Molecular mechanism of acute and chronic liver injuries

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We examine the pathophysiological roles of interferon (IFN)-γ in the pathogenesis of acetaminophen-induced acute liver injury. In wild-type mice, intraperitoneal injection of a lethal dose of acetaminophen induced intrahepatic IFN-γ mRNA expression and a marked increase in serum transaminase levels, leading to acute lethality of about 45 %. Histopathological analysis demonstrated centrilobular hepatic necrosis with leukocyte infiltration and a large number of apoptotic hepatocytes later than 10 hr after acetaminophen injection. Concomitantly, mRNA expression of adhesion molecules, pro-inflammatory cytokines, chemokines, Fas, and inducible NO synthetase (iNOS) was enhanced in the liver of wild-type mice injected with a lethal dose of acetaminophen. When IFN-γ-deficient mice were treated in the same manner, all mice survived with reduced serum transaminase elevation and attenuated hepatic necrosis, leukocyte infiltration, and hepatocyte apoptosis. The gene expression of all molecules was significantly attenuated in IFN-γ-deificient mice. Administration of an anti-IFN-γ neutralizing antibody even at 2 and 8 hr after acetaminophen challenge to wild-type mice alleviated acetaminophen-induced liver injury, and all mice survived. Therefore, IFN-γ is responsible for acetaminophen-induced liver injury by mediating leukocyte infiltration, hepatocyte apoptosis, and NO production as well as cytokine and chemokine production.

We also examined the molecular mechanism of chronic liver diseases such as liver fibrosis, particularly focusing on tumor necrosis factor (TNF)-α. TNF-α has pleiotropic functions, but its role in liver fibrosis has not yet been clarified. To understand the pathophysiologic role of the TNF-α/TNF receptor (TNF-R) p55 signals in liver fibrosis, 10 mg/kg of dimethylnitrosamine, a specific hepatotoxicant, was administered twice a week into the peritoneal cavity of both TNF-Rp55 knock-out (KO) and wild-type mice, and the severity of fibrosis was monitored histologically and biochemically. In wild-type mice, histologic analysis demonstrated evident fibrotic changes 1 week after the initiation of dimethylnitrosamine administration, consistent with increased liver collagen contents. Concomitantly, the numbers of Kupffer cells and activated hepatic stellate cells (HSCs) were increased in liver tissue. On the contrary, fibrotic changes were attenuated and the numbers of Kupffer cells and HSCs were decreased in TNF-Rp55-KO mice. Moreover, gene expression of TNF-α and monocyte chemoattractant protein-1, which are involved in Kupffer cell activation or migration, was decreased in the liver of TNF-Rp55-KO mice. Collectively, TNF-Rp55-mediated signals may regulate activation of Kupffer cells and HSCs and eventually enhance fibrotic process.

References

Ishida, Y., Kondo, T., Ohshima, T., Fujiwara, H., Iwakura, Y., and Mukaida, N. (2002) A pivotal involvement of IFN-γ in the pathogenesis of acetaminophen-induced acute liver injury. FASEB J. 16: 1227-1236.

Kitamura, K., Nakamoto, Y., Akiyama, M., Fujii, C., Kondo, T., Kobayashi, Ki., Kaneko, S., and Mukaida, N. (2002) Pathogenic roles of tumor necrosis factor receptor p55-mediated signals in dimethylnitrosamine-induced murine liver fibrosis. Lab. Invest. 82: 571-583.