



Virginia Commonwealth University
VCU Scholars Compass

Hepatobiliary Cancers: Pathobiology and
Translational Advances

Dept. of Pathology

2017

Autophagy is Involved in HDAC6 Mediated Ciliary Loss, and Increases Malignancy in Cholangiocarcinoma Models

Estanislao Peixoto

The Hormel Institute, University of Minnesota, epeixoto@hi.umn.edu

Stephanie Holtorf

The Hormel Institute, University of Minnesota, stephanie.holtorf@mnsu.edu

Kristen Thelen M. Thelen

The Hormel Institute, University of Minnesota, kxthel10@smumn.edu

See next page for additional authors

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

 Part of the [Medicine and Health Sciences Commons](#)

© The Author(s)

Downloaded from

http://scholarscompass.vcu.edu/hepa_cancers/26

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.

Authors

Estanislao Peixoto, Stephanie Holtorf, Kristen Thelen M. Thelen, Maria J. Lorenzo Pisarello, Nicholas F. LaRusso, Sujeong Jin, and Sergio A. Gradilone

Primary cilia are cellular organelles involved in different signaling pathways. Its malfunction has been linked with diseases. The reduced expression of cilia has been reported in different tumors, including cholangiocarcinoma, and experimental ciliary loss in cultured normal cholangiocytes induces a malignant phenotype. HDAC6 is involved in the process of ciliary disassembly, and its inhibition in tumor cells attenuates malignancy, but the mechanisms are unknown. We hypothesize that autophagy may be related to cilia disassembly.

Therefore, we performed electron-microscopy on CCA patient's tissues, and immunofluorescence on normal and tumor cell lines to visualize autophagosomes and ciliary components. CCA patient samples and cell lines showed increased number of autophagosomes compared to normal, and colocalization with ciliary components were observed. Western blot analysis showed that LC3 levels in CCA cell lines were increased after inhibition of HDAC6 suggesting an inhibition of the autophagic flux. Ciliary frequency increased after treatment with the autophagy inhibitor chloroquine, ACY-1215 (HDAC6 inhibitor) or the combination of both inhibitors as measured with immunofluorescence using specific antibodies for cilia, correlating with decreased proliferation. Furthermore, ciliary lengths were measured after siRNA inhibition of different autophagy cargo proteins, CALOCOCO2 and NBR1, and increased lengths were observed. Finally, treatment with chloroquine decreased tumor growth in a rat orthotopic model of CCA.

This results suggest that ciliary disassembly is mediated by an HDAC6-regulated autophagic process, i.e ciliophagy. The inhibition of ciliophagy may decrease malignancy in cholangiocarcinoma and may be further investigated as a potential therapeutic approach.