Nrf2 Deficiency Augments the Activity of Hepatic Progenitor Cells during Cholestasis

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Transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) is a central regulator of cellular defense against oxidative stress and inflammation and is also involved in regulating liver regeneration. The aim of the study is to evaluate whether Nrf2 mediates hepatic repair response during cholestasis. Wild-type and Nrf2-null mice were subjected to bile duct ligation or sham operation. Various assessments were performed at 5, 10, 15, 25, and 40 days following surgery. Significant genotype-dependent differences in liver injury, cell proliferation, and collagen deposition were not seen over the time course of the study, in line with several reports. However, Nrf2-null mice exhibited a more prominent network of septual tissue containing laminin and α-fetal protein expressing cells at 15 days after injury, suggesting a stronger repair response, than their wild-type litter mates. In the livers of both genotypes of mice, cytokeratin 19 (CK19), a marker of bipotent liver epithelial progenitors and immature billiary epithelial cells, were expressed in the epithelial cells of newly formed bile ducts and a population of hepatocytic-appearing cells in parenchyma. Notably, Nrf2-null mice showed higher hepatic protein expression of CK19 at 5 days following BDL, indicating earlier onset of the activation of CK19+ progenitor cells, than wild-types. CD133, a marker of liver progenitors, were found to be expressed by newly generated bile duct epithelial cells and a population of hepatocytic-appearing parenchymal cells in the livers of the two genotypes of mice. Hepatic CD133 protein expression was gradually elevated, paralleling continuous increase in the number of CD133+ hepatocytic-appearing cells, as the cholestasis progressed. Remarkably, the lack of Nrf2 led to markedly higher magnitudes of the increases in hepatic CD133 protein level and in the number of CD133+ hepatocytic-appearing cells. Collectively, our data demonstrate that Nrf2 deficiency evokes higher activity of liver progenitor cells and thus stronger liver repair response. The findings indicate that Nrf2 is an important regulator of the activity of hepatic progenitor/stem cells during chronic liver injury.

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