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Notch2 Controls Hepatocyte-Derived Cholangiocarcinoma Formation in Mice

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Background: Liver cancer comprises a group of malignant tumors, among which hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are the most common. ICC is especially pernicious and associated with poor clinical outcome. Studies have shown that a subset of human ICCs may originate from mature hepatocytes. However, the mechanisms driving the trans-differentiation of hepatocytes to malignant cholangiocytes remain poorly defined. **Methods:** We adopted lineage tracing techniques and established murine hepatocyte derived ICC models by hydrodynamic injection of activated forms of AKT (myr-AKT) and Yap (YapS127A) proto-oncogenes. Wild-type, *Notch1*^{flox/flox} and *Notch2*^{flox/flox} mice were used to investigate the role of canonical Notch signaling and Notch receptors in AKT/Yap driven ICC formation. Human ICC and HCC cell lines were transfected with siRNA against Notch2 to study whether Notch2 regulates biliary marker expression in liver tumor cells. **Results:** We confirmed that AKT/Yap induced ICC formation is hepatocyte derived and this process is strictly dependent on the canonical Notch signaling pathway *in vivo*.

Deletion of *Notch2* in AKT/Yap induced tumors switched the phenotype from ICC to hepatocellular adenoma-like lesions, while inactivation of *Notch1* in hepatocytes did not result in significant morphological changes. Finally, *in vitro* studies revealed that Notch2 silencing in ICC and HCC cell lines down-regulates the expression of Sox9 and EpCAM biliary markers. **Conclusion:** Notch2 is the major determinant of hepatocyte derived ICC formation in mice.