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# TGF-β signaling antagonist Smad7 in hepatocarcinogenesis: functional characterization, clinical correlation and expression regulation

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TGF-β is cytostatic towards damage induced compensatory hepatocyte proliferation. This function is frequently lost during hepatocarcinogenesis, thereby switching the TGF-β role from tumor suppressor to tumor promoter. Smad7 is one of the most important negative regulators of TGF-β pathway. Here, I investigated the role of Smad7 in hepatocarcinogenesis by transgenic hepatocyte specific Smad7 overexpression and knockout mice in diethylnitrosamine (DEN) induced HCC model. I found that Smad7 suppressed tumor development in this animal model as proven by less tumors in transgenic mice and more tumors in knockout mice compared to wild type mice. Further, modulation of Smad7 expression changed the sensitivity of Huh7, FLC-4, HLE and HLF HCC cell lines for cytostatic TGF-β effects which were related to p21 regulation. In a cohort of 140 HCC patients, Smad7 transcripts were elevated in 41.4% of HCC samples as compared to adjacent tissue, with significant positive correlation to tumor size, whereas low Smad7 expression levels (relative to rS18) in both tumor tissue and surrounding tissue were significantly associated with worse clinical outcome. Univariate and multivariate analysis indicate Smad7 levels as independent predictor for overall ($p<0.001$) and disease free survival ($p=0.012$). Delineating a mechanism for Smad7 transcriptional regulation in HCC, I identified cold shock Y-box protein-1 (YB-1), a multifunctional transcription factor. YB-1 RNAi reduced TGF-β induced and endogenous Smad7 expression in Huh7 and FLC-4 cells, respectively. YB-1 and Smad7 mRNA expression levels correlated positively ($p<0.0001$). Furthermore, nuclear colocalization of Smad7 and YB-1 proteins was present in cancer cells of those patients. In summary, our study provides further insight into the role of the TGF-β inhibitor Smad7 in hepatocarcinogenesis from cell line, mice and patient based data.