Ute Schütte, Savita Bisht, Lukas C. Heukamp, Moritz Kebschull, Alexandra Florin Jens Haarmann, Per Hoffmann, Gerd Bendas, Reinhard Buettner, Peter Brossart, Georg Feldmann (2014). Hippo signaling mediates proliferation, invasiveness and metastatic potential of clear cell renal cell carcinoma. *Translational Oncology*. Apr;7(2):309-21.

Recent work has identified dysfunctional Hippo signaling to be involved in maintenance and progression of various human cancers, although data on clear cell renal cell carcinoma (ccRCC) have been limited. Here, we provide evidence implicating aberrant Hippo signaling in ccRCC proliferation, invasiveness, and metastatic potential. Nuclear overexpression of the Hippo target Yes-associated protein (YAP) was found in a subset of patients with ccRCC. Immunostaining was particularly prominent at the tumor margins and highlighted neoplastic cells invading the tumor-adjacent stroma. Short hairpin RNA-mediated knockdown of YAP significantly inhibited proliferation, migration, and anchorage-independent growth of ccRCC cells in soft agar and led to significantly reduced murine xenograft growth. Microarray analysis of YAP knockdown versus mock-transduced ccRCC cells revealed down-regulation of endothelin 1, endothelin 2, cysteine-rich, angiogenic inducer, 61 (CYR61), and c-Myc in ccRCC cells as well as up-regulation of the cell adhesion molecule cadherin 6. Signaling pathway impact analysis revealed activation of the p53 signaling and cell cycle pathways as well as inhibition of mitogen-activated protein kinase signaling on YAP down-regulation. Our data suggest CYR61 and c-Myc as well as signaling through the endothelin axis as bona fide downstream effectors of YAP and establish aberrant Hippo signaling as a potential therapeutic target in ccRCC