

# Accepted Manuscript

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PII: S0006-291X(16)30030-4

DOI: [10.1016/j.bbrc.2016.01.030](https://doi.org/10.1016/j.bbrc.2016.01.030)

Reference: YBBRC 35147

To appear in: *Biochemical and Biophysical Research Communications*

Received Date: 23 December 2015

Accepted Date: 6 January 2016

Please cite this article as: F. Zhang, F. Wan, Z. Li, M. Fu, 4SC-202 activates ASK1-dependent mitochondrial apoptosis pathway to inhibit hepatocellular carcinoma cells, *Biochemical and Biophysical Research Communications* (2016), doi: 10.1016/j.bbrc.2016.01.030.

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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 potentially inhibit human HCC cells.

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

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