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## Targeting hepatocellular carcinoma through TGF- $\beta$ pathway E3 Ligases

Kazufumi Ohshiro

*The George Washington University Medical School, kazufumiohshiro@gmail.com*

Jian Chen


*The University of Texas MD Anderson Cancer Center, jianchen@mdanderson.org*

Shulin Li

*The University of Texas MD Anderson Cancer Center, SLi4@mdanderson.org*

*See next page for additional authors*

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**Authors**

Kazufumi Ohshiro, Jian Chen, Shulin Li, Jon White, Asif Rashid, and Lopa Mishra

## Targeting hepatocellular carcinoma through TGF- $\beta$ pathway E3 Ligases

Kazufumi Ohshiro<sup>1</sup>, Jian Chen<sup>2</sup>, Shulin Li<sup>3</sup>, Jon White<sup>4</sup>, Asif Rashid<sup>5</sup>, and Lopa Mishra<sup>1,4</sup>

<sup>1</sup>Center for Translational Research, Department of Surgery, George Washington University, Washington DC, USA; <sup>2</sup>Department of Gastroenterology, Hepatology, and Nutrition, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; <sup>3</sup>Departments of Pediatrics, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; <sup>4</sup>Surgical Service, Veterans Affairs Medical Center, Washington, DC, USA; <sup>5</sup>Department of Pathology, The University of Texas MDACC, Houston, TX, USA

\*corresponding author

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- $\beta$  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- $\beta$  deficient ( $\beta$ 2SP<sup>+/-</sup>/Smad3<sup>+/-</sup>) mice, which develop a human stem cell syndrome and HCC. Analyses of primary HCC datasets reveal increased PJA1 correlates with decreased levels of TGF- $\beta$ /Smad3 and their regulated genes including Smad9 and TGFBR3. PJA1 interacts with the Smad3 MH2 domain and  $\beta$ 2SP N- and C-terminal domains to promote ubiquitin-mediated Smad3 degradation in a TGF- $\beta$  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  $\beta$ 2SP and TGF- $\beta$  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<sup>+/-</sup> mice. Taken together, these studies demonstrate that loss of  $\beta$ 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.