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 Pkh1del4/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: Pkh1del4/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) Pkh1del4/del4 mice, but not in WT. Pkh1del4/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 Pkh1del4/del4 mice. CONCLUSIONS: The cholangiocytes of aged Pkh1del4/del4 mice show premalignant features of dysplasia and have activated YAP. Treatment with TAA accelerated the progression to CAA in Pkh1del4/del4 but not in WT mice, indicating that Pkh1del4/del4 mice are prone to develop CCA, as in human Caroli Disease and could represent an interesting model.