

Plasminogen mediates the pleiotropic properties of urokinase in the liver.

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Background:

Urokinase (uPA) and plasminogen are serine proteases involved in hemostasis and wound healing. In the liver, uPA facilitates hepatocellular proliferation while plasminogen regulates tissue repair. Unexpectedly, the overexpression of uPA in the liver leads to neonatal liver injury in transgenic mice, followed by repopulation of diseased livers by regenerative nodules.

Hypothesis:

Based on the role of uPA as a plasminogen activator, we proposed the hypothesis that liver injury results from the activation of plasminogen to plasmin by the uPA transgene within hepatocytes.

Methods/Results:

To address this hypothesis, we mated uPA transgenic (uPAT) mice with plasminogen knock-out (Plg^{-/-}) mice and generated uPAT/Plg^{-/-} mice, as confirmed by PCR. At 3 weeks of age, livers of uPAT mice had hepatocyte injury throughout the liver lobule. In contrast, uPAT/Plg^{-/-} livers appeared normal, both macro and microscopically. To explore whether uPA overproduction would increase liver cell proliferation and rescue the abnormal repair of Plg^{-/-} livers, we administered carbon tetrachloride intraperitoneally to uPAT/Plg^{-/-} mice and control littermates. Histological analysis of liver samples from mice of all genotypes showed a similar centrilobular lesion at 2 days, which normalized in wild type and uPAT livers by 7 days. In contrast, livers of uPAT/Plg^{-/-} and Plg^{-/-} mice continued to show centrilobular lesion at both 7 and 14 days, with no evidence of ongoing repair. BrdU labeled hepatocytes peaked at 2 days in mice of all genotypes. Immunohistochemical staining demonstrated an accumulation of fibrin in diseased areas of uPAT/Plg^{-/-} and Plg^{-/-} livers.

Conclusion:

1) In vivo loss of plasminogen prevents the toxic effects of uPAT in the liver, and 2) uPA overproduction does not correct the abnormal repair of Plg^{-/-} livers. We speculate that uPA-mediated properties occur via plasminogen activation in the hepatic environme