.

Despite the abundant and consistent expression of TSP-1 in lesions, its effect does not appear to be consistent throughout the plaque development. At the initial stages, the absence of TSP-1 was protective; the total plaque area was smaller in Tsp1−/− mice at 6 months, with the most obvious difference in the abdominal area. However, lesion size in the aortic root became similar in both genotypes by 9 months, and in developed lesions, TSP-1 deficiency accelerated maturation and necrosis.

Concentrating on the effects of TSP-1 deficiency in the developed plaque, Moura et al24 noted that the number of SMCs was significantly decreased in Tsp1−/−/ApoE−/− mice as compared to ApoE−/− mice, indicating attenuated migration and/or proliferation of SMCs in the lesion. The amount of collagen in the lesion was increased in Tsp1−/−/ApoE−/− as compared to ApoE−/− mice and may have stabilized the lesions and counteracted the effect of reduced SMC number in the fibrous caps of the lesions. Thus, a potentially higher vulnerability to plaque rupture in mature Tsp1−/−/ApoE−/− plaques that might have resulted from lower SMC numbers in the fibrous cap may have been counterbalanced by increased collagen content. As the lesions grew, TSP-1 deficiency manifested as increased inflammation in the plaque: by 9 months, the number of both CD45-positive cells (leukocytes) and macrophages was significantly higher in Tsp1−/−/ApoE−/− compared to ApoE−/− mice. One of the mechanisms by which TSP-1 affects inflammation is its role as a TGFβ activator. However, in this case, the increased inflammation in the absence of TSP-1 was not attributable to the reduced TGFβ activation: the levels of TGFβ were similar in 2 genotypes, and there was no difference in activation of TGFβ signaling pathway. The increased number of inflammatory cells in the plaques of Tsp1−/−/ApoE−/− was accompanied by increased
abundantly expressed in atherosclerotic lesions, perhaps as a defense mechanism aimed to reduce inflammation and maturation and rupture of lesions.

The article by Moura et al24 has not and could not possibly have answered all of the questions concerning the mechanisms of lesion development affected by TSP-1. We still do not understand why the development of early lesions was slowed by TSP-1 deficiency, what mechanisms mediate phagocytosis in presence of TSP-1, why the number of inflammatory cells increased in Tsp−/− plaques, whether the expression of other thrombospondins with similar properties influenced plaque formation or maturation in the face of TSP-1 deficiency, etc. However, this report has described the TSP-1–dependent phenomena taking place in vivo and raises new questions to be addressed in different animal models and in the next round of in vitro experiments.

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None.

References

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