Editorial

Do PAI-1 and Vitronectin Promote or Inhibit Neointima Formation?

The Exact Role of the Fibrinolytic System in Vascular Remodeling Remains Uncertain

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In this issue of Arteriosclerosis, Thrombosis and Vascular Biology, de Waard et al. report enhanced neointima formation and luminal stenosis following carotid artery ligation in mice deficient for plasminogen activator inhibitor-1 (PAI-1) or vitronectin (VN) compared with their wild-type counterparts. Their findings appear to contradict those of a recently published study by Peng et al., thus adding fuel to the ongoing discussion and growing uncertainty about the exact role of PAI-1 and VN in the vascular remodeling process underlying atherosclerosis and restenosis. In this brief editorial, we review the evidence that suggests that PAI-1 and VN should influence this process, and then we attempt to reconcile the two publications.

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Interest in the involvement of the fibrinolytic system, and particularly PAI-1, in the development and complications of human atherosclerosis was sparked by several clinical studies which reported elevated plasma concentrations of the inhibitor in patients with acute coronary syndromes. In addition, histological observations consistently demonstrated that PAI-1 gene expression was upregulated in macrophages and smooth muscle cells (SMCs) present in human atherosclerotic lesions and in lesions that develop in animal models of atherosclerosis. Finally, inflammatory proatherosclerotic mediators, including oxidized LDL, were shown to upregulate the expression of PAI-1 in endothelial cells and vascular SMCs in culture. Taken together, these observations implicate PAI-1 in the pathology of the vessel wall that develops in response to vascular insult.

As the principal physiological inhibitor of plasminogen activation, PAI-1 would seem to play a key role in the regulation of vascular homeostasis at sites of arterial injury. This important function of PAI-1 is facilitated by VN, a 75-kDa glycoprotein that binds the inhibitor with high affinity, stabilizes the inhibitor in its active conformation, and mediates the binding of the inhibitor to fibrin clots. The binding of PAI-1 to VN also broadens the specificity of the inhibitor, converting it into a reasonable thrombin inhibitor, and a potent inhibitor of activated protein C (APC). Interestingly, all of the active PAI-1 in blood circulates in complex with VN. Taken together, these observations suggest that VN is a cofactor for PAI-1. It turns out that VN is also present in atheromatous plaques, and it appears to colocalize with PAI-1 and thrombin. It is still unclear, however, whether the VN is actually synthesized by cells in the vessel wall, or derived from plasma.

So, do PAI-1 and VN promote or inhibit neointima formation in atherosclerosis and/or restenosis after vascular injury (eg, following spontaneous plaque rupture or “therapeutic” coronary angioplasty of stenotic lesions)? A review of the literature suggests that the answer may depend on which phase of the wound healing response and what part of the vasculature are analyzed. In both cases, the critical feature may be the presence or absence of thrombus/fibrin. This hypothesis is based on the observation that apart from being an acute, potentially lethal complication of advanced atherosclerosis, thrombus formation/fibrin deposition is also the initiating event in the healing of ruptured or eroded plaques. During this healing process, the thrombus participates in plaque growth and progressive luminal narrowing. Our recent studies with the ferric chloride model of carotid artery injury in the mouse confirmed the importance of thrombus organization for neointima formation and luminal narrowing in vivo. In these experiments, application of ferric chloride to the adventitia of mouse carotid vessels resulted in a marked thrombotic response with subsequent fibrinolysis, organization of the remaining platelet-rich thrombus, and neointima formation over a 3-week period. PAI-1 and VN were shown to be essential for stabilization of the arterial thrombi in this model, as they were in the rose bengal injury model which also reproducibly results in carotid artery thrombosis. Additional studies showed that the absence of PAI-1 was associated with reduced neointima formation and luminal stenosis both in normolipidemic mice and in hypercholesterolemic apolipoprotein E knockout mice after injury with ferric chloride. Similar observations were obtained with a copper-induced injury model, a model also characterized by thrombosis and marked fibrin deposition in the injured carotid artery wall. Finally, induction of a modest, transient increase in PAI-1 expression in balloon-injured rat carotid arteries resulted in increased cell proliferation and neointima formation 2 weeks after injury, and these changes again correlated with fibrinogen immunoreactivity. Thus, in the presence of thrombus/fibrin, neointima formation seems
to correlate consistently with PAI-1, increasing as PAI-1 is increased, decreasing in its absence.

How then can we account for observations which show that the absence of PAI-1 enhances neointima formation and luminal narrowing in mouse models of electrical or mechanical (balloon) arterial injury, while high systemic PAI-1 levels seem to suppress neointima formation? Well, part of the explanation may lie in the fact that, in contrast to vascular injury induced by ferric chloride, rose bengal, or copper, the mechanical and electrical injury models were not associated with a prominent thrombotic reaction in mouse vessels. Thus, these latter studies raise the possibility that in the absence of fibrin, PAI-1 deletion may enhance neointima formation, while increased PAI-1 may inhibit it. Is this hypothesis plausible? Certainly, because in some instances cell migration after vascular injury occurs in the absence of fibrin accumulation. This observation suggests that in this case, the fibrinolytic system may influence other, “non-fibrin-related” steps in the vascular remodeling process. In this regard, PAI-1 may directly inhibit uPA-mediated pericellular proteolysis, which may then decrease the activation of matrix metalloproteinases by plasmin. According to this latter scenario, the presence of PAI-1 stabilizes the extracellular matrix and prevents SMC migration within the vessel wall. An alternative (or additional) mechanism by which PAI-1 may prevent cell migration could involve the binding of the inhibitor to the somatomedin B domain of vitronectin in the extracellular matrix. This interaction may prevent both uPA receptor-mediated and integrin-mediated cell attachment to the glycoprotein.

Can these considerations of thrombus formation/fibrin deposition provide a satisfactory explanation for the difference between the observations of de Waard et al in this issue and those previously reported by Peng et al? Perhaps. The difficulty is that both studies applied the same carotid artery ligation model to study neointima formation in wild-type, PAI-1 knockout, and VN knockout mice. However, Peng et al strongly implicated thrombus/fibrin in the vascular response to ligation, and they argued that the enhanced fibrinolysis (and thus reduced thrombus/fibrin) caused by the absence of PAI-1, VN, or both, was the cause of the reduced neointima formation in their knockout animals. In contrast, no thrombus/fibrin was detected in the studies by de Waard and coworkers. These authors attribute the increased neointima formation they observed in mice lacking PAI-1 or VN to the inhibitory effects of the PAI-1-VN complex on thrombin activity. They reasoned that thrombin activity would increase in the absence of PAI-1 or VN, leading to an increase in thrombin-induced SMC proliferation and thus to increased neointima formation. To support this thesis, they show that hirudin, a potent thrombin inhibitor, reverses the effect of PAI-1 deficiency on neointima formation after ligation. One problem with the interpretation of these studies is the difficulty differentiating between the potential mitogenic effects of thrombin on the one hand, and its procoagulant (ie, fibrin generating) effects on the other. In this regard, although the authors did not detect thrombi in the injured (ligated) mouse vessels, other investigators using the same system did. Thus, the reduction of the neointima after administration of hirudin in the present study could (also) result from attenuation of the thrombotic response and decreased fibrin formation. These considerations raise the possibility that the contradicting observations in the two studies may reflect the different locations chosen for morphometric analysis of the neointima, with Peng et al examining locations containing thrombus/fibrin, and de Waard et al studying segments lacking it. Systematic examination of the entire carotid artery after ligation for the presence of neointima/thrombus/fibrin may help resolve this question. In this regard, we have preliminary data showing that the status of the neointima 3 weeks after arterial injury with ferric chloride reflects the amount of thrombus/fibrin observed 1 to 2 days after injury. Apart from differences in the arterial segment studied, it is also possible that the differences in thrombosis/fibrin deposition in the two studies may have resulted from differences in the ligation process itself (ie, interobserver variability in the degree of injury). Furthermore, there may be some variability in the response of individual mice to vascular injury. Thus, it is possible that the extent of thrombus formation and fibrin deposition after vascular injury varied considerably between the groups, even though the same injury models and protocols were used. Such differences may alter the overall effects of the PAI-1–VN complex on vascular remodeling (ie, early fibrin stabilization versus late inhibition of cell migration on the extracellular matrix).

In conclusion, the study by de Waard et al will certainly stimulate more interest in the potential role of PAI-1, VN, and thrombin on neointima formation after injury. However, comparison of the results of this study with those of Peng et al emphasizes that the effects of the fibrinolytic system on vascular remodeling during the various phases of the wound healing response are complex and difficult to study causally using a single model of arterial injury in the mouse. Finally, it must be born in mind that none of the mouse models currently under investigation completely reproduce the pathophysiology of human atherosclerosis or restenosis after angioplasty. Nevertheless, careful examination of these models will continue to be useful for dissecting the mechanisms underlying these complex processes.

References

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doi: 10.1161/01.ATV.0000047462.65341.22
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

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