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PANCREATIC CANCER

SURPRISING ROLE FOR FIBROSIS

Two recent studies have demonstrated an unexpected role for fibrosis in pancreatic cancer; instead of contributing to progression of cancer (as widely assumed), myofibroblasts and fibrosis might actually prevent the cancer from spreading.

"Pancreatic ductal adenocarcinoma (PDAC) has the highest amount of stroma when compared to other solid tumours," explains Raghu Kalluri, corresponding author of one of the studies. Thus, Kalluri and his colleagues set out to investigate the functional role of stroma in this setting by using genetically engineered mice with PDAC and specific depletion of myofibroblasts. Contrary to expectations, these mice actually had diminished overall survival. Notably, reduced survival was also observed in humans with PDAC and reduced numbers of myofibroblasts. Further experiments showed that genes associated with tumour immunity were suppressed in myofibroblast-depleted tumours.

In the second study, the researchers also used a mouse model of PDAC—this time using genetic deletion or pharmacologic blockade of Hedgehog (Hh) signalling to deplete stromal cells. This depletion was expected to result in impaired tumorigenesis, but surprisingly the opposite was observed. Tumours from these mice were more aggressive, leading to reduced survival compared with control PDAC mice (without loss of Hh signalling). These tumours also had undifferentiated histology, and had increased vascularity and proliferation. Treatment with an inhibitor of vascular endothelial growth factor receptor increased survival in mice with these undifferentiated tumours. "This study raises the possibility that a subset of patients with pancreatic cancer—those with poorly differentiated and well-vascularized tumours— might be amenable to antiangiogenic therapy," says author Ben Stanger.

The findings of these two studies could lead to a paradigm shift in treatment approaches for pancreatic cancer that target fibroblasts and other stromal elements. "This supportive tissue that's abundant in pancreatic cancer tumours is not a traitor as we thought but rather an ally that is fighting to the end," says Kalluri.

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Original articles Özdemir, B. C. *et al*. Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival. *Cancer Cell* doi:10.1016/j.ccr.2014.04.005 | Rhim, A. D. *et al.* Stromal elements act to restrain, rather than support, pancreatic ductal adenocarcinoma. *Cancer Cell* doi:10.1016/j.ccr.2014.04.021