**EPHB6 receptor negatively regulates chemotherapy sensitivity and gastric cancer cell growth by suppressing ERK-mediated Bcl-2 expression**

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BACKGROUND: Cisplatin-based chemotherapy is commonly used in gastric cancer, and displays excellent therapeutic activity. Eph receptors, as the largest family of receptor tyrosine kinases, are involved in cancer development and progression. However, the role of kinase-dead Eph receptor EPHB6 has not been characterized completely. In this study, we investigated the role of EPHB6 in gastric cancer cell growth and chemoresistance.

HYPOTHESIS: An siRNA library targeting RTK signaling was used to screen a key RTK gene regulating gastric cancer cell growth and cisplatin sensitivity. Human gastric cancer cell lines MGC803 and SGC7901 were used to investigate cell proliferation, colony formation, apoptosis, and tumorigenesis by CCK8, plate clone, flow cytometery, and xenograft models after EPHB6 silenced. The activity of related signaling pathways and the expression of cell apoptosis-related proteins were measured by Western blot.

METHODS: Using the siRNA library, we identified EPHB6 as a key regulator of gastric cancer cell proliferation and ciaplatin sensitivity. EPHB6 knockdown dramatically increased gastric cancer cell proliferation, tumor growth, and hypersensitized cells to cisplatin treatment both in vitro and in vivo. Mechanistic research revealed that knockdown of EPHB6 increased phosphorylated ERK and Bcl-2 expression, while total ERK expression had no change. Furthermore, Bcl-2 protein expression was suppressed after cisplatin treatment in control cells in a time-dependent manner, but not in EPHB6 knockdown cells. And these effects could be blocked by treatment of ERK inhibitor. Cisplatin combined with ERK inhibitor induced increased apoptosis compared to treatment of cisplatin, or ERK inhibitor alone.

RESULTS: Our results suggest that loss of EPHB6 may contribute to cisplatin-based chemotherapy resistance via activating ERK-mediated Bcl-2 expression. Thus, ERK inhibitor might help to sensitize gastric cancer patients particularly with EPHB6-negative tumors to cisplatin-based chemotherapy.