Neural fractalkine expression is closely linked to pain and pancreatic neuritis in human chronic pancreatitis.

Abstract:
The chemokine fractalkine induces migration of inflammatory cells into inflamed tissues, thereby aggravating inflammatory tissue damage and fibrosis. Furthermore, fractalkine increases neuropathic pain through glial activation, which can be diminished by blocking of its receptor, CX3CR1, through neutralizing antibodies. As chronic pancreatitis (CP) is characterized by tissue infiltration of inflammatory cells, fibrosis, pancreatic neuritis and severe pain, the roles of fractalkine and CX3CR1 were investigated in CP (n=61) and normal pancreas (NP, n=21) by QRT-PCR, western blot and immunohistochemistry analyses. Their expression correlated with the severity of pancreatic neuritis, fibrosis, intrapancreatic nerve fiber density and hypertrophy, pain, CP duration and with the amount of inflammatory cell infiltrate immuno-positive for CD45 and CD68. To investigate the influence of fractalkine on pancreatic fibrogenesis, human pancreatic stellate cells (hPSCs) were isolated from patients with CP, incubated with fractalkine and then Collagen-1 and alpha-smooth muscle actin (alpha-SMA) expressions were measured. CX3CR1, but not fractalkine, mRNA was overexpressed in CP. In contrast, the protein levels of both CX3CR1 and fractalkine were upregulated. Neuro-immunoreactivity for fractalkine and CX3CR1 was strongest in patients suffering from
severe pain and pancreatic neuritis. Long-term suffering from CP was noticeably related to increased neural immunoreactivity of fractalkine. Furthermore, fractalkine and CX3CR1 mRNA overexpressions were associated with enhanced lymphocyte and macrophage infiltration. Advanced fibrosis was associated with increased fractalkine expression, whereas in vitro fractalkine had no significant impact on collagen-1 and alpha-SMA expressions in hPSCs. Therefore, pancreatic fractalkine expression appears to be linked to visceral pain and to the recruitment of inflammatory cells into the pancreatic tissue and nerve fibers, with subsequent pancreatic neuritis. However, pancreatic fibrogenesis is probably indirectly influenced by fractalkine. Taken together, these novel findings suggest that CX3CR1 represents a potential novel therapeutic target to reduce inflammation and modulate pain in CP.