KUPFFER CELL INVOLVEMENT IN NONGENOTOXIC HEPATOCARCINOGENESIS: ETHANOL AS A MODEL

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Abstract: Non-genotoxic carcinogens encompass a diverse grouping of environmental chemicals and pharmaceutical agents that cause liver cancer through several non-DNA reactive modes of action. Kupffer cells, the liver macrophage, produce several growth modulating cytokines as well as reactive oxygen species (ROS) following activation. Recent evidence demonstrates that Kupffer cells participate in the growth response elicited by selective tumor promoting chemicals. Chronic consumption of ethanol is associated with an increased risk for hepatocellular cancer in rodents and humans. While the mechanism(s) underlying ethanol-induced disease etiology and pathology are not understood, studies in rodents have demonstrated that ethanol functions at the promotion stage of the carcinogenesis process. We questioned whether Kupffer cells participated in ethanol-induced liver growth. Exposure to ethanol (0-5% w/v in liquid diet) in male C57Bl/6 mice for 7 days increased hepatic DNA synthesis (~2-fold over control) at non-hepatotoxic doses (2-3%), whereas doses of ethanol that produced liver toxicity (4-5%, evidenced by increased ALT and AST) were without effects on hepatic DNA synthesis. In addition, non-toxic doses of ethanol (1-3%) promoted the growth of preneoplastic liver lesions, confirming that ethanol functions at the promotion stage of the cancer process. To assess the role of the Kupffer cell on hepatic DNA synthesis, Kupffer cells were depleted using clodronate-encapsulated liposomes (CL). 3% Ethanol was given to mice for 7 days in the presence or absence of CL. CL decreased Kupffer cell number >90% (accessed via F4/80 immunohistochemistry), and reduced ethanol-induce DNA synthesis to below control levels (~1.5% compared to ~2.0% in controls). Ethanol (between 1-5%), produced dose-related increases in the expression of the ROS-sensing transcription factor, Nrf2 (up to 4-fold over control). However, Kupffer cell depletion prevented the increased Nrf2 protein seen following 3% ethanol (~70% of control). In a similar manner, ethanol increased ERK1/2 phosphorylation (upto 18-fold over control), and was inhibited by Kupffer cell depletion (~80% of control). Collectively, these results suggest that Kupffer cells participate in the hepatic growth response seen following non-lethal doses of ethanol, and appear to provide a source of ROS that lead to the activation of MAP kinase signaling cascades.

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