Role of Early Growth Response Factor-1 and Hepatocellular Hypoxia in the Development of Chronic Liver Disease

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Hepatocyte injury during cholestasis depends in part on the release of proinflammatory mediators that cause neutrophils to accumulate in the live rand become activated to damage hepatocytes. The mechanism by which cholestasis stimulates production of proinflammatory mediators in the liver is not completely understood.

The studies presented here tested the hypothesis that the transcription factor, early growth response factor-1 (Egr-1), is required for upregulation of proinflammatory mediators that stimulate neutrophils to accumulate in the liver and become activated to damage hepatocytes during cholestasis. Several lines of evidence indicate that Egr-1 is an important regulator of inflammation. Egr-1 response elements are present in the promoters of several proinflammatory genes. The results of these studies show that Egr-1 mRNA was rapidly upregulated in the livers of mice subjected to bile duct ligation, and animal model of cholestasis. Immunohistochemical staining revealed that Egr-1 was primarily expressed by hepatocytes in cholestatic mice.

To determine whether Egr-1 was required for inflammation and hepatocyte injury during cholestasis, bile duct ligation was performed in wild-type and Egr-1 knockout mice. Hepatocyte injury, neutrophil accumulation, and upregulation of macrophage inflammatory protein-2 (MIP-2) and intercellular adhesion molecule-1 (ICAM-1) in the liver were significantly reduced in Egr-1 knockouts. Since hepatocytes are exposed to elevated concentrations of bile acids during cholestasis, it was determined whether bile acids upregulate Egr-1 in primary mouse hepatocytes.

Our results show further that the stimulus for upregulationi of Egr-1 in the liver during cholestasis may be elevated concentrations of bile acids. Egr-1 was rapidly upregulated in the liver by 24 hours after bile duct ligation. This suggested that the stimulus for upregulation of Egr-1 must have also increased rapidly after bile duct ligation. One possibility was bile acids, the concentrations of which increased 40-fold by 24 hours after ligation of the bile duct. Therefore, the hypothesis was tested that bile acids upregulated Egr-1 in hepatocytes. Our studies showed that deoxycholic acid dose-dependently increased Egr-1 protein levels in primary mouse hepatocytes. These studies

suggest that elevated concentrations of bile acids are important stimulus for upregulation of Egr-1 in the liver during cholestasis.

Overall, our studies indicate that Egr-1 is a critical regulator of inflammation in the liver during cholestasis, and may be the critical link between elevated concentrations of bile acids and the production of proinflammatory mediators. Taken together, our studies suggest that during early stages of cholestasis, elevated concentrations of bile acids upregulate Egr-1 in hepatocytes, which increases expression of proinflammatory mediators that cause neutrophils to accumulate in the liver and become activated to damage hepatocytes.