

Role of the CXCL12/CXCR4 axis in peritoneal carcinomatosis of gastric cancer.

Yasumoto K, Koizumi K, Kawashima A, Saitoh Y, Arita Y, Shinohara K, Minami T, Nakayama T, Sakurai H, Takahashi Y, Yoshie O, Saiki I.

Peritoneal carcinomatosis is a frequent cause of death in patients with advanced gastric carcinoma. Because chemokines are now considered to play an important role in the metastasis of various malignancies, we hypothesized that they may be involved in the development of peritoneal carcinomatosis by gastric carcinoma. Human gastric carcinoma cell lines, which were all highly efficient in generating malignant ascites in nude mice upon i.p. inoculation, selectively expressed CXCR4 mRNA and protein. In particular, NUGC4 cells expressed CXCR4 mRNA at high levels and showed vigorous migratory responses to its ligand CXCL12. CXCL12 enhanced proliferation and rapid increases in phosphorylation of protein kinase B/Akt and extracellular signal-regulated kinase of NUGC4 cells. We also showed that AMD3100 (a specific CXCR4 antagonist) effectively reduced tumor growth and ascitic fluid formation in nude mice inoculated with NUGC4 cells. Additionally, we examined human clinical samples. Malignant ascitic fluids from patients with peritoneal carcinomatosis contained high concentrations of CXCL12 (4.67 ng/mL). Moreover, immunohistochemical analysis showed that 22 of 33 primary gastric tumors with peritoneal metastasis were positive for CXCR4 expression (67%), whereas only 4 of 16 with other distant metastasis were positive (25%). Notably, 22 of 26 CXCR4-expressing primary tumors developed peritoneal metastases (85%). CXCR4 positivity of primary gastric carcinomas significantly correlated with the development of peritoneal carcinomatosis ($P < 0.001$). Collectively, our results strongly suggest that the CXCR4/CXCL12 axis plays an important role in the development of peritoneal carcinomatosis from gastric carcinoma. Thus, CXCR4 may be a potential therapeutic target for peritoneal carcinomatosis of gastric carcinoma.