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Letter to the Editor

Inhibition of the JNK signaling pathway increases sensitivity of hepatocellular carcinoma cells to cisplatin by down-regulating expression of P-glycoprotein

Dear Editor,

hepatocellular carcinoma (HCC) is the most common primary liver cancer with a high incidence and mortality worldwide[1]. The risk factors traditionally included are chronic hepatitis and cirrhosis due to several factors such as viral (HBV-HCV) or metabolic (NAFLD)[2], but the 20% of patients with HCC present no chronic hepatic disease[3].

A complete system for HCC classification should include multifunctional and phenotypic characteristics of the tumor. According to immunohistochemistry, proteomics and clinical criteria, the biopsies and the use of newer molecular approaches highlighted the variability among different types of HCC[4]. The future goal of the research will be to identify molecular targets for developing the new personalized therapeutic strategies for the treatment of HCC[5].

For this reason, we read with great interest the recent study published by Liu et al[6] that focused on a relevant biological issue: the HCC resistant to cisplatin treatment. In this paper, the authors have supposed and then identified in c-Jun N-terminal kinase (JNK) signaling pathway, one of the signals involved in HCC sensitivity cells to cisplatin. Based on hepatocellular carcinoma cell line model (HepG2) and cisplatin-resistant clone (HepG2/DDP) they found and highlighted several up-regulated genes and proteins involved in drug resistance, like MDR1, MRP1, MPR2 and the P-glycoprotein (P-gp). On the others hand, the expression of the anti-apoptotic genes Bcl-2 and Bcl-XL resulted significantly up-regulated; while pro-apoptotic genes Bak and Bad were significantly down-regulated. Although the activation of JNK via cisplatin treatment on Hep-G2 was obtained by phosphorylation, with an elegant model, the SP600125 (JNK inhibitor) was able to down-regulate the expression of P-gp and increase the sensitivity of HCC cells to cisplatin.

Other recent studies also investigated the cisplatin and the resistance mechanisms, in HCC.

In their study, Jiliang et al[7] evaluated the role of the TR4 nuclear receptor in HCC. Knocking down TR4 with TR4-siRNA in HCC, first *in vitro* and then *in vivo*, Huh7 and Hep3B cells increased cisplatin chemotherapy resistance. Instead, the overexpression of TR4 with TR4-cDNA in HCC LM3 and SNU387 cells may enhance the efficacy of cisplatin chemotherapy to suppress the HCC progression. For the authors, TR4 might function through altering the ATF3 expression at the transcription level to enhance the sensitivity to cisplatin chemotherapy, with the modification of ATF3 expression via ATF3-siRNA.

Liang et al[8] showed a favourable effect of cisplatin in HCC treatment and the possibility of a new approach to control HCC by the combination of traditional chemotherapy with immunotherapy. They evaluated the possibility of cisplatin in enhancing the efficacy of NK cell immunotherapy to suppress HCC progression altering the androgen receptor (AR)-UL16-binding protein 2 (ULBP2) signals both *in vitro*, using cell cytotoxicity test, and *in vivo* liver orthotopic xenograft mice model. The cisplatin could suppress AR expression both increasing miR-34a-5p to suppress AR expression and altering the ubiquitination to

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accelerate the AR protein degradation. By suppressing AR, cisplatin might function through up-regulating ULBP2, a natural-killer group 2 member D ligand, and so up-regulate cytotoxicity of NK cells in HCC.

Even Runt-related transcription factor 3 (RUNX3) is a tumor suppressor associated with HCC. Kataoka et al[9] wanted to analyze the expression of RUNX3 protein and multidrug resistance-associated protein by immunoblotting in 23 HCC specimens resected from patients with HCC. Using the human HCC cell lines Hep3B, Huh7 and HLF, they introduced RUNX3 cDNA into Hep3B and Huh7 cells, which were negative for endogenous RUNX3 expression; instead, RUNX3 siRNA was transfected into HLF cells, which were positive for endogenous RUNX3. They used MTT assays to determine the effects of RUNX3 expression on 5-fluorouracil (5-FU) and cisplatin sensitivity. The study demonstrated that the exogenous RUNX3 expression reduced the expression of MRP1, MRP2, MRP3 and MRP5 in the RUNX3-negative cells and his knockdown in the HLF cells stimulated MRPs expression. In the HCC tissues, the loss of RUNX3 expression contributed to 5-FU and cisplatin resistance by inducing MRP expression. Another finding of the cisplatin resistance in cancer should be looking for in epigenetic mechanism. Nogales et al[10] focused on epigenetic gene alteration that is nowadays pointed as one of the factors able to drive tumors drug sensitivity. Through DNA methylation microarray on a panel of human cancer cell lines compared to CpG methylation status and cisplatin/carboplatin sensitivity they found that the putative DNA/RNA helicase Schlafen-11 promoter was hypermethylated and associated with increased resistance to platinum compounds.

The mentioned studies show the variability of genetic and epigenetic mechanisms involved in resistance to cisplatin therapy in HCC. The JNK is one of the most relevant signaling pathways. However, this is a piece of a puzzle still far from being completed.

Abbrevations

HCC = hepatocellular carcinoma; JNK = c-Jun N-terminal kinase; HepG2 = hepatocellular carcinoma cell line model; HepG2/DDP = cisplatin-resistant clone; P-gp = P-glycoprotein; AR = androgen receptor; ULBP2 = UL16-binding protein 2; RUNX3 = Runt-related transcription factor 3; 5-FU = 5-fluorouracil.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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