

Comment on Isenberg et al, page 1945

Thrombospondin says no to NO

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Isenberg and colleagues report that thrombospondin-1 (TSP1) acts as an antagonist of nitric oxide (NO)-induced vascular relaxation and limits ischemic tissue survival. This finding identifies a new modulator of vascular contraction and expands the functional repertoire of TSP1.

Tissue perfusion, a process that is limited in ischemic conditions, is mediated by the relaxation of vascular smooth muscle cells (VSMCs). This process is regulated by the activation of cGMP-dependent kinase leading to the modulation of intracellular Ca^{2+} availability and the activity of myosin light chain (MLC) phosphatase. Contraction requires the binding of Ca^{2+} to calmodulin and the phosphorylation of MLC. These interactions control the association between F-actin-containing stress fibers and the contractile protein myosin leading to contraction. NO, a vasodilatory gas, induces the formation of cGMP leading to VSMC relaxation by promoting actin disassembly. Previously, *in vitro* studies with VSMCs have shown TSP1 to be an antagonist of NO.¹ However, both the mechanism and the biologic relevance of this antagonistic function remained unclear.

In this issue of *Blood*, Isenberg and colleagues expanded on their previous *in vitro* findings by identifying a mechanism through which TSP1 inhibits the effects of NO on VSMCs. Specifically, the authors demonstrate that TSP1 antagonizes the NO-induced dephosphorylation of MLC, resulting in the prevention of relaxation of contracted VSMCs. Presumably, the effect is mediated by modulation of the cGMP-dependent activation of MLC phosphatase, but this is not confirmed. In addition, Isenberg et al show enhanced NO-mediated increase in skeletal muscle perfusion and myocutaneous flap survival in a model of ischemic injury in TSP1-null mice. Taken together, these observations identify a novel function for TSP1 in the regulation of blood vessel physiology involving its ability to antagonize NO function.

As a potent inhibitor of angiogenesis, TSP1 has been shown to be proapoptotic and antiproliferative for endothelial cells and to mediate the adhesive state of vascular cells.² In addition, TSP1 has been shown to inhibit the

activation of proangiogenic enzymes such as matrix metalloproteinases (MMPs).³ Now, the ability of TSP1 to attenuate the effects of NO in VSMCs can be added to the growing list of TSP1 functions.

What is the contribution of this mechanism in the development of ischemia? Recently, it was shown that TSP1 expression is highly induced in ischemic muscle and displays perivascular deposition.⁴ Bone marrow transplant studies suggested a hematopoietic source for TSP1 and implicated a mechanism involving the activation of stroma cell-derived factor-1 by MMP-9. It is also expected that TSP1 would exert its antiangiogenic effect by direct

interaction with endothelial cells. Are these, and perhaps other yet-to-be-defined TSP1-specific mechanisms, contributing to the reduced blood flow in ischemic tissues? Studies aimed at the determination of the relative contribution of these mechanisms, perhaps by investigating the participation of specific TSP receptors such as CD36 and CD47, could provide more insight.

The author declares no competing financial interests. ■

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● ● ● CLINICAL TRIALS AND OBSERVATIONS

Comment on Collins et al, page 1870

Acquired hemophilia A: is more better?

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Collins and colleagues report the epidemiology, clinical course, and treatment outcomes of a 2-year observational study of all patients with acquired hemophilia A in the United Kingdom.

Acquired hemophilia A is a rare autoimmune disorder characterized by the development of IgG antibodies that neutralize coagulation factor VIII activity; these antibodies are termed inhibitors. The antibodies found in acquired hemophilia display type 2 inactivation kinetics characterized by the finding of residual factor VIII activity in plasma in the face of variable titers of antibody.¹ As a result, the patient may have severe bleeding out of proportion to that expected for the concentration of plasma factor VIII activity. A significant percentage of affected patients have an underlying diagnosis. Thus, therapeutic strategies require attention to treatment of hemorrhagic complications, treatment of any

underlying disorder, and eradication of the inhibitor.

Approaches to therapy have relied on previous observational studies of patient groups referred to specialized centers² and on reports of successful outcomes in relatively small patient groups. Collins and colleagues have provided important new knowledge regarding the incidence, clinical characteristics, and outcomes of treatment of acquired hemophilia A through complete ascertainment of all patients diagnosed in the United Kingdom in a 2-year period. Evaluation of this unbiased cohort of 172 patients revealed an incidence of 1.48 per million per year. Patients were significantly older than previously reported; mortality was