Tripartite motif 8 promotes the progression of hepatocellular carcinoma via mediating ubiquitination of HNF1α

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Background: Hepatocellular carcinoma (HCC) is a prevalent and aggressive malignancy with limited effective treatment options and poor prognosis. Emerging evidence suggests that dysregulation of post-translational modifications, particularly ubiquitination mediated by E3 ligases, plays a crucial role in tumor progression. TRIM8, a member of the tripartite motif family (TRIM), has been identified as an oncogene in various cancers; however, its precise role and underlying molecular mechanisms in HCC remain poorly understood. HNF1α is a vital liver-specific transcription factor that maintains hepatocyte differentiation and inhibits HCC progression, but its protein stability and degradation pathways in HCC are not fully elucidated.

Objective: To investigate the role of TRIM8 in HCC, elucidate the molecular mechanisms by which TRIM8 promotes HCC progression, and evaluate its potential as a prognostic biomarker and therapeutic target.

Results: This study demonstrates that TRIM8 is significantly upregulated in HCC tissues and is also closely associated with aggressive clinicopathological features, such as vascular invasion and advanced tumor stage, as well as poor prognosis and shorter life expectancy of patients. Functional assays reveal that overexpression of TRIM8 enhances HCC cell proliferation, invasion, and migration, while knockdown or knockout of TRIM8 inhibits these malignant behaviors, indicating its role as an oncogenic driver. Mechanistically, TRIM8 directly interacts with the transcription factor HNF1α and promotes its K48-linked polyubiquitination specifically at lysine 197, which targets HNF1α for proteasomal degradation. RNA-seq in conjunction with bioinformatics analysis reveals that the TRIM18/ HNF1α axis is highly correlated with the activation of tumor-promoting signaling pathways such as Wnt/β-catenin and TGF-β, both of which are known to facilitate tumor progression and metastasis. Importantly, restoring HNF1α stability using a K197R mutant, which is resistant to ubiquitination, effectively abolishes TRIM8's oncogenic effects both in vitro and in vivo xenograft tumor model. Clinical analyses further show that high TRIM8 expression correlates with lower HNF1α protein levels, as well as with more advanced tumor features and poorer prognosis in HCC patients.

Conclusion: These findings suggest that TRIM8 functions as an oncogenic driver in HCC primarily by mediating the ubiquitination and subsequent degradation of HNF1α. The mechanism of TRIM8-mediated reduction of HNF1α underlying TRIM8-promoted HCC malignant progression highlights TRIM8 as a promising prognostic biomarker and therapeutic target. Interventions aimed at disrupting the interaction between TRIM8 and HNF1α or preventing HNF1α degradation could offer a novel and effective strategy for HCC treatment.