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学位論文の題名	Enhancement of the CXCL12/CXCR4 axis due to acquisition of gemcitabine resistance in pancreatic cancer. effect of CXCR4 antagonists.（膵癌における Gemcitabine 耐性化に伴う CXCL12/CXCR4 シグナルの活性化と CXCR4 拮抗薬の有効性） BMC Cancer. 2016:16;305
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Background: The CXCL12-CXCR4 signaling axis in malignant tumor biology has increased in importance, and these peptides are implicated in tumor growth, invasion and metastasis. The aim of our study was to examine the important role of the axis in pancreatic cancer (PaCa) cells' relationship with stromal cells in gemcitabine-resistant (GEM-R) tumors and to confirm the effectiveness of CXCR4 antagonists for the treatment of GEM-R PaCa cells.

Methods: We established two GEM-R PaCa cell lines using MIA PaCa-2 and AsPC-1 cells. The expression of CXCR4 mRNA in PaCa cells and the expression of CXCL12 mRNA in fibroblasts were examined by reverse transcription polymerase chain reaction (RT-PCR). The expression of CXCR4 protein in PaCa cells was examined by immunosorbent assay (ELISA) and immunocytochemistry. Using Matrigel invasion assays and animal studies, we then examined the effects of two CXCR4 antagonists, AMD11070 and KRH3955, on the invasiveness and tumorigenicity of GEM-R PaCa cells stimulated by CXCL12.

Results: We found that the expression of CXCR4 in GEM-R PaCa cells was significantly enhanced by GEM but not in normal GEM-sensitive (GEM-S) PaCa cells. In RT-PCR and ELISA assays, the production and secretion of CXCL12 from fibroblasts was significantly enhanced by co-culturing with GEM-R PaCa cells treated with GEM. In Matrigel invasion assays, the invasiveness of GEM-R PaCa cells treated with GEM was significantly activated by fibroblast-derived CXCL12 and was significantly inhibited by CXCR4 antagonists, AMD11070 and KRH3955. In vivo, the tumorigenicity of GEM-R PaCa cells was activated by GEM, and it was significantly inhibited by the addition with CXCR4 antagonists.

Conclusions: Our findings demonstrate that the CXCL12-CXCR4 signaling axis plays an important role in PaCa cells' resistance to GEM. CXCR4 expression was significantly enhanced by the exposure to GEM in GEM-R PaCa cells but not in GEM-S PaCa cells. Furthermore, CXCR4 antagonists can inhibit the growth and invasion of GEM-R PaCa cells. These agents may be useful as second-line chemotherapy for GEM-R PaCa in the future.