Cancer stem cells have established mechanisms that contribute to tumor heterogeneity as well as resistance to therapy. Over 40% of hepatocellular carcinomas (HCCs) are considered to be clonal and arise from a stem-like/cancer stem cell. Moreover, HCC is the second leading cause of cancer death worldwide, and an improved understanding of cancer stem cells and targeting these in this cancer are urgently needed. In this talk I dissect the evidence obtained from mouse and human liver regeneration, and mouse genetics, to provide insight into the role of TGF-β in regulating the cancer stem cell niche.