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Hepatic cirrhosis is the unifying risk factor for greater than 80% of hepatocellular carcinomas (HCCs). There is substantial evidence that the tumor microenvironment exerts a major role in carcinogenesis, and that stromal fibroblasts promote tumorigenesis. Despite the almost unique association between HCC and liver fibrosis, it is currently not known whether activated hepatic stellate cells, the main fibrogenic cell population of the liver, promote the development of HCC. We propose three Aims to provide evidence that hepatic fibrosis and HCC are not merely parallel, but functionally linked biological responses during chronic liver injury. In Aim 1, we will investigate whether isolated liver fibrosis promotes the development of HCC. For this purpose, we will use conditional deletion of the transcription factor Lhx2 as a novel genetic model of liver fibrosis. This model selectively activates hepatic stellate cells without the induction of inflammation and injury, and therefore allows to specifically determine the influence of hepatic fibrosis on chemically-induced hepatocarcinogenesis. In Aim 2, we seek to investigate whether deletion of the EGF receptor ligand epiregulin affects hepatocarcinogenesis. Our preliminary data show that epiregulin, a potent hepatomitogen, is highly and selectively upregulated in activated hepatic stellate cells in the chronically injured liver. Using epiregulin knockout mice, we will determine whether epiregulin deletion reduces hepatocellular proliferation and tumor formation in a fibrotic model of chemical hepatocarcinogenesis. In Aim 3, we will determine whether inhibition of lysyl oxidase reduces HCC development. Lysyl oxidase promotes collagen crosslinking and has been shown to promote cancer progression and metastasis in other organs. Lysyl oxidase is one of the most highly upregulated genes in activated hepatic stellate cells. Using two different inhibitors, we will determine whether inhibition of lysyl oxidase reduces the HCC lesion number and size in a fibrotic model of chemical hepatocarcinogenesis. In summary, the three Aims of this proposal may establish the functional link between liver fibrosis and HCC, and are likely to point towards hepatic stellate cells as additional targets for HCC prevention or treatment.
