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Low SPOP Expression and High MDM2 expression Are Associated with Tumor Progression and Predict Poor Prognosis in Hepatocellular Carcinoma

Authors : Chang Liang, Weizhi Gong, Yan Zhang

Abstract : Purpose: Hepatocellular carcinoma (HCC) is a malignant tumor with a high mortality rate and poor prognosis worldwide. Murine double minute 2 (MDM2) regulates the tumor suppressor p53, increasing cancer risk and accelerating tumor progression. Speckle-type POX virus and zinc finger protein (SPOP), a key of subunit of Cullin-Ring E3 ligase, inhibits tumor genesis and progression by the ubiquitination of its downstream substrates. This study aimed to clarify whether SPOP and MDM2 are mutually regulated in HCC and the correlation between SPOP and MDM2 and the prognosis of HCC patients. Methods: First, the expression of SPOP and MDM2 in HCC tissues were detected by TCGA database. Then, 53 paired samples of HCC tumor and adjacent tissues were collected to evaluate the expression of SPOP and MDM2 using immunohistochemistry. Chi-square test or Fisher's exact test were used to analyze the relationship between clinicopathological features and the expression levels of SPOP and MDM2. In addition, Kaplan–Meier curve analysis and log-rank test were used to investigate the effects of SPOP and MDM2 on the survival of HCC patients. Last, the Multivariate Cox proportional risk regression model analyzed whether the different expression levels of SPOP and MDM2 were independent risk factors for the prognosis of HCC patients. Results: Bioinformatics analysis revealed the low expression of SPOP and high expression of MDM2 were related to worse prognosis of HCC patients. The relationship between the expression of SPOP and MDM2 and tumor stem-like features showed an opposite trend. The immunohistochemistry showed the expression of SPOP protein was significantly downregulated while MDM2 protein significantly upregulated in HCC tissue compared to that in para-cancerous tissue. Tumors with low SPOP expression were related to worse T stage and Barcelona Clinic Liver Cancer (BCLC) stage, but tumors with high MDM2 expression were related to worse T stage, M stage, and BCLC stage. Kaplan–Meier curves showed HCC patients with high SPOP expression and low MDM2 expression had better survival than those with low SPOP expression and high MDM2 expression ($P < 0.05$). A multivariate Cox proportional risk regression model confirmed that a high MDM2 expression level was an independent risk factor for poor prognosis in HCC patients ($P < 0.05$). Conclusion: The expression of SPOP protein was significantly downregulated, while the expression of MDM2 significantly upregulated in HCC. The low expression of SPOP and high expression. of MDM2 were associated with malignant progression and poor prognosis of HCC patients, indicating a potential therapeutic target for HCC patients.

Keywords : hepatocellular carcinoma, murine double minute 2, speckle-type POX virus and zinc finger protein, ubiquitination
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