Expression and potential function of the CXC chemokine CXCL16 in pancreatic ductal adenocarcinoma.

Abstract:
CXC chemokines have a major influence on the angiogenesis, growth and metastatic potential of pancreatic ductal adenocarcinoma. CXCL16 is a unique transmembrane CXC chemokine, which is shed by members of the disintegrins and metalloproteases (ADAMs), in particular by ADAM10 and ADAM17. In our study, we evaluated expression and potential function of CXCL16 and its receptor CXCR6. CXCL16 and the receptor CXCR6 are upregulated in pancreatic ductal adenocarcinoma (PDAC) and chronic pancreatitis tissues in contrast to normal pancreatic tissues at the mRNA and protein levels. In 85 and 100% of the investigated samples, tumor cells showed positive immuno-staining for CXCL16 and CXCR6, respectively; furthermore, tubular complexes of chronic pancreatitis and the invasive front of PDAC were immunopositive for CXCL16 and CXCR6. Stimulation of PDAC cells with proinflammatory cytokines increased CXCL16 protein levels, whereas silencing of ADAM10 with siRNA transfection led to a decrease in CXCL16 protein levels in cell culture supernatants. No effects on cell viability were notable after incubation of cancer cells with CXCL16. However, CXCL16 markedly increased invasiveness of PDAC cells. Clinically, 82.5% of PDAC patients had higher CXCL16 serum values than the highest value seen in healthy donors. SELDI-TOF-MS analysis
confirmed the upregulation of CXCL16 in sera of PDAC patients. In conclusion, CXCL16 in both transmembrane and soluble forms, and its receptor CXCR6, seem to play an important role in the pathobiology of pancreatic cancer and might be potential markers for pancreatic cancer diagnosis and a target for multimodal therapy concepts in the future.