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Pharmacological inhibition of DUSP6 suppresses gastric cancer growth and metastasis and overcomes cisplatin resistance

Qi-Nian Wu ^{a,1}, Yi-Fu Liao ^{c,1}, Yun-Xin Lu ^{a,1}, Yun Wang ^a, Jia-Huan Lu ^a, Zhao-Lei Zeng ^a, Qi-Tao Huang ^a, Hui Sheng ^a, Jing-Ping Yun ^b, Dan Xie ^a, Huai-Qiang Ju ^{a*}, and Rui-Hua Xu ^{a*}

^a Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, 510060, China;

^b Sun Yat-sen University Cancer Center, department of pathology, Guangzhou, 510060, China

^c Guangdong General Hospital, Guangdong Neuroscience Institute, Guangdong Academy of Medical Sciences, Department of Neurology, Guangzhou, 510080, China.

¹ These authors contributed equally to this work.

* Correspondence: Rui-Hua Xu, E-mail: xurh@sysucc.org.cn; Huai-Qiang Ju, E-mail: juhq@sysucc.org.cn. Address: 651 Dongfeng East Road, Guangzhou 510060, China; Tel: +86-20-8734-3228; Fax: +86-20-8734-3392;

Abstract

Gastric cancer (GC) is the second cause of cancer-related death. Cisplatin (CDDP) is widely used as the standard GC treatment, but relapse and metastasis are common because of intrinsic or acquired drug resistance. The mitogen-activated protein kinase phosphatases (MAPK)-extracellular signal regulated kinases (ERK) pathway contributes to GC progression and drug resistance, but targeting the MAPK-ERK pathway is challenging in GC therapy. Here, we demonstrated that dual-specificity phosphatases 6 (DUSP6) was overexpressed in GC and predicted poor overall survival and progression-free survival. Knockdown DUSP6 inhibited GC proliferation, migration, invasion and induced apoptosis. (E/Z)-BCI hydrochloride (BCI), a DUSP6 small molecule inhibitor, increased the activity of ERK but interestingly decreased the expression of ERK response genes in BGC823, SGC7901 and CDDP-resistant SGC7901/DDP cells. BCI also caused cell death through the DNA damage response (DDR) pathway. Moreover, BCI inhibited cell proliferation, migration and invasion in a receptor-independent manner and enhanced CDDP cytotoxicity at pharmacological concentrations in the GC cells. *In vivo* experiments further showed that BCI enhances the antitumor effects of CDDP in cell-based xenografts and PDX models. In summary, our findings indicated that disruption of DUSP6 by BCI enhanced CDDP-induced cell death and apoptosis in GC may partly through ERK and DDR pathways. Thus, this study suggests that DUSP6 is a potential prognostic biomarker and a promising target for GC therapy.

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