Editorial Desk

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From the Editor's desk...

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Richard Moreau*, Ramon Bataller, Thomas Berg, Jessica Zucman-Rossi, Rajiv Jalan

SELECTION OF THE MONTH

Non-selective beta blockers (NSBBs) improve the survival of ACLF patients

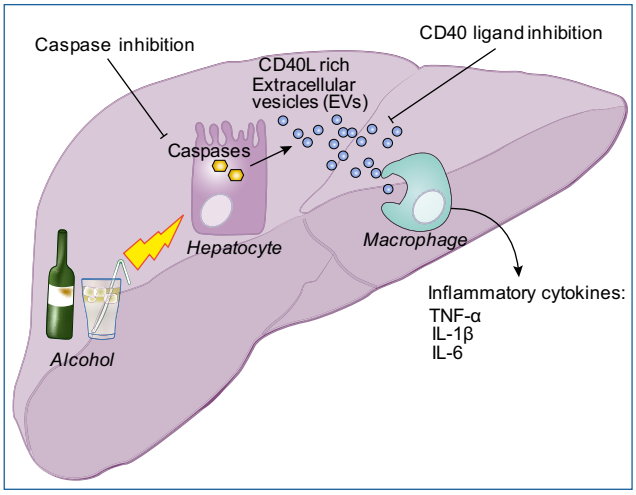
NSBBs have been the mainstay of pharmacological therapy for portal hypertension in cirrhotic patients for over 25 years. Data in the past few years have indicated that mortality of patients with refractory ascites or spontaneous bacterial peritonitis may be increased if NSBBs are continued. The important paper by Mookerjee *et al.* analyses the data obtained in the prospective observational study in patients with acute deterioration of cirrhosis requiring hospital admission: the CANONIC study. The results show that the **patients that were being treated with NSBBs at the time of hospital admission with ACLF had a significantly lower mortality, which was associated with a less severe inflammatory response**. However, the doses of NSBBs used were relatively low suggesting that the protective effect may be due to mechanisms other than its known hemodynamic effects. The data argues against stopping NSBBs in cirrhotic patients unless there are specific contraindications.

ALCOHOLIC LIVER DISEASE (ALD)

Hepatocytes exposed to alcohol drive inflammation, the proto-oncogene c-myc promotes disease initiation and progression

The mechanisms by which hepatocyte exposure to alcohol results in stimulation of resident macrophages (i.e., Kupffer cells) and/or recruitment of monocytes are unknown. Verma *et al.* were interested in CD40 ligand (CD40L, also known as tumor necrosis factor (TNF) ligand superfamily member 5) whose interaction with CD40 (known as TNF receptor superfamily member 5) triggers the inflammatory NF-κB pathway. They show that when exposed to alcohol, hepatocytes overexpressing alcohol-metabolizing enzymes release extracellular vesicles containing CD40L in a caspase-dependent manner, which can stimulate macrophages to produce inflammatory cytokines. **These results suggest a new model in which hepatocyte injury/stress (the nature of which remains elusive) promotes inflammation by stimulating resident macrophages**.

The proto-oncogene c-myc (encoded by *MYC*) is a multifunctional, nuclear phosphoprotein that plays a role in cell cycle progression, apoptosis and cellular transformation. It functions as a transcription factor that regulates transcription of specific target genes. The potential role of c-myc in the development of ALD is unknown. Here Nevzorova *et al.* address this question by using mice with transgenic expression of c-myc in hepatocytes that received alcohol or not. **They find that expression of c-myc and alcohol synergistically accelerates the progression of ALD, presumably due to a loss of p53-dependent protection**.

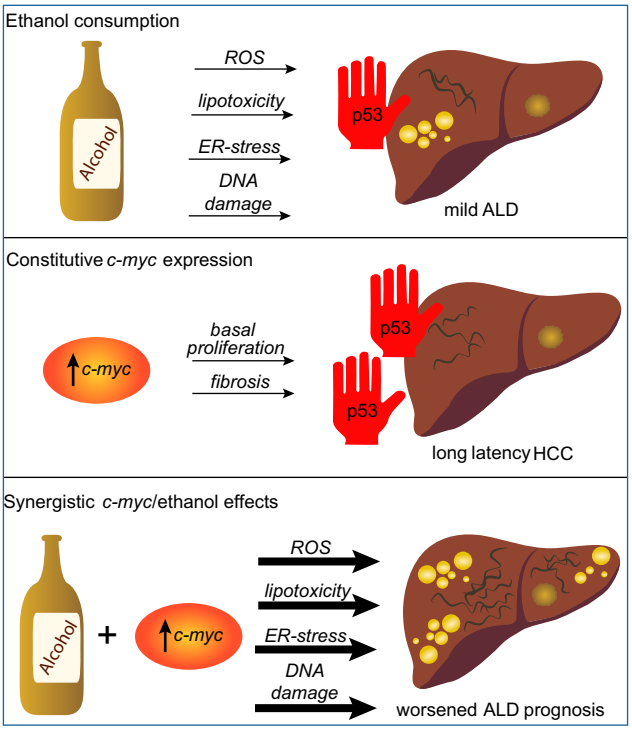


Verma *et al.* 2016

HEPATOCELLULAR CARCINOMA (HCC)

Hedgehog signaling, Laminin-332 and cancer stem cells, complete removal of tumor-bearing portal territory, blood transfusion (PBT) and HCC resection

The Hedgehog (Hh) family of secreted signaling proteins plays a crucial role in the

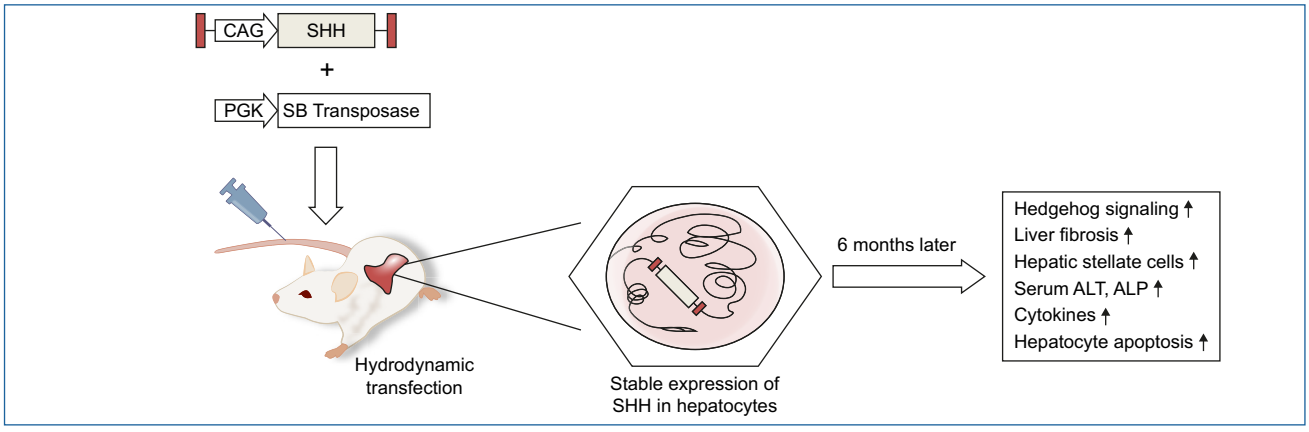


Nevzorova *et al.* 2016

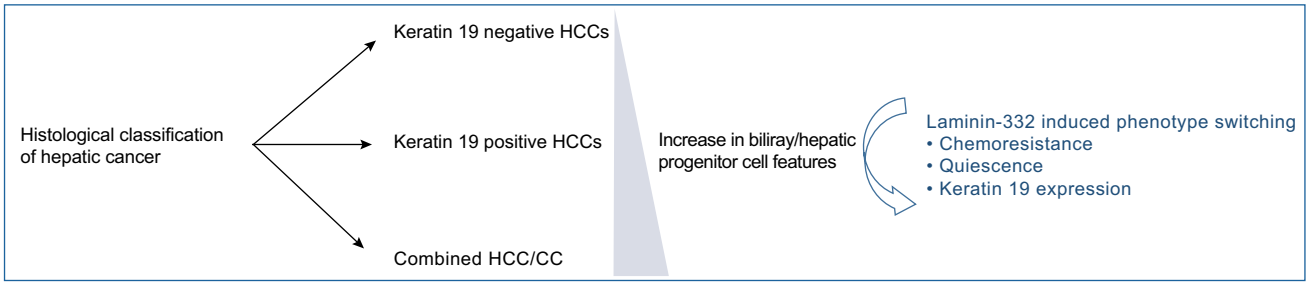
development of diverse animal phyla, from Drosophila to humans, regulating morphogenesis of a variety of tissues and organs. Hh signaling is also involved in the control of stem cell proliferation in adult tissues and aberrant activation of the Hh pathway has been linked to multiple types of human cancer. Members of the Hh family bind to patched (ptc), thus releasing smoothened (smo) to transduce a signal. Transcriptional activation occurs through the GLI family of proteins resulting in activation of target genes. There are three human Hh proteins: Sonic hedgehog (Shh), Desert hedgehog (Dhh) and Indian hedgehog (Ihh). Little is known on the role of Hh signaling in liver fibrosis and HCC. Chung *et al.* using a transgenic model of Shh hepatic expression show that **this expression induces liver fibrosis with concurrent activation of hepatic stellate cells and fibrogenic genes. It can also enhance liver carcinogenesis induced by other oncogenes**.

Cancer stem cells (CSCs) may persist in tumors due to their chemoresistance and cause relapse and metastasis. Govaere *et al.* using elegant approaches in HCC and under *in vivo* and *in vitro* conditions, identify an important role for **laminin (Ln)-332 and more precisely its γ2-chain as part of the specialized CSC niche in maintaining and supporting 'stemness'**. The γ2-chain of Ln-332 could be a novel target in the treatment of HCC.

Although anatomic resection of the tumor-bearing portal territory has been reported to be associated with decreased recurrence of HCC, its oncologic advantage is controversial.



Chung *et al.* 2016



Govaere *et al.* 2016