



VCU

Virginia Commonwealth University
VCU Scholars Compass

Hepatobiliary Cancers: Pathobiology and
Translational Advances

Dept. of Pathology

2017

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

eleanna kaffe Mrs

Yale University, eleanna.kaffe@yale.edu

carlo spirli

Yale University, carlo.spirli@yale.edu

Luca Fabris

University of Padua, luca.fabris@unipd.it

Massimiliano Cadamuro

University of Padua, massimiliano.cadamuro@gmail.com

Mario Strazzabosco

Yale University, mario.strazzabosco@yale.edu

Follow this and additional works at: http://scholarscompass.vcu.edu/hepa_cancers



Part of the [Digestive, Oral, and Skin Physiology Commons](#)

© The Author(s)

Downloaded from

http://scholarscompass.vcu.edu/hepa_cancers/29

This Abstract Accepted for Presentation is brought to you for free and open access by the Dept. of Pathology at VCU Scholars Compass. It has been accepted for inclusion in Hepatobiliary Cancers: Pathobiology and Translational Advances by an authorized administrator of VCU Scholars Compass. For more information, please contact libcompass@vcu.edu.

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

Eleanna Kaffe¹, Carlo Spirli¹, Luca Fabris², Massimiliano Cadamuro², Mario Strazzabosco¹.

- 1) Dept of Internal Medicine, Section of Digestive Diseases, Yale University. 2) Dept of Molecular Medicine, University of Padua.

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.