Thrombospondin-1 (TSP-1) is a homotrimeric glycoprotein with multiple functional domains that serves as a key mediator of a number of diverse cellular and physiologic processes. TSP-1 is the major component of the α granule of platelets. On stimulation by thrombin, TSP-1 is released and binds to the platelet surface. It then mediates platelet aggregation by crosslinking fibrinogen-GPIIb/IIIa complexes, which further secures platelets and tethers the thrombus. Given its prominent role in thrombosis, it is not surprising that TSP-1 is also a key mediator of neointimal hyperplasia and vascular disease. TSP-1 is found in the lumen and media of diseased and injured vessels and anti-TSP-1 antibodies decrease neointimal hyperplasia in a carotid artery injury model. Interestingly, a single nucleotide polymorphism in the TSP-1 gene may be associated with familial early myocardial infarctions. TSP-1 appears to play contradictory roles in angiogenesis, both stimulating neovascularization and preventing NO signaling through cGMP, thereby exacerbating tissue ischemia in these clinical settings. In addition to promoting platelet aggregation, TSP-1 released from platelets would promote formation of platelet thrombus. On stimulation by thrombin, TSP-1 is released and binds to the platelet surface. It then mediates platelet aggregation by crosslinking fibrinogen-GPIIb/IIIa complexes, which further secures platelets and tethers the thrombus. Given its prominent role in thrombosis, it is not surprising that TSP-1 is also a key mediator of neointimal hyperplasia and vascular disease. TSP-1 is found in the lumen and media of diseased and injured vessels and anti-TSP-1 antibodies decrease neointimal hyperplasia in a carotid artery injury model.

As there are multiple cell surface receptors for TSP-1, the diverse and sometimes dichotomous functions of TSP-1 may involve ligation of different receptors and combinations of receptors through its distinct domains. Heparan sulfate proteoglycans, β1 integrins, LRPCalreticulin, CD36, and CD47 have been identified as mediators of the effects of TSP-1. The ability to intervene on or manipulate any TSP-1 dependent pathway or process will ultimately depend on an understanding of the receptor or combination of receptors that are used in that particular biological context. Previous findings suggested that TSP-1 inhibits endothelial cell and vascular smooth muscle responses to nitric oxide (NO) by binding to CD36. However, contrary to these findings, native TSP-1 inhibits NO signaling in vascular cells from CD36 null mutants, suggesting that other receptors must play a role. More recent data demonstrate that it is actually CD47 that mediates these effects of TSP-1.

CD47, or integrin-associated protein, is a transmembrane receptor of the immunoglobulin superfamily that also functions as a receptor for TSP-1. Isenberg and colleagues recently found that activation of CD47 by TSP-1 at picomolar concentrations inhibits responses to NO and that vascular cells derived from CD47 null mice do not respond to TSP-1. Collectively, these results demonstrate that binding of either CD36 or CD47 by TSP-1 can inhibit NO-dependent cellular responses, but CD47 appears to mediate responses at more physiologically relevant concentrations of TSP-1.

The observation that inhibitory antibodies and knockdown of CD47 with small interfering RNA abrogate the effects of TSP-1 on endothelial cell morphology is consistent with the idea that CD47 is the predominate receptor that mediates TSP-1 signaling at the endothelial cell surface.

The TSP-1/CD47 coupled response undoubtedly evolved to act locally in the setting of vascular injury. In addition to promoting platelet aggregation, TSP-1 released from platelets would promote unopposed vasoconstriction by limiting NO signaling via CD47, thus promoting hemostasis. In this issue, Isenberg and colleagues demonstrate what can happen when this mechanism of hemostasis becomes more widespread, as seen in ischemic injury to tissue. The authors demonstrate that antibody mediated blockade of TSP-1 or CD47 promotes vascular remolding and increases survival of tissue after ischemic injury. An antisense oligonucleotide, which hybridizes to a sequence that is conserved between human and murine CD47, also had similar beneficial effects.

Beyond demonstrating that CD47 is the key receptor that mediates TSP-1 effects in ischemic tissues in vivo, these findings have a number of implications. Given the profound effects of obviating the TSP-1/CD47 interaction in the setting of ischemia, the use of blocking antibodies to TSP-1 or CD47 might prove clinically useful in fields such as plastic and reconstructive surgery, where tissue ischemia can result in damage and loss of the newly grafted tissue. The hind limb ischemia model used in this study also suggests that similar therapies might be beneficial in the setting of acute arterial insufficiency, which represents a relatively common problem associated with substantial morbidity. While further study will clearly be required, the use of the antisense morpholino oligonucleotide used in this set of experiments to reduce CD47 expression might also serve as a means to prevent tissue ischemia in these clinical settings.

Through this and previous studies, the authors have provided mechanistic insight into the signaling pathways used by these molecules at the cellular and molecular level. TSP-1 binds to CD47 and prevents NO signaling through cGMP, thereby exacerbating tissue ischemia (Figure). Targeting the specific components of this molecular pathway may find even broader clinical application than what has been outlined here. Wound healing, tumor growth and progression, and ischemia reperfusion as observed in myocardial infarctions, trauma, hemorrhagic shock, elective liver surgery, and organ transplantation represent a few of the myriad clinical scenar-
where blockade of the TSP-1/CD47 interaction might find clinical utility.

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None.

References

Binding of TSP-1 to CD47 inhibits NO-dependent production of cGMP. Endothelial nitric oxide synthase (eNOS) catalyzes the conversion of arginine to nitric oxide (NO). NO stimulates the production of cyclic GMP (cGMP) through soluble guanylate cyclase (sGC), leading to downstream events, such as vasorelaxation. On release from platelet granules and other sources, TSP-1 engages CD47 at the cell surface and this interaction prevents NO-mediated cGMP production.
Targeting CD47: NO Limit on Therapeutic Potential
David J. Kaczorowski and Timothy R. Billiar

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