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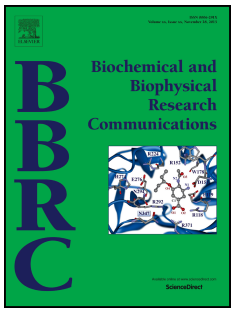

4SC-202 activates ASK1-dependent mitochondrial apoptosis pathway to inhibit hepatocellular carcinoma cells

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4SC-202 activates ASK1-dependent mitochondrial apoptosis pathway to inhibit hepatocellular carcinoma cells

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Abstract. The aim of the present study is to investigate the potential anti-hepatocellular carcinoma (HCC) cell activity by 4SC-202, a novel class I HDAC inhibitor (HDACi). The associated signaling mechanisms were also analyzed. We showed that 4SC-202 treatment induced potent cytotoxic and proliferation-inhibitory activities against established HCC cell lines (HepG2, HepB3, SMMC-7721) and patient-derived primary HCC cells. Further, adding 4SC-202 in HCC cells activated mitochondrial apoptosis pathway, which was evidenced by mitochondrial permeability transition pore (mPTP) opening, cytochrome C cytosol release and caspase-3/-9 activation. Inhibition of this apoptosis pathway, by caspase-3/-9 inhibitors, mPTP blockers, or by shRNA-mediated knockdown of cyclophilin-D (Cyp-D, a key component of mPTP), significantly attenuated 4SC-202-induced HCC cell death and apoptosis. Reversely, over-expression of Cyp-D enhanced 4SC-202's sensitivity in HCC cells. Further studies showed that 4SC-202 induced apoptosis signal-regulating kinase 1 (ASK1) activation, causing it translocation to mitochondria and physical association with Cyp-D. This mitochondrial ASK1-Cyp-D complexation appeared required for mediating 4SC-202-induced apoptosis activation. ASK1 stable knockdown by targeted-shRNAs largely inhibited 4SC-202-induced mPTP opening, cytochrome C release, and following HCC cell apoptotic death. Together, we suggest that 4SC-202 activates ASK1-dependent mitochondrial apoptosis pathway to potently inhibit human HCC cells.

Keywords: Hepatocellular carcinoma (HCC); HDAC inhibitor; 4SC-202; Mitochondrial apoptosis pathway; ASK1 and cyclophilin-D.