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Targeting hepatocellular carcinoma through TGF- β pathway E3 Ligases

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Targeting hepatocellular carcinoma through TGF- β pathway E3 Ligases

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Although RING-finger E3 ligases are instrumental in the regulation of inflammatory, apoptosis and cancer, their role in hepatocellular cancer (HCC) was unknown. We therefore analyzed the TCGA database 29 TGF- β pathway associated E3 ligases in HCC and identified mRNA alteration in 55% of the tumors, most prominently for UCHL5, PJA, WWP2, SMURF1/2 and KEAP1. We recently uncovered increased PJA1 expression in TGF- β deficient (β 2SP^{+/-}/Smad3^{+/-}) mice, which develop a human stem cell syndrome and HCC. Analyses of primary HCC datasets reveal increased PJA1 correlates with decreased levels of TGF- β /Smad3 and their regulated genes including Smad9 and TGFBR3. PJA1 interacts with the Smad3 MH2 domain and β 2SP N- and C-terminal domains to promote ubiquitin-mediated Smad3 degradation in a TGF- β dependent manner. In addition, we found that PJA1 expression in HCC is negatively associated with the expression of c-FOS and SERPINE1. Overexpression of a RING-domain-deleted PJA1 reduced HCC cell proliferation and PJA1 knockdown significantly decreased HCC anchorage-independent growth and tumorigenicity. E3 ligase inhibitors, RTA402/405, originally identified as inhibitors for KEAP1, blocking KEAP1-dependent Nrf2 ubiquitination was shown to inhibit HCC cell proliferation and tumor growth in nude mice. RTA402/405 increased β 2SP and TGF- β signaling target expression and luciferase activity and RTA402 was shown to bind PJA1 RING-finger domain by molecular docking experiment. Finally, our results demonstrate that PJA1 promotes liver cancer stem cell formation in Smad3^{+/-} mice. Taken together, these studies demonstrate that loss of β 2SP and Smad3 through PJA1 could play an important role in the development of HCC and reveals that PJA1 may be novel therapeutic targets for this lethal disease.