

## **Reg4 activates the MAPK-Bim-caspase3 signaling pathway in 5-fluorouracil resistant gastric cancer**

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**BACKGROUND:** Reg4 is a member of the Reg multigene family, and is highly up-regulated in many gastrointestinal cancers. Gastric cancer cells with high Reg4 expression is resistant to 5-fluorouracil (5-FU), but the mechanism is not very clear.

**HYPOTHESIS:** Reg4 may play an important role in 5-FU-induced cell death.

**METHODS:** Protein expression of Reg4 in gastric cancer cells was analyzed by western blot. Experiments on over-expression and siRNA knockdown of Reg4 were conducted for 5-FU sensitivity and apoptosis analyses. 5-FU metabolism and intracellular signaling were examined by real time PCR and western blot.

**RESULTS:** Western blot showed Reg4 expression was low or null in SGC-7901, BGC-823 gastric cancer cell lines, and high in AGS, MKN28, MKN45 gastric cancer cell lines. Both overexpression and knockdown of Reg4 demonstrated that low Reg4 expression promoted the sensitivity to 5-FU, and 5-FU-induced apoptosis. There were no significant influences on the mRNA levels of thymidylate synthase, orotate phosphoribosyltransferase and dihydropyrimidine dehydrogenase. Further investigation showed enhanced Reg4 expression activated the P42/P44 phosphorylation, and regulated 5-FU sensitivity through MAPK/Erk/Bim signaling pathway.