α2 Antiplasmin and Microvascular Thrombosis in Ischemic Stroke

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Stroke occurs in 2 forms, ischemic and hemorrhagic, with ≈87%, being of ischemic origin. Ischemic strokes are characterized by the rapid onset of focal neurological symptoms, and the prompt restoration of blood flow should be the most effective approach for treating ischemic stroke. Currently, tissue-type plasminogen activator (tPA), a highly specific serine protease of the fibrinolytic cascade, is the only thrombolytic agent approved by the US Food and Drug Administration for the treatment of ischemic stroke. However, emerging evidence has suggested that the beneficial effects of reperfusion associated with thrombolytic treatment are counterbalanced by potentially harmful activities of tPA, including a significant increase in the risk of hemorrhagic conversion, a serious complication that is associated with high mortality. Thus, although treatments, such as thrombolysis and thrombectomy, have been successful, it is estimated that <5% of ischemic stroke patients receive treatment, and 1 major reason for this low percentage is the risk of hemorrhagic conversion.

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The mechanism by which tPA works to restore vascular patency and reperfusion is straightforward and well understood. tPA activates plasminogen to plasmin, which in turn dissolves the occluding thrombus to recanalize the blocked vessel (Figure). Factors that modulate plasmin activity would therefore be expected to act in the same pathway as tPA and to contribute to the fate of clot dissolution and stroke outcome in a manner consistent with modulation of tPA activity. However, an earlier study in mice genetically deficient in α2-antiplasmin (α2AP−/−) had paradoxically suggested that removing profibrinolytic, α2AP activity can significantly improve stroke outcome. Their data indicate that thrombus-bound α2AP is less important than circulating α2AP for infarct size, even if clot bound α2AP is critical for dissolution of the primary thrombus. This result further illustrates the importance of secondary microthrombi formed downstream of primary thrombus for stroke evolution.

Despite this interesting and important concept, several limitations of the study should be taken into account. For instance, this study does not differentiate between possible effects of α2AP in the vascular compartment or in brain parenchyma. In addition, this thromboemboli stroke model is an extreme example of ischemic stroke with high mortality rates. For example, in tPA-treated mice mortality reached 100% by 50 hours after treatment, whereas control mice, mortality reached >65%, both of which are much higher than in other experimental models or in the clinic.

Still, the study by Reed et al provides the reader with the interesting and important concept that inhibiting circulating α2AP may promote endogenous fibrinolysis in downstream areas of secondary thrombosis and that this may reduce infarct expansion. Finally, it is interesting to note that hemorrhage in this model was significantly worse in mice receiving tPA than in mice completely deficient in α2AP. This suggests that the simple concept that tPA induces hemorrhage by promoting unregulated plasmin activity may not be correct and supports the hypothesis that the association of thrombolytic tPA with an increased risk of hemorrhage may be because of tPA’s action on substrates other than plasminogen. Whether inhibiting α2AP may be useful for treating ischemic stroke in the clinical trial has been reported testing the safety of the latter approach. Nonetheless, the idea of targeting α2AP has not received much attention. This may be because α2AP supplementation was shown to reduce bleeding complications in a rabbit model of thrombolysis with tPA, or possibly because it is counterintuitive that reducing a systemic plasmin inhibitor would be a safe alternative to thrombolysis. What Reed et al add to the story is the importance of secondary microvascular thrombosis to infarct size and how α2AP affects this process. Their data suggest that secondary microvascular thrombosis in the ischemic penumbra plays a critical role in infarct expansion, and that enhancing endogenous fibrinolysis by reducing α2AP activity can significantly improve stroke outcome. To achieve this, plasma α2AP activities were modulated either genetically with α2AP−/− mice, or via intravenous infusion of recombinant α2AP, creating different circulating levels of α2AP in mice.

In addition, the authors elegantly differentiate the effects of circulating and thrombus-bound α2AP on stroke. To accomplish this, the authors generate artificial thromboemboli made from normal plasma or α2AP-deficient plasma and then inject these into the middle cerebral artery of α2AP−/− mice. Their data indicate that thrombus-bound α2AP is less important than circulating α2AP for infarct size, even if clot bound α2AP is critical for dissolution of the primary thrombus. This result further illustrates the importance of secondary microthrombi formed downstream of primary thrombus for stroke evolution.

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clinic remains to be seen; however, to the extent that stroke evolution is dependent on microvascular thrombi formation, than agents promoting endogenous fibrinolysis are certainly worth further study.

Disclosures
None.

References
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