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# Bilirubin and PTEN/PI3K/AKT interactions on the proliferative and inflammatory signaling pathways in cholangiocytes

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PTEN is a negative regulator of the PI3K/AKT pathway. Therefore, PTEN deletion induces constitutive activation of the PI3K/AKT pathway. Recently we found that enlargement of the extrahepatic bile duct from inflammation, fibrosis, ductal cell proliferation and metaplasia began to develop as early as 1 month after birth when PTEN was deleted in extrahepatic biliary epithelial cells in vivo. In the PTEN-KD mice model, we checked the roles of the PTEN-AKT pathway in the inflammation-neoplasia spectrum during extrahepatic CCA formation. The histology carries all the features of cholangitis. Importantly, the dysplastic duct cells progress to early precancerous lesions at 3 months after birth. We aslo investigate the proliferative and pro-fibrotic signaling pathways of bile acids and their interactions with PTEN-AKT in immortalized cholangiocyte cell lines.To test whether bile salts activate the PTEN-AKT signaling pathway in cholangiocytes to initiate a cholangitis-CCA continuum, we use cholangiocyte cell line H69 to establish PTEN-KD cell line. Then we investigate the PTEN-KD effect on proliferation, MAPK signaling, PI3K/AKT signaling and EMT in H69 cells. And we find that MAPK and PI3K signaling pathways are activated in PTEN-KD H69 cells and PTEN-KD induces EMT as well. To evaluate the roles of bilirubin on biliopancreatic system, normal biliopancreatic cells were treated with bilirubin, and the downstream signaling pathways were checked by Western blot. We find that bilirubin could impact not only bile duct cells but also normal pancreatic cells. In summary, we have investigated bilirubin and PTEN/PI3K/AKT interactions on the proliferative and inflammatory signaling pathways in cholangiocytes.