Editorial

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)−/−–induced AAA has been used extensively in studies of AAA, Wang et al used this method in apolipoprotein E (apoE)−/− mice, showing that 

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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 in protease activity 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 upregulation 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 al1 and Deng et al1 First, the ages at which the mice were used in the experiments differed greatly, with Uchida et al1 using 8- to 12-week-old mice and Deng et al3 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 al1 using the low-density lipoprotein receptor−/− mouse model and Deng et al3 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.11–13 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 al1 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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