**Elevated expression of WSB2 degrades p53 and activates the IGFBP3-AKT-mTOR-dependent pathway to drive hepatocellular carcinoma**

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**Background:**Dysregulation of wild-type p53 turnover is a key cause of hepatocellular carcinoma (HCC). WSB2 is a new p53 destabilizer that promotes K48-linked p53 polyubiquitination at the Lys291 and Lys292 sites in HCC cells, leading to p53 proteasomal degradation. Degradation of p53 causes IGFBP3-dependent AKT/mTOR signaling activation.

**Objective/Hypothesis:** Provide evidence showing that WSB2 could ubiquitinate and degrade wild-type p53 in hepatocellular carcinoma, followed by activation of mTOR signaling via the IGFBP3/AKT axis.

**Results:**

The author investigated WSB2 expression levels in 30 paired HCC tumors and adjacent normal liver tissues through qPCR and Western blotting. The findings revealed a significant increase in WSB2 expression in HCC tumor tissues compared to the matching adjacent normal liver tissues at both the mRNA and protein levels. The author then tested the effect of WSB2 on HCC cell proliferation and metastasis by knocking down or overexpressing WSB2 in HepG2 and SK-Hep1 cells. The results showed that WSB2 promotes HCC cell proliferation, migration, and invasion in vitro, as well as tumor growth and lung metastasis in vivo. These results suggest that WSB2 plays a crucial role in HCC tumorigenesis and development. To validate the relationship between WSB2 and p53, the author performed a co-IP experiment and found that endogenous WSB2 interacts with endogenous p53 in p53 wild-type HCCs. A time-course analysis following cycloheximide (CHX) blockade of protein synthesis indicated that WSB2 overexpression shortened the half-life of p53 in HCC cells, suggesting potential degradation via the ubiquitin-proteasome system. As expected, the proteasome inhibitor MG132 significantly blocked WSB2-mediated downregulation of p53 expression. The study further explored how WSB2 influences hepatocellular carcinoma (HCC) by degrading p53. WSB2 overexpression led to the degradation of p53, resulting in the downregulation of specific downstream genes (BAX, CDKN1A, and IGFBP3) in HCC cells. Among these, IGFBP3 emerged as a key player in WSB2-mediated cell proliferation and metastasis. WSB2 was shown to reduce p53 and IGFBP3 expression, subsequently activating the AKT/mTOR pathway in TP53 wild-type cells. Everolimus, an oral mTOR inhibitor approved by the U.S. FDA for various cancers, was suggested to effectively inhibit WSB2-triggered HCC tumorigenesis and metastasis. In HCC samples, patients with high WSB2, low p53, and high p-mTOR had a worse prognosis than those with low WSB2, high p53, and low p-mTOR expression, indicating a negative correlation between WSB2 and p53 and a positive association with mTOR activation in HCC patients.

**Conclusion:**This study demonstrated that WSB2 is frequently upregulated in HCC. Elevated WSB2 ubiquitinates p53at the Lys291 and Lys292 sites via the K48-linked polyubiquitination pathway. WSB2 degrades p53, which leads to decreasedIGFBP3 expression and increased AKT Ser 473 phosphorylation, subsequently activating mTOR signaling and contributing to HCC carcinogenesis and metastasis.