

## **Stem Cells in Hepatocellular Cancer**

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Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, yet to date, carries a poor prognosis. Risk factors contributing to HCC include chronic hepatitis B and C virus infection, cirrhosis, obesity and prolonged exposure to aflatoxin B1. Although the risk factors are well defined, the molecular mechanisms of hepatocarcinogenesis are unclear; however, HCC is now often considered to result from proliferating tumor stem cells. These ideas have drawn attention to pathways that control stem-cell proliferation. Among these, the transforming growth factor beta (TGF- $\beta$ ), Myb, Myc, Wnt and Hedgehog pathways are of particular relevance to cancer. For instance, genetic inactivation of the TGF- $\beta$  type II receptor results in accelerated HCC, and inactivation of a key adaptor protein for this pathway, ELF, results in spontaneous HCC development. Both TBR2 and ELF label normal hepatocyte progenitor cells, and are lost in HCC. Activation of multiple other signaling pathways, particularly where the TGF- $\beta$  pathway is inactivated in HCC, now presents important therapeutic options in difficult-to-treat HCC. For instance, hepatocyte growth factor (HGF), and c-met, are activated in HCC with inactivation of TGF- $\beta$  signaling, suggesting these as targets for new therapeutics. These findings have led to the development of a number of small-molecule compounds targeting the TGF- $\beta$  pathway, and where TGF- $\beta$  pathway is inactivated, therapeutics aimed at activated receptor tyrosine kinases, their ligands or degradative pathways (eg, CDK4 inhibitors and Smad inducers [triterpenoids]), are now in phase I trials in the United States.