A complex, tissue-specific role for plasmin and its regulators in modulating fibrogenic activity

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IT HAS LONG BEEN KNOWN THAT tissue injury often leads to the infiltration of interstitial spaces with plasma, resulting in the polymerization of fibrin as a provisional matrix to support the migration of cells that mediate healing process. When all goes well, during the course of tissue repair the fibrin is broken down through the liberation of the serine protease plasmin from plasminogen via cleavage by either tissue plasminogen activator (tPA) and/or urokinase plasminogen activator (uPA). Left unchecked, however, it has been assumed that persistence of the provisional fibrin matrix promotes the accumulation of extracellular matrix, promoting the development of fibrotic disease (1).

In addition to fibrin, plasmin can degrade fibronectin and laminin matrix and activate collagenases. Thus the regulation of plasmin activity has been an important topic in the field of fibrosis. The plasminogen activators uPA and tPA are inhibited by plasminogen activator inhibitor-1 (PAI-1), and once liberated, plasmin activity can be directly inhibited by α2-antiplasmin. Collectively, these molecules comprise a system for tight regulation of plasmin activity. Thus the effect of dysregulation of the system components on fibrogenesis might seem quite predictable. An increasing body of evidence indicates that this is not necessarily the case.

In the bleomycin-induced lung fibrosis model, for example, infusion of uPA into the lungs of mice following bleomycin treatment protects against fibrosis (9), plasminogen-deficient mice show increased fibrosis (10), and PAI-1 gene deletion treatment protects against fibrosis (9), plasminogen-deficient mice show increased fibrosis (10), and PAI-1 gene deletion treatment protects against fibrosis (9), plasminogen-deficient mice show increased fibrosis (10), and PAI-1 gene deletion treatment protects against fibrosis (9), plasminogen-deficient mice show increased fibrosis (10), and PAI-1 gene deletion treatment protects against fibrosis (9), plasminogen-deficient mice show increased fibrosis (10), and PAI-1 gene deletion treatment protects against fibrosis (9), plasminogen-deficient mice show increased fibrosis (10), and PAI-1 gene deletion treatment protects against fibrosis (9), plasminogen-deficient mice show increased fibrosis (10), and PAI-1 gene deletion treatment protects against fibrosis (9). Thus, it would appear that the plasmin directly influences ERK-mediated signaling, providing a second example where a component of the fibroinolytic pathway can possess activities that both promote and attenuate fibrosis.

Given that uPAR attenuates fibrosis and PAI-1 promotes fibrosis in the UUO model, it would follow that uPA would be expected to attenuate fibrosis. As exemplified by the role of plasmin in this system, however, one does not always observe what one expects. Indeed, uPA has been shown to be profibrotic in some fibrosis systems and antifibrotic in others. In this issue of the journal, Yamaguchi et al. (11) address the role of uPA in the progression of renal fibrosis in UUO mice. Despite the fact that uPA is markedly induced in proximal tubular epithelial cells of fibrotic kidneys, no difference in the progression of fibrosis was observed in uPA-deficient UUO mice compared with wild-type mice. Thus it would appear that the antifibrotic effects of PAI-1 on renal fibrosis are completely independent of plasmin, tPA, and now uPA.

The findings that uPA does not influence renal fibrosis differ from similar experiments performed in the bleomycin-induced lung fibrosis model, where reduced uPA activity was associated with attenuated fibrosis, illustrating the organ-specific influence of uPA on fibrotic mechanisms (4, 9). In addition to organ specificity, one must also consider the nature of the fibrosis model. Studies in an acute fibrosis model of renal fibrosis associated with significant fibrin deposition showed reduced glomerular disease in uPA null mice compared with wild-type mice (6). This exemplifies the possibility that influences of the fibroinolytic system on fibrosis might be distinct for different renal diseases even though many still consider fibrosis as a common pathway.

Finally, it is worthwhile to remember that this fibrinolytic “system” has a historical context. Indeed, this system represents a tight and robust means of modulating plasmin activity, but we are finding that the serine proteases uPA, tPA, and plasmin possess a multitude of biological functions including regulation of growth factor and MMP activation and cell signaling influences. Considering this, the pleotropic effects of these factors on different models and mechanisms of fibrosis are not so surprising and underscore how much more we need to know about this important class of molecules.

REFERENCES

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