**Ruprecht-Karls-Universität Heidelberg**
**Medizinische Fakultät Mannheim**
**Dissertations-Kurzfassung**

# The TGF-β Signaling Pathway in Cholangiocarcinoma : Der TGF-β Signaltransduktionsweg bei Cholangiokarzinomen

Autor: Stefan Michael Munker
Institut / Klinik: II. Medizinische Klinik
Doktorvater: Prof. Dr. S. Dooley

Cholangiocarcinomas are often difficult to diagnose and account for 3% of all gastrointestinal tumors. Even in early, resectable stages, the prognosis of cholangiocarcinomas is poor. Cholangiocarcinomas generally are supported by a dense, reactive stroma. To date, TGF-β signaling and further components of downstream signaling in intrahepatic cholangiocarcinomas have not been investigated systematically. Smad2 and Smad3 are the major signal transducers of TGF-β. In the present study, the phosphorylation at C-terminal/linker sites of Smad2/3 in 25 cases of intrahepatic cholangiocarcinomas (iCCAs) was investigated and correlated with the clinical characteristics and prognosis of iCCA. Cell lines derived from cholangiocarcinomas were used to elucidate signalling pathways. Immunohistochemistry and Western blot were performed to detect the levels of TGF-β, p-Smad2/3C, p-Smad2L(ser250/255) and p-Smad3L (ser204, ser208 and ser213) in 50 resected specimens, including 25 iCCAs, 20 controls with cirrhosis and 5 healthy liver samples.

This study shows that compared to surrounding non-tumor tissues, TGF-β expression is often increased, Smad3 phosphorylation at linker serine 213 is decreased and Smad2 and Smad3 phosphorylation at C-terminal sites is increased in iCCA. The survival analysis shows that two markers may serve as prognostic parameters (high Smad2 and high linker Smad3 correlating with a better prognosis and a differentiated phenotype). *In vitro* targeting (siRNA knockdown) of Smad3 in CCA cell lines resulted in increased proliferation, the induction of p21 and the absence of EMT, whereas overexpression of Smad3 (by adenoviral vector) shows opposing effects.

Taken together, the current study suggests p-Smad3L (ser213) to be a potential biomarker predicting prognosis of iCCA. Targeting Smad3 might be a useful therapeutic approach to inhibit TGF-β-mediated EMT in cholangiocarcinoma. Further research is required to elucidate how the TGF-β and its canonical/non-canonical signaling pathways contribute to the progression of cholangiocarcinoma. Strategies interfering these signaling pathways will help us to develop new treatment approaches for CCAs.