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Critical Role of Plasmin in Macrophage Activation During Liver Injury

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Activation of hepatic macrophages is critical for liver repair after injury. The mechanism by which liver injury stimulates macrophage activation is not fully understood. We tested the hypothesis that the fibrinolytic enzyme, plasmin, is critical for macrophage activation after liver injury. To test this hypothesis, mice were exposed to a hepatotoxic dose of acetaminophen followed by treatment with tranexamic acid (1200 mg/kg i.p., administered twice daily), a drug that inhibits the conversion of plasminogen to plasmin. Exposure of mice to acetaminophen stimulated rapid macrophage activation, increasing cytokine production and macrophage-mediated phagocytosis of necrotic cells. This activation was reduced by plasmin inhibition, leading to impaired liver repair. Next, we determined whether plasmin directly activates macrophages. Treatment of either bone marrow-derived macrophages or Kupffer cells with plasmin increased expression of the proinflammatory cytokines Cxcl1, Cxcl2, and tumor necrosis factor-α in an Erk1/2 and p38-dependent manner. Studies have indicated a role for high-mobility group B1 protein (HMGB1), a damage-associated molecular pattern molecule, in the activation of macrophages. Therefore, we determined whether HMGB1 affects plasmin-mediated activation of macrophages. While HMGB1 alone at concentrations that are detected in the serum of acetaminophen-treated mice did not increase expression of proinflammatory cytokines in macrophages, it synergistically enhanced plasmin-mediated upregulation of cytokines. Furthermore, necrotic hepatocytes from wild-type mice enhanced plasmin-mediated activation of macrophages, whereas necrotic hepatocytes from hepatocyte-specific HMGB1 knockout mice did not. Collectively, these studies demonstrate that plasmin is an important activator of macrophages after liver injury. Further characterization of this pathway could lead to the development of novel therapies aimed at enhancing macrophage-mediated liver repair in patients suffering from acute liver injury.

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