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## **CXCL8 and CXCL12 Cooperatively Promote Invasion and Angiogenesis of Pancreatic Cancer**

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**Background:** CXC-chemokines are physiologically involved in the chemotaxis of lymphocytes and monocytes. Under pathologic conditions, however, CXC-chemokines promote tumor cell growth, invasion, and angiogenesis. There is a strong interplay between tumor cells and associated stroma to produce these chemokines. Ductal pancreatic cancer (PaCa) and the endothelial cells secrete CXCL8/interleukin-8 (IL-8), and stromal fibroblasts secrete CXCL12/SDF-1 $\alpha$  in PaCa. CXCR2 binds to CXCL8, and CXCR4 binds to CXCL12 to promote angiogenesis and invasion/metastasis in PaCa. However, little is known about tumor-stromal interactions of CXC-chemokines in promoting invasion/angiogenesis of PaCa.

**Aim:** To study the cooperative effects of CXCL8 (secreted by PaCa) and CXCL12 (secreted by fibroblasts) in promoting invasion/angiogenesis of PaCa.

**Methods and Results:** CXCR2 was detected only on human umbilical vein endothelial cells (HUVEC) but CXCR4 was detected in multiple PaCa cells and HUVEC (by reverse transcription polymerase chain reaction [RT-PCR] and western blots). PaCa cells secreted CXCL8 (high: BxPC-3 and SW1990; low: Capan-2 and MIAPaCa-2) and fibroblasts secreted CXCL12 (by enzyme-linked immunosorbent assay [ELISA]) under basal conditions. Co-culture of fibroblasts with PaCa cells enhanced CXCL12 production

( $P < .01$ ), which is blocked by platelet-derived growth factor receptor (PDGFR) inhibitor (imatinib). CXCL8 did not promote PaCa cell proliferation but strongly increased HUVEC proliferation (MTS assay) and migration/invasion (Matrigel assay) in a dose-dependent manner by signaling through CXCR2. PaCa cell-derived conditioned medium also promoted HUVEC proliferation and migration/invasion, which can be partially blocked by CXCL8-neutralizing monoclonal antibody (mAb) and completely blocked by CXCR2-neutralizing mAb. CXCL12 potently increased PaCa and HUVEC migration/invasion, which can be blocked by CXCL12 and CXCR4 mAbs. Finally, in co-culture experiments (PaCa + fibroblasts + HUVEC), we showed that PaCa cell-derived CXCL8 strongly promoted HUVEC tube formation (in vitro angiogenesis assay) in a dose-dependent manner, which can be blocked by CXCL8-neutralizing antibody. Fibroblast-derived CXCL12 contributes to this process by increasing HUVEC migration prior to tube formation.

**Conclusion:** We showed that PaCa cell-derived CXCL8 and fibroblast-derived CXCL12 cooperatively induce angiogenesis (in vitro) by promoting HUVEC proliferation, migration/invasion, and tube formation. Thus, corresponding receptors, CXCR2 and CXCR4, are potential antiangiogenic and antimetastatic therapeutic targets in PaCa.