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CCA development in the background of Congenital Hepatic Fibrosis/Caroli Disease

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CCA development in mouse models of Congenital Hepatic Fibrosis/Caroli Disease

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BACKGROUND: Congenital Hepatic Fibrosis (CHF) and Caroli disease (CD) are genetic cholangiopathies caused by mutations in the PKHD1 gene. CD/CHF may progress to Cholangiocarcinoma (CCA) in about 15% of patients. CCA progress through a multistep process which includes the development of precursor lesions of low, intermediate and high grade dysplasia. **OBJECTIVES:** We aimed to investigate the presence of dysplastic lesions that could be prone to neoplastic transformation in *Pkhd1*$^{del4/del4}$ mouse, an orthologous model of CHF/CD. **METHODS:** Mucous production was examined by Alcian blue staining. Ezh2 and YAP expression in biliary cells was evaluated by immunofluorescence. The DNA aneuploidy was examined by FACS. *Muc13* gene expression levels were evaluated by RT-PCR. Thioacetamide (TAA) was administrated in the drinking water (300 mg/L). **RESULTS:** *Pkhd1*$^{del4/del4}$ mice, but not the WT controls, display an age-dependent increase of mucous production and nuclear YAP expression. DNA aneuploidy, Ezh2 expression and *Muc13* gene expression (a marker of early stage cancer) were detected only in aged (9- 12-months-old) *Pkhd1*$^{del4/del4}$ mice, but not in WT. *Pkhd1*$^{del4/del4}$ mice treated with TAA develop CCA after 6 months, whereas WT controls only show ductular reaction and fibrosis. Ezh2, a marker of cell transformation, showed a step-wise increased expression from the untreated to TAA treated *Pkhd1*$^{del4/del4}$ mice. **CONCLUSIONS:** The cholangiocytes of aged *Pkhd1*$^{del4/del4}$ mice show premalignant features of dysplasia and have activated YAP. Treatment with TAA accelerated the progression to CAA in *Pkhd1*$^{del4/del4}$ but not in WT mice, indicating that *Pkhd1*$^{del4/del4}$ mice are prone to develop CCA, as in human Caroli Disease and could represent an interesting model.