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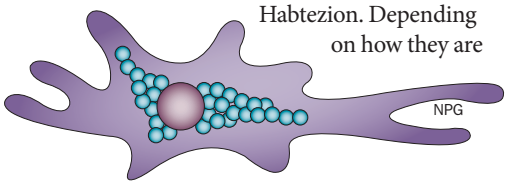
PANCREATITIS

# Alternatively activated macrophages mediate fibrosis

New findings confirm the contribution of alternatively activated macrophages (AAMs) to fibrosis in chronic pancreatitis.

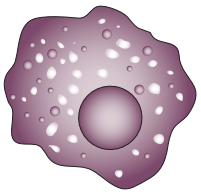
Inflammatory damage in chronic pancreatitis is irreversible and can lead to fibrosis and pancreatic cancer. "Unfortunately, there are no active therapies for either acute or chronic pancreatitis and no known agents that would alter the progression or natural course of the diseases," explains corresponding author, Aida Habtezion.

Activated pancreatic stellate cells (PSCs) have a key role in fibrogenesis in chronic pancreatitis and can be stimulated by toxic factors or immune cells. "Our previous work shows that macrophages are important in the pathogenesis of pancreatitis and we took advantage of macrophage plasticity to see if we can alter the behaviour of these cells and their interaction with PSCs," says Habtezion. Depending on how they are activated, macrophages produce a range of cytokines resulting in different functions and specializations.




To induce chronic pancreatitis, mice were treated with caerulein for 4 weeks. Higher levels of profibrotic and monocyte or macrophage-specific cytokines were evident in mice with chronic pancreatitis than in untreated controls. As expected, macrophages accumulated in the pancreas of treated animals, owing to increased proliferation of resident cells and monocyte recruitment from the bone marrow. The macrophages in mouse and human chronic pancreatitis tissue samples were found to be AAMs, expressing characteristic M2 genes, such as *MRC1*, *IL10*, *TGFB1* and *PDGFB*.

Isolated PSCs from mice and human patients with chronic pancreatitis secreted cytokines that promoted fibrosis (TGF-β) and AAMs (IL-4, IL-13). These PSCs were also found to actively polarize macrophages into AAMs in co-culture. Alternative activation, in turn, enabled the macrophages to potently activate PSCs, inducing a positive feedback loop that ultimately promoted fibrosis and pancreatic damage. When chronic pancreatitis was induced in mice with a myeloid-specific IL-4 receptor subunit α deletion, pancreatic fibrosis and fibrosis-associated gene expression was lower than in wild-type mice. The efficiency of a IL-4/IL-13-blocking peptide on mice with established chronic pancreatitis (2 weeks caerulein) was also assessed. Inhibitor treatment prevented alternative macrophage activation in mouse and human cells cultured *ex vivo* and limited pancreatic fibrosis in mice *in vivo*.



"Our study shows that [IL-4 receptor] blockade is effective even in already established experimental chronic pancreatitis and not necessary at the start or induction of the disease," notes Habtezion.

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