The Controversial Role of the Urokinase System in Abdominal Aortic Aneurysm Formation and Rupture

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In the current issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Uchida et al report the use of a urokinase plasminogen activator (uPA)−/− low-density lipoprotein receptor−/− mouse model to investigate the role of uPA in the development of abdominal aortic aneurysm (AAA) in a hyperlipidemic setting. Surprisingly, they show that uPA deficiency has a detrimental role in the rupture of AAA, but not a role in AAA formation. AAA results from progressive degeneration of the aortic wall due to degradation of key extracellular matrix proteins, namely collagen and elastin. This leads to gradual weakening and instability of the vessel wall, dilatation of the vessel, and eventual rupture. Rupture is life threatening, accounting for approximately 15,000 deaths per year in the United States. Although recent progress has been made in detection and repair of AAA, few molecular mechanisms have been elucidated in the pathogenesis of AAA, including those related to inflammation, infection, protease activation, and underlying genetic mutations. Several families of proteinases are implicated in AAA development, including aspartic, serine, and metalloproteinases. Particularly, the matrix metalloproteinase family has been extensively studied and linked to AAA formation and expansion. Recently, the focus has shifted to serine proteinases involved in fibrinolysis, namely tissue plasminogen activator (tPA) and uPA, as potential mediators of inflammation and proteolysis in AAA (Figure). uPA and tPA cleave plasminogen to plasmin, which can in turn activate matrix metalloproteinases, potentially increasing the proteolytic activity of nearby cells. However, the exact mechanisms linking the uPA/urokinase receptor (uPAR) system to AAA have yet to be fully identified.

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Historically, uPA has been shown to be involved in the formation and persistence of AAAs. Shireman et al showed an increase in the amount of uPA in human aneurysmal infrarenal aortic tissue as compared with undamaged tissue. A mouse model of angiotensin II (Ang II)−/− AAA has been used extensively in studies of AAA, Wang et al used this method in apolipoprotein E (apoE)−/− mice, showing that aneurysm formation leads to increased uPA activity in the abdominal aorta as early as 10 days following Ang II infusion. Additional studies in apoE−/− uPA−/− knockout mice revealed protective effects of uPA deficiency on vessel breakdown and AAA rupture. Therefore, the upregulation of uPA in damaged abdominal aortas serves to increase protease activation locally, leading to degradation of the vessel and growth of the aneurysm. More recently, Deng et al convincingly showed that uPA is required for formation of Ang II−/− AAA in the apoE−/− mouse model, although uPA does not have any effect on the surrounding tissue. Adding credence to these findings, the same group showed that local overexpression of plasminogen activator inhibitor-1, the inhibitor of uPA, at the site of aneurysm completely protected apoE−/− mice from Ang II−/− AAA and slowed aneurysm expansion. Moreover, Schultz et al found that deficiency of thrombin-activatable procoagulasepeptidase B, an inhibitor of clot-bound plasmin generation, leads to enhanced AAA formation and rupture in a porcine pancreatic elastase-induced model of AAA. The formation and rupture of these aneurysms was prevented by treatment with tranexamic acid, an inhibitor of plasmin generation, suggesting that increased plasmin activity in the absence of procoagulasepeptidase B has a role in inducing inflammation and degeneration of the aorta. The current findings of Uchida et al completely contradict the historical findings implicating uPA in the formation and progression of AAA. The original focus of the article was not uPA itself but its cognate receptor uPAR and the role of uPAR in AAA formation and progression. This led the authors to hypothesize that loss of uPAR would have similar beneficial effects to that of uPA loss. Although there was a marked increase in uPAR and uPA in aneurysmal tissue in low-density lipoprotein receptor−/− mice infused with Ang II, deficiency of uPAR had no effect on the incidence, size, or rupture of AAA in these animals. This finding is not totally linked to uPA, because uPA can function independently of its receptor. In addition, they found that uPA deficiency did not alter the formation or size of AAA but increased rupture of the aneurysms. This finding directly opposes those of Deng et al, in that uPA-deficient mice did in fact form aneurysms, suggesting that uPA is not necessary for formation of AAA and that loss of uPA was actually detrimental as opposed to protective. Uchida et al then performed bone marrow transplants and found that aneurysm rupture was not observed in mice repopulated with uPA−/− bone marrow but was increased in mice repopulated with uPA−/− bone marrow. These results suggest that a cell type of hematopoietic origin, possibly macrophages, is responsible for the increased AAA rupture. However, they rule out uPA...
deficiency–induced increase in matrix metalloproteinases as a possible mechanism.

The cleavage of plasminogen to plasmin by tPA and uPA is a critical step in thrombus resolution (Figure). To explain the increased rate of aneurysm rupture seen in uPA-deficient mice, Uchida et al suggest that in the absence of uPA there is less resolution of early phase transmural thrombi, promoting rupture. It is true that uPA deficiency results in delayed thrombus resolution in mouse models of venous thrombosis, and this is likely mediated by hematopoietic-derived uPA producing cells. Although intuitively, one would think that an increase in protease activity as opposed to a decrease would promote aneurysm rupture by causing degradation and thinning of the vessel wall. It is possible that prolonged presence of a thrombus could mediate weakening of the vessel wall and subsequent rupture; however, no data exist to support this hypothesis. Furthermore, a compensatory up-regulation of tPA in the vessel wall could contribute to enhanced aneurysm rupture. Neither Deng et al nor Uchida et al reported altered tPA levels in uPA-deficient mice during AAA. Human data in AAA patient samples show substantial increases in plasma tPA levels compared with uPA. This result could implicate an equally important role for tPA in the vessel wall in promoting AAA and aneurysm rupture. However, these findings have not been confirmed in mouse models of AAA. The potential involvement of proteases other than plasminogen activators and matrix metalloproteinases cannot yet be ruled out in this model. A more thorough protease screening will need to be performed in mouse models of Ang II–induced AAA to know for certain.

It should be noted that there were significant differences in the methodology of Uchida et al and Deng et al. First, the ages at which the mice were used in the experiments differed greatly, with Uchida et al using 8- to 12-week-old mice and Deng et al using 7- to 11-month-old mice. These age differences may be a source of underlying variation between the 2 groups and may account for some of the differences in the results obtained from the 2 groups. Second, the 2 groups used different models of hyperlipidemia, with Uchida et al using the low-density lipoprotein receptor−/− mouse model and Deng et al using the apoE−/− mouse model. Although the models would seem complementary, with apoE binding to low-density lipoprotein receptor physiologically, differences between the 2 models have been well documented. Although both groups used normolipidemic control studies, the results obtained are still in opposition to one another, suggesting strain differences between the 2 models. Therefore, underlying differences in atherosclerotic model choice cannot be ruled out as a source of deviation between the results of the 2 groups.

In conclusion, Uchida et al have provided data to discount a role of the uPA/uPAR complex in Ang II–induced AAA development but suggest a role for uPA deficiency in aneurysm rupture in hypercholesterolemic mice. Although this publication is contrary to the widely accepted role of uPA in AAA, it suggests the potential for paradoxical roles for uPA in the development of AAA versus aneurysm rupture. Additional studies are necessary to mechanistically define this interesting phenomenon.

Disclosures

None.

References


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