IP-10/CXCL10 induction in human pancreatic cancer stroma influences lymphocytes recruitment and correlates with poor survival.

Abstract:
Pancreatic ductal adenocarcinoma (PDAC) is characterized by an abundant desmoplastic reaction driven by pancreatic stellate cells (PSCs) that contributes to tumor progression. Here we sought to characterize the interactions between pancreatic cancer cells (PCCs) and PSCs that affect the inflammatory and immune response in pancreatic tumors. Conditioned media from mono- and cocultures of PSCs and PCCs were assayed for expression of cytokines and growth factors. IP-10/CXCL10 was the most highly induced chemokine in coculture of PSCs and PCCs. Its expression was induced in the PSCs by PCCs. IP-10 was elevated in human PDAC specimens, and positively correlated with high stroma content. Furthermore, gene expression of IP-10 and its receptor CXCR3 were significantly associated with the intratumoral presence of regulatory T cells (Tregs). In an independent cohort of 48 patients with resectable pancreatic ductal adenocarcinoma, high IP-10 expression levels correlated with decreased median overall survival. Finally, IP-10 stimulated the ex vivo recruitment of CXCR3+ effector T cells as well as CXCR3+ Tregs derived.
from patients with PDAC. Our findings suggest that, in pancreatic cancer, CXCR3+ Tregs can be recruited by IP-10 expressed by PSCs in the tumor stroma, leading to immunosuppressive and tumor-promoting effects.