potent inhibition of RNA synthesis, PCNA expression, T-cell proliferation, and reduced interleukin-2 production by T cells.

Sotrastaurin is a drug that is currently being used to inhibit graft rejection in renal transplantation and to treat certain inflammatory diseases such as psoriasis. Therefore, these results are of great interest because they suggest that the combination of MPA and sotrastaurin could be used in the future as a highly potent regimen to modulate lymphocyte activation (see figure) in the context of transplantation or to treat certain autoimmune diseases. However, sotrastaurin is a paninhibitor and more studies are warranted to assess whether other immune cells will be affected. In addition, sotrastaurin may affect more than just rRNA synthesis or growth within 1 cell and this needs to be addressed as well to truly evaluate the possibility of using this drug combination safely in patients. These studies will be highly relevant because therapies such as transplantation rely heavily on successful and effective immunosuppression.

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indicating normal clotting parameters. Hence, this model of TBI causes only a mild coagulopathy. Nonetheless, the extent of ICH steadily increased over time but did not correlate with D-dimer levels or platelet count. Instead, the extent of ICH correlated with an increase in fibrinolysis, but the interest here is in the detail. Fibrinolytic activity increased in the cerebrospinal fluid but not in the blood of injured mice. However, both tPA−/− and uPA−/− mice developed less ICH after TBI, but only tPA−/− mice became coagulopathic; D-dimer levels and platelet counts were essentially unchanged in uPA−/− mice. Urokinase was therefore causing a pronounced effect on the hemostatic system.

To further support the role of the fibrinolytic system in promoting ICH, the authors forced coagulopathy by anticoagulating mice with warfarin. Warfarin increased the INR to a similar extent in WT, tPA−/−, and uPA−/− mice, but only WT mice developed a greater degree of ICH following TBI. The lack of ICH expansion in warfarin-treated tPA−/− or uPA−/− mice strengthens the idea that both uPA and tPA were driving ICH. The capacity of both u-PA and t-PA to promote ICH and the increase in ICH seen in anticoagulated WT mice were inhibited by an inactive t-PA variant (tPA-S481A).

Together, these findings are relevant considering current efforts to attenuate consumptive coagulopathy in severe trauma patients using antifibrinolytic drugs. Most prominent here is the use of the lysine analog tranexamic acid (TXA). The CRASH-2 trial indicated a net benefit of TXA following brain injury and pharmacological stimulation. Lab Invest. 2011;91(7):1079-1091.

Despite this evidence, some authors have suggested that TXA actually promotes the ability of uPA to activate plasminogen. This is because the binding of TXA to plasminogen causes a conformational change allowing it to be more efficiently cleaved by uPA. Could the selective increase in uPA at the later time point explain the “TXA paradox”? The authors treated WT-mice with TXA and observed reduced ICH at 2 hours post-TBI, consistent with blocking the effect of tPA. However, when TXA was administered to mice 8 hours post-injury, at a time when uPA levels were at the highest level and tPA levels had subsided, an increase in ICH was seen, reminiscent of the findings of the CRASH-2 trial (see figure).

This evidence points to the possibility that the increase in ICH by TXA was due to the known effect of TXA in increasing the efficiency of uPA-mediated plasminogen activation. However, the authors did not determine if fibrinolytic activity was actually increased in the brain after TXA treatment, nor did they perform this experiment in uPA−/− mice to formally associate uPA with this effect. Although the evidence supports a causal role for tPA and uPA in promoting ICH after TBI, what remains to be determined is the mechanism for how this occurs.

The fibrinolytic system is well known to have a major effect on the neurovascular unit. Although most of this work has been in the context of ischemic stroke, endogenous brain-derived tPA has also been shown to enhance edema and promote protein extravasation into the brain following TBI. The delayed increase in uPA levels following TBI is consistent with earlier findings, where uPA was shown to increase in the hours following cerebral ischemia subsequent to the rise in tPA activity.

Nonetheless, this paper has a bearing on the clinical management of TBI in humans, in particular, the capacity of TXA to worsen ICH. Clearly, any new antifibrinolytic approaches aimed at reducing ICH following TBI should be tailored to annul the effects of both tPA and uPA. So, at the end, there is really no paradox. What appears to be happening is actually consistent with what was already known about the differential effects of TXA on tPA- and uPA-mediated plasminogen activation. We must now wait with interest to see if tPA or other antifibrinolytic approaches can be harnessed more effectively in patients with severe trauma.

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The traumatic side of fibrinolysis

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