

Hepatobiliary Cancer

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ZBP-89 Enhances the Efficacy of Anti-Tumor Agents on Hepatocellular Carcinoma

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Background: Tumors in patients with hepatocellular carcinoma (HCC) are often unresectable at the time of diagnosis because of widespread intra- or extra-hepatic involvement or limited hepatic reserve. Chemotherapy is the only remaining treatment choice for unresectable HCC, although many patients are resistant to currently available agents. Therefore, novel treatments for HCC are needed. ZBP-89 (zinc finger binding protein-89) is known to participate in the control of cell proliferation and growth. We and others have demonstrated that ZBP-89 stabilizes p53.

Methods: We investigated effects of the anti-tumor agents staurosporine (STS) and 5-fluorouracil (5-FU) on the proliferation of HCC cells with different p53 statuses. PLC/PRF/5 and Huh7 cells have p53 mutations at codon 249 and 220, respectively; p53 is deleted in Hep3B cells; and SK-Hep-1 and HepG2 cells contain wild-type p53. These cells were transfected with AdZBP-89 (adenoviral ZBP-89) and treated with either STS or 5-FU for 24, 48, and 72 hours. At the end of the treatment, cell proliferation was measured by MTT assay.

Results: ZBP-89 treatment alone significantly inhibited the proliferation of HepG2, Huh7 and PCL/PRF/5 cells, slightly decreased the proliferation of SK-Hep-1 cells, and did not

affect the proliferation of Hep3B cells. STS monotherapy reduced proliferation in all cells except SK-Hep-1, and 5-FU monotherapy had an inhibitory effect on all cells tested. ZBP-89 enhanced the sensitivity of HepG2, PLC/PRF/5, SK-Hep-1 and Huh7 but not Hep3B cells to STS treatment. ZBP-89 also increased the efficacy of 5-FU in HepG2 and Huh7 but not in Hep3B, PLC/PRF/5, and SK-Hep-1 cells. Caspase-6 activity was also determined, and ZBP-89 enhanced the activity of caspase-6, especially in the cells whose proliferation was obviously suppressed by ZBP-89.

Conclusions: ZBP-89 significantly enhanced the effects of STS and 5-FU treatments in most of the HCC cells tested. HCC cells without p53 appear to be resistant to ZBP-89, and the inhibitory function of ZBP-89 is associated with an increase in caspase-6 activity.

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