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[Hepatobiliary Cancer](#)

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Transcriptional Regulation of Stat3 by TGF- β Signaling in Liver Cancer Cells

Ling Lin¹, Kyi Soe¹, Zhixing Yao², Wilma S. Jogunoori², Lopa Mishra², **Aiwu Ruth He**¹

¹Department of Medicine and Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA

²Cancer Genetics, Digestive Diseases, and Developmental Molecular Biology, Department of Surgery, Georgetown University, Washington, DC, USA

Background: Hepatocellular cancer (HCC) is one of the most common malignant tumors worldwide. At least 40% of HCC are clonal, suggesting that HCC may develop from liver progenitor/stem cell transformation. We have previously reported that human and mouse HCC tissues with aberrant TGF- β signaling showed increased expression of the interleukin 6 (IL6)/STAT3, and that down-regulation of the IL-6/STAT3 pathway by *itih4*^{-/-} (inter-alpha-trypsin inhibitor-heavy chain-4) ablation resulted in the inhibition of HCC formation. Furthermore, we have shown that the STAT3 protein and tyrosine phosphorylated STAT3 are significantly greater in human HCC tissues than in human normal liver ($P < .0030$ and $P < .0455$, respectively).

Methods: To elucidate the molecular mechanisms of the regulation of STAT3 by TGF- β signaling, we carried out this study by using molecular biology approaches such as quantitative real-time RT-PCR, gene transfection, western blotting, site-directed mutagenesis, chromatin immunoprecipitation (ChIP) and luciferase reporter assay in mouse embryonic fibroblast cells (MEF) and HCC cells.

Results: Here we report that β 2SP, a beta-spectrin and a downstream adaptor protein of TGF- β signaling, modulates STAT3 function. Expression of transcript of *Stat3* is increased significantly by knocking out *β 2SP* gene in MEF cells. Mechanistic analysis revealed that β 2SP and Smad3 bind to the *Stat3* gene promoter upon TGF- β treatment. Overexpression of β 2SP and Smad3 suppress *Stat3* gene promoter activity in the absence or presence of IL-6 stimulation. Site-directed mutagenesis in several transcription factor binding sites in the *Stat3* gene promoter such as E-box, a low affinity STAT3-binding element

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(SBE) and a cAMP-responsive element (CRE), showed that the CRE site might be crucial for the β 2SP and Smad3-mediated suppression of Stat3 promoter activity.

Conclusions: The up-regulation of transcription of *Stat3* gene upon the disruption of TGF- β signaling might play an important role in the carcinogenesis of HCC. Inhibition of IL6/STAT3 and targeting the interaction between TGF- β and STAT3 is an effective approach in management of HCCs.