Liver Cancer

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Editorial

Molecular Link between Liver Fibrosis and Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the most common form of liver cancer, which is usually associated with a very poor prognosis [1], and is the third leading cause of cancer deaths worldwide. Most HCCs develop in the context of severe liver fibrosis and cirrhosis caused by chronic liver inflammation. Chronic infections with hepatitis B virus (HBV) or hepatitis C virus (HCV) as well as hepatosteatosis, are the major risk factors for both liver cirrhosis and HCCs. In the case of HCV, HCC develops after one or more decades of chronic infection, and an elevated risk of HCC progression is restricted largely to patients with cirrhosis or advanced fibrosis. Thus, the risk of hepatocarcinogenesis depends on background liver factors, of which fibrosis is a major determinant. Development and progression of liver fibrosis are associated with hepatocyte death and a subsequent inflammatory response [2], both of which involve reactive oxygen species (ROS) accumulation in injured hepatocytes. Given that the risk of human HCC recurrence after hepatectomy is positively correlated with protein oxidation in the liver, augmented oxidative stress of liver parenchymal cells may explain the close relationship between liver fibrosis and hepatocarcinogenesis [3].

In this issue, Ramakrishna et al. review possible molecular links between liver fibrosis and HCC [4]. Critical regulators of liver cancer development are inflammation in the context of the NF-κB/STAT3/JNK axis and inflammasome, and also cellular senescence. Like IKKβ, the catalytic subunit of the IκB kinase complex required for NF-κB activation, p38α prevents ROS accumulation and excessive JNK activation, thereby maintaining hepatocyte survival and suppressing liver injury [3, 5]. Hepatocyte IKKβ and p38α inhibit hepatocarcinogenesis by suppressing accumulation of ROS and inflammation, whereas JNK activation promotes ROS accumulation, hepatitis, and carcinogenesis [5, 6]. p38 is essential for ras-induced senescence, an important tumor-suppressing defense mechanism [7], while JNK suppresses p53-dependent senescence [8]. p38 and JNK antagonistically control senescence and cytoplasmic $p16^{INK4A}$ expression in doxorubicin-treated endothelial progenitor cells [9]. A better understanding of cross-talk between inflammation and cellular senescence is of great importance.

Identification of the cellular origin of HCC will help in targeted therapeutics directed towards the most dreadful consequence of chronic inflammation, HCC development. The concept that tumors are maintained by dedicated stem cells, the so-called cancer stem cell hypothesis, has attracted much interest. According to this hypothesis, cancer cannot be viewed as simple monoclonal expansions of functionally equal tumor cells. Instead, only a small minority of tumor cells, the cancer stem cells or tumor-initiating cells, have the ability to maintain the malignant population [10]. Deletion of IKKβ enhances proliferation of tumor-initiated cells and accelerates HCC development. These effects of IKKβ are correlated

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with increased accumulation of ROS that leads to JNK and STAT3 activation [11]. The positive cross-talk between JNK and stem cell expansion is evident in human HCC studies [12]. Deletion of p38α, which leads to JNK activation, upregulates expression of SOX2 and Gankyrin, which may be involved in cancer stem cell maintenance [3]. The NF-κB/STAT3/JNK signaling pathway in cancer stem cells may be a promising therapeutic target.

The molecular etiology of HCC has been extensively studied using transgenic or chemically induced mouse models [13, 14]. The chemical procarcinogen diethylnitrosamine (DEN)-induced HCC depends on production of the NF-κB-regulated cytokine IL-6 by resident Kupffer cells [15]. In this case, Kupffer cells are activated by IL-1α released by apoptosing hepatocytes [5]. Interestingly, male mice produce more IL-6 upon DEN administration than females, which accounts for the marked male bias in HCC induction studies. Mice administered thioacetamide for 10 months develop HCCs subsequent to appearance of severe liver fibrosis, thus providing a model that closely mimics the natural history of human HCV-related liver disease [3]. These animal models are critical for finding answers to key questions raised by the authors.

Unlike most solid tumors, the incidence and mortality of HCC have increased in the United States and Europe in the past decade. The findings implicating a pivotal signaling pathway in HCC development suggest the potential use for blocking agents and/or modulators for HCC treatment. Therefore, it is important to improve our understanding of the molecular pathogenesis of HCC.

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