Inhibiting the Inhibitor

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Like any hemostatic system worth its salt, fibrinolysis is governed by competing influences, some of which promote lysis whereas others resist lysis. Reduced to the bare minimum, tissue-type plasminogen activator (t-PA) is profibrinolytic, whereas plasminogen activator inhibitor-1 (PAI-1) neutralizes t-PA and is therefore antifibrinolytic. Simple enough, but now add to the equation the participating plasma proteins such as fibrinogen, plasminogen, plasmin and antiplasmin, matrix components, especially vitronectin, and endothelial cells and platelets, which modulate the reaction. Next, expand the theater of operation to any potential site of fibrin formation and orchestrate sequences of vascular injury and thrombosis and physiological recovery, all superimposed on therapeutic antithrombotic or fibrinolytic intervention. Now the scenario is complex, just what we have come to expect of the discipline of hemostasis and thrombosis and just when it was becoming comprehensible.

The report by Levi et al in this issue of Circulation attempts to simplify the issue by testing the relevance of a single key factor in the process, PAI-1. In vitro studies suggest that PAI-1 is synthesized by the liver for plasma circulation and by endothelial cells for local secretion abuminally onto subcellular matrix where it binds to its matrix receptor, vitronectin. PAI-1 is transported by platelets in α granules, providing ready access at sites of hemostatic need, for example, where accumulation of a fibrinolytic inhibitor could help to stabilize a small clot until vascular repair has occurred. Clearly, the process is fine tuned: Clotting must first proceed efficiently but only where needed and then be dampened; afterward, the clot must remain in place while a continual reorganization of the injured site revascularizes the channel, and the vessel wall is healed. During this process, opposing tendencies of fibrinolytic inhibition and fibrinolytic activation play important roles in the timing and molecular locations of these competing influences.

One example of a disordered fibrinolytic response occurs in patients who have a hereditary PAI-1 disorder. With poorly functional inhibitor, hemostatic plugs are unstable and short lived, leading to a hemorrhagic state that can be managed with fibrinolytic inhibitors. In the atherosclerotic artery, the dramatic activation of clotting initiated by rupture of a plaque is quickly countered by activation of the fibrinolytic system and the tendency for "spontaneous" thrombus dissolution. The response in the vessel depends on both the prothrombotic potency of the stimulus and the magnitude of the physiological response, and PAI-1 is right in the middle of the action. If PAI-1 concentration is high to start, this may predispose the patient to the initial thrombosis or to recurrent infarction or limit the therapeutic effectiveness of thrombolytic therapy. More impressively, transgenic mice with a high plasma concentration of PAI-1 suffer frank ischemic and necrotic events in digits and at the tip of the tail, indicating just how active a role the inhibitor may play in vessel fibrinolytic dynamics.

Levi et al ask whether PAI-1 retards the physiological fibrinolytic response to a thrombus, and they test the hypothesis by blocking PAI-1 action with a monoclonal antibody: The inhibitor is inhibited. The results show that incorporation of the anti-PAI-1 antibody into an experimental (human) clot in the rabbit jugular vein accelerates physiological thrombolysis, presumably by neutralizing the effect of platelet PAI-1 to retard thrombolysis. The monoclonal antibody also prevents thrombus extension by potentiating both the physiological t-PA response and the response to therapeutic t-PA infusion.

The data have relevance for understanding the physiology of fibrinolysis, and they cement our understanding of the role of PAI-1. However, a cautionary note is indicated because the antibody is active only if it has been incorporated into the forming thrombus. This limits the applicability of such an approach and virtually precludes its use in acute myocardial infarction, unless the antibody (or some portion thereof, or a small peptide mimicking its inhibitory action) could somehow enter the formed thrombus and attach to the fibrin-bound PAI-1. The approach could be applicable for prophylactic use, however, perhaps in preventing thrombotic reocclu-
sion after successful thrombolysis or thrombosis of a vessel after angioplasty.

There is another caveat regarding the clinical expectations of utilizing an inhibitor of PAI-1 in patients receiving thrombolytic treatment. Can one expect that PAI-1 inhibition might occur in hemostatic plasms as well as in thrombi, thereby accelerating their disintegration and increasing the incidence and/or severity of bleeding in animal models or in patients? We know that the administration of PAI-1 in an animal model of thrombolytic bleeding limits blood loss, so inhibition of PAI-1 may promote thrombolytic bleeding. Therefore, whereas a monoclonal antibody against PAI-1 could well accelerate therapeutic thrombolysis, this effect might be accomplished only at the cost of increased hemorrhagic complications. These new questions need to be tested in appropriate model systems. Meanwhile, inhibiting the inhibitor does help to understand the role of PAI-1 in thrombolysis.

References


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