Hepatocellular carcinoma originates from hepatocytes and not from the progenitor/biliary compartment.

In many organs, including the intestine and skin, cancers originate from cells of the stem or progenitor compartment. Despite its nomenclature, the cellular origin of hepatocellular carcinoma (HCC) remains elusive. In contrast to most organs, the liver lacks a defined stem cell population for organ maintenance. Previous studies suggest that both hepatocytes and facultative progenitor cells within the biliary compartment are capable of generating HCC. As HCCs with a progenitor signature carry a worse prognosis, understanding the origin of HCC is of clinical relevance. Here, we used complementary fate-tracing approaches to label the progenitor/biliary compartment and hepatocytes in murine hepatocarcinogenesis. In genotoxic and genetic models, HCCs arose exclusively from hepatocytes but never from the progenitor/biliary compartment. Cytokeratin 19-, A6- and ?-fetoprotein-positive cells within tumors were hepatocyte derived. In summary, hepatocytes represent the cell of origin for HCC in mice, and a progenitor signature does not reflect progenitor origin, but dedifferentiation of hepatocyte-derived tumor cells.