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PANCREATIC CANCER

Fibroblast co-conspirators

> "treatment with CXCR2 inhibitors decreased tumour volume and significantly increased survival"

The importance of the tumour microenvironment for cancer progression is now well established, but can tumour–stromal interactions be targeted for therapeutic benefit? Using a mouse model of pancreatic ductal adenocarcinoma (PDAC), Hideaki Ijichi and colleagues have provided preclinical data showing that targeting chemokine signalling in stromal fibroblasts can improve survival.

The authors previously generated mice that have expression of activated *Kras* (*Kras*^{G12D}) and deletion of transforming growth factor-β receptor type II (*Tgfbr2*) specifically in the pancreatic epithelium (*Ptf1a*$^{cre/+}$;*LSL-Kras*$^{G12D/+}$;*Tgfbr2*$^{flox/flox}$ mice). These mice develop PDAC that is histologically similar to the human disease and that includes expanded stromal tissue and fibrosis (desmoplasia) in PDAC lesions. A screen for factors that are secreted by PDAC cells from *Ptf1a*$^{cre/+}$;*LSL-Kras*$^{G12D/+}$;*Tgfbr2*$^{flox/flox}$ mice (as compared with pre-invasive pancreatic intraepithelial neoplasia (PanIN) cells from *Ptf1a*$^{cre/+}$;*LSL-Kras*$^{G12D/+}$ mice) using cytokine antibody arrays revealed the increased secretion of several proteins, including the CXC chemokines CXCL1, CXCL2 and CXCL5.

How might signalling by these chemokines affect pancreatic tumours? Inhibition of CXCR2, the receptor for all three of the identified chemokines, did not block PDAC cell proliferation; instead, CXCR2 was more highly expressed in fibroblasts that were isolated from the pancreas of *Ptf1a*$^{cre/+}$;*LSL-Kras*$^{G12D/+}$ mice. Stimulation of these pancreatic fibroblasts with CXCL1, CXCL2 or CXCL5 induced the transcription of connective tissue growth factor (*Ctgf*), which encodes a pro-fibrotic, tumour-promoting factor, and similar results were obtained when pancreatic fibroblasts were stimulated with conditioned media from PDAC cells (but not with media from PanIN cells). Furthermore, the pharmacological inhibition of CXCR2 suppressed *Ctgf* expression.

Is this pathway relevant *in vivo*? Subcutaneous injection of nude mice with PDAC cells plus pancreatic fibroblasts resulted in significantly faster tumour growth, which was blocked by a CXCR2 inhibitor, compared with injection of PDAC cells alone. In addition, subcutaneous tumour growth was significantly reduced when CXCR2 was knocked down by short hairpin RNA in the fibroblasts, compared with knockdown in the PDAC cells, indicating that stromal CXCR2 is crucial. The authors also demonstrated the importance of this signalling pathway in the more clinically relevant *Ptf1a*$^{cre/+}$;*LSL-Kras*$^{G12D/+}$;*Tgfbr2*$^{flox/flox}$ mice, in which treatment with CXCR2 inhibitors decreased tumour volume and significantly increased survival compared with control mice (62 versus 52 days; $P = 0.0044$). Finally, they showed that the CXCR2 inhibitor reduced CTGF expression in the stroma, as well as microvessel density, which is consistent with previous reports that CXCR2 signalling and CTGF can induce angiogenesis.

If this chemokine signalling pathway operates in human PDAC, then inhibition of CXCR2 in the tumour stroma might provide new treatment options for this often lethal tumour type.

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ORIGINAL RESEARCH PAPER Ijichi, H. *et al.* Inhibiting Cxcr2 disrupts tumor-stromal interactions and improves survival in a mouse model of pancreatic ductal adenocarcinoma. *J. Clin. Invest.* 19 Sep 2011 (doi:10.1172/JCI42754)