KUPFFER CELLS MODULATE ETHANOL-INDUCED HEPATOCYTE DNA SYNTHESIS

Danielle A. McShan¹, Stacy M. Corthals², Craig L. Walker² and Lisa M. Kamendulis²

¹Department of Chemistry, Jackson State University, Jackson, MS 39211, USA
²Department of Pharmacology and Toxicology, Indiana University School of Medicine, Indianapolis, IN 46202, USA

Abstract: Chronic ethanol consumption has been linked to an increased risk of hepatocellular cancer in humans and rodents, however, the mechanism(s) involved have not been resolved. Research examining the mechanisms leading to ethanol-induced hepatotoxicity has shown that Kupffer cell activation, resulting from increased endotoxin levels; appear to mediate hepatocyte damage and necrosis. Since Kupffer cells produce bioactive products such as reactive oxygen species and cytokines following their activation, substances that can also elicit growth stimulatory effects, we questioned whether the Kupffer cell participates in increased hepatocellular growth following ethanol exposure. To identify doses of ethanol that increased hepatocellular growth and were not hepatotoxic, a dose response study for ethanol (0 – 5% ethanol (w/v) in liquid diet) was conducted in male C57Bl mice. Exposure to ethanol for 7 days increased hepatic DNA synthesis (~2-fold over control) at concentrations of 2% and 3% ethanol (w/v). Higher ethanol doses (4% and 5%) failed to increase DNA synthesis, but increased hepatotoxicity as evidenced by increased serum ALT and AST. Ethanol doses between 1 – 3% ethanol were without toxicity. We next examined the role of the Kupffer cell on ethanol-induced DNA synthesis by exposing mice to 3% ethanol in the presence and absence of Kupffer cell depletion (using clodronate liposomes). Clodronate liposome treatment resulted in >90% depletion of Kupffer cells, assessed using F4/80 immunohistochemistry. 3% ethanol produced the expected increase (~2-fold), in DNA synthesis relative to control levels. However, Kupffer cell depletion reduced ethanol-induced hepatic DNA synthesis to below control levels (~1.5% compared to ~2.0% in controls). Reactive oxygen species (ROS) may be involved in the increased DNA synthesis by ethanol since Nrf2 protein expression increased following ethanol exposure in addition to Kupffer cell depletion which decreased Nrf2 expression compared to controls. These studies support that Kupffer cells participate in ethanol-induced DNA synthesis and have identified a model system in which the mechanisms involved in ethanol-induced cell growth can be studied.