

Role of the CXCL12/CXCR4 axis in Peritoneal Carcinomatosis of Gastric Cancer

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Peritoneal carcinomatosis is a frequent cause of death in patients with advanced gastric carcinoma. Since chemokines are now considered to play an important role in the metastasis of various malignancies, we hypothesized that they may also be involved in the development of peritoneal carcinomatosis by gastric carcinoma. We found that three out of seven human gastric carcinoma cell lines selectively expressed CXCR4 mRNA and protein at high levels. These three cell lines were those that were all highly efficient in generating malignant ascites in nude mice upon intraperitoneal inoculation. In particular, NUGC4 cells expressed CXCR4 mRNA at high levels and showed vigorous migratory responses to its ligand CXCL12 (also called stromal-derived factor-1a, SDF-1a). Furthermore, CXCL12-treated NUGC4 cells showed enhanced proliferation and rapid increases in phosphorylation of protein kinase B/Akt and extracellular signal-regulated kinase (ERK). We also demonstrated that AMD3100 (a specific CXCR4 antagonist) effectively reduced tumor growth and ascitic fluid formation in nude mice inoculated with NUGC4 cells. We next examined human clinical samples. We found that malignant ascites fluids from patients with peritoneal carcinomatosis contained CXCL12 (average, 4.67 ng/mL) enough to exhibit biological effects on NUGC4 cells. Moreover, immunohistochemical analysis revealed that 22 out of 33 primary gastric tumors with peritoneal metastasis were scored positive for CXCR4 expression (67%), and only 4 out of 16 with other distant metastasis were positive (25%). Notably, 22 out of 26 CXCR4-expressing primary tumors developed peritoneal metastases (85%). CXCR4-positivity of primary gastric carcinomas significantly correlated with the development of peritoneal carcinomatosis. 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.