

Kiss-1 suppresses MMP-9 expression by activating with p38 MAP kinase in human stomach cancer

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Background: Kiss-1 has been identified as a putative human metastasis suppressor gene in various human malignancies. However, there is little information about its possible role in gastric carcinoma.

Objective and Method: In this study, we evaluated a study to determine whether the Kiss-1 gene negatively regulates MMP-9 expression. To identify the genes associated with metastasis by hepatocyte growth factor (HGF), we used cDNA microarray Technology and selected genes up or down - regulated in the stomach cell lines, NUGC-3 and MKN-28.

Results: Kiss-1 RNA and protein were confirmed to be up-regulated. HGF induced Kiss-1 and MMP-9 production in a dose-dependent manner. In order to investigate roles of HGF signaling in tumor progression and metastasis, we determined effects of a specific MEK1 inhibitor (PD 098059) and a p38 kinase inhibitor (SB 203580) on HGF-mediated cell proliferation and MMP-9. Pretreatment with PD 098059 reduced MMP-9 and HGF-mediated cell proliferation but increased Kiss-1 expression. In contrast, SB 203580 pretreatment enhanced MMP-9 and cell proliferation, but decreased Kiss-1 expression. Co-treatment of PD098059 and SB203580 increased the p38 phosphorylation stimulated by HGF. These results suggest that the HGF-mediated Kiss-1 over-expression were regulated mainly by the p38 activation and furthermore, the activation of ERK might affect HGF-mediated Kiss-1 expression indirectly by the regulation of p38 kinase. Consistent with this, expression of p38 phosphorylation strongly repressed by transfected of Kiss-1 short hairpin RNA(shRNA). Down regulation of Kiss-1 using Kiss-1 shRNA induced increase in in vitro cell invasion.

Conclusion: Kiss-1 suppresses MMP-9 expression by activating with p38 MAP kinase.