2017

Notch2 Controls Hepatocyte-Derived Cholangiocarcinoma Formation in Mice

Jingxiao Wang
University of California, San Francisco, jingxiao.wang@ucsf.edu

Mingjie Dong
University of California, San Francisco, mingjie9867@163.com

Xinhua Song
University of California, San Francisco, xinhua.song@ucsf.edu

Kaiwen Hu
Beijing University of Chinese Medicine, Kaiwenh@163.com

Xin Chen
University of California, San Francisco, xin.chen@ucsf.edu

Notch2 Controls Hepatocyte-Derived Cholangiocarcinoma Formation in Mice

Jingxiao Wang[1, 2], Mingjie Dong[1, 3], Xinhua Song[1], Kaiwen Hu[2], Xin Chen[1]

[1] Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, San Francisco, the United States

[2] Beijing University of Chinese Medicine, Beijing, China

[3] 307 Hospital of Academy of Military Medical Science, Beijing, China

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.