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USP8 positively regulates hepatocellular carcinoma tumorigenesis and confers ferroptosis resistance through β-catenin stabilization

Jianing Tang[1,2], Guo Long[1,2], Liang Xiao[1,2]✉ and Ledu Zhou[1,2]✉

Hepatocellular carcinoma (HCC) is the most common type of primary hepatic carcinoma, which is a growing public health problem worldwide. One of the main genetic alterations in HCC is the deregulated Wnt/β-catenin signaling, activation of β-catenin is associated with the progression of HCC. In the present study, we aimed to identify novel modulators in controlling β-catenin ubiquitination and stability. USP8 was overexpressed in HCC tissues and correlated with β-catenin protein level. High expression of USP8 indicated poor prognosis of HCC patients. USP8 depletion significantly decreased β-catenin protein level, β-catenin target genes expression and TOP-luciferase activity in HCC cells. Further mechanistic study revealed that the USP domain of USP8 interacted with the ARM domain of β-catenin. USP8 stabilized β-catenin protein via inhibiting K48-specific poly-ubiquitination process on β-catenin protein. In addition, USP8 depletion inhibited the proliferation, invasion and stemness of HCC cells and conferred ferroptosis resistance, which effects could be further rescued by β-catenin overexpression. In addition, the USP8 inhibitor DUB-IN-3 inhibited the aggressive phenotype and promoted ferroptosis of HCC cells through degradation of β-catenin. Thus, our study demonstrated that USP8 activated the Wnt/beta-catenin signaling through a post-translational mechanism of β-catenin. High expression of USP8 promoted the progression and inhibited ferroptosis of HCC. Targeting the USP8 may serve as a promising strategy for patients with HCC.

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INTRODUCTION

Liver cancer is one of the most urgent public health problems worldwide, which is the sixth most common neoplasm and is the fourth leading cause of cancer-related deaths in all tumors worldwide [1]. Hepatocellular carcinoma (HCC) originates predominantly from hepatocytes, it is the most common histological type of primary hepatic carcinoma, accounting for approximately 90% of primary liver cancers. HCC is known as its high malignance, rapid progression, high metastatic potency, easy recurrence, poor clinical outcomes and is usually indetectable [2]. Despite the developments in major clinical interventions, including surgery, transplantation, chemotherapy, radiotherapy, drug-targeted therapy, and immunotherapy. The advanced stage of HCC is still a therapeutic challenge, and the overall 5-year survival rate of patients with HCC is less than 20% [3–5]. Therefore, it is an urgent need to identify the novel molecular markers and develop effective approaches to treat patients with HCC.

Wnt/β-catenin pathway is a highly conserved pathway that mainly controls cell proliferation. The activation of Wnt/β-catenin pathway is associated with haematopoietic system development, hair follicle renewal, liver metabolism and regeneration, lung tissue repair and metabolism, and the maturation of osteoblast [6–9]. This pathway comprises the following segments: the extracellular signal; trans-membraned segment; cytoplasmic compounds including glycogen synthase kinase 3 β (Gsk3β), adenomatous polyposis coli (Apc), Axin/conductin, casein kinase1α (CK1α), and disheveled (Dvl in mammals and Dsh in drosophila); the nuclear segment mainly contains β-catenin and TCF/LEF family members [10]. The activation of Wnt/β-catenin pathway is mediated by the binding of extracellular Wnt ligands to membrane receptors through autocrine/paracrine methods. β-catenin functions as the ultimate effector of Wnt/β-catenin pathway [11, 12]. After receiving the upstream activation signals, intracellular β-catenin is rapidly accumulated. Then β-catenin is trans-localized into the nucleus and binds to TCF/LEF family members to drive transcription of Wnt/β-catenin target genes involved in cell survival, differentiation, proliferation, and migration [13].

At the off state of Wnt/β-catenin signalling pathway, β-catenin binds to the cytoplasmic sides of cadherin and a degradation complex (DC) comprising APC, AXIN, CK1 and GSK3 protein is formed. β-catenin is captured and phosphorylated by DC, thus activating the ubiquitin proteasome-mediated degradation of β-catenin and keep the low level of free β-catenin in the cytoplasm [14]. Abnormal activation of the Wnt/β-catenin

[1]Department of Liver Surgery, Xiangya Hospital, Central South University, Changsha 410008 Hunan, China. [2]National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China. ✉email: xiaoliangrick@csu.edu.cn; zhould@csu.edu.cn

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