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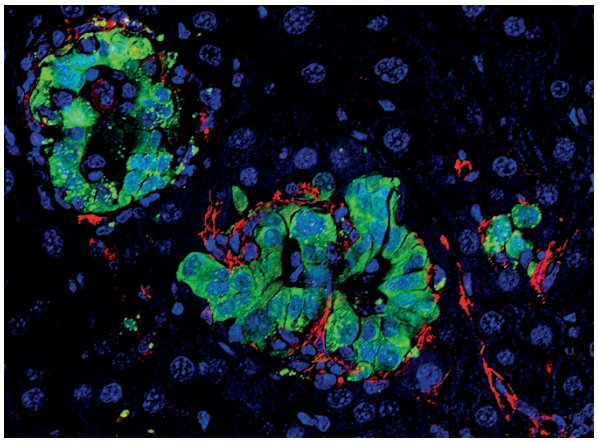
PANCREATIC CANCER

Infiltrating macrophages support liver metastasis



Granulin secreted by MAMs induces expression of periostin in myofibroblasts (red), promoting metastatic growth of cancer cells (green) in the liver. Nuclei are stained blue.

> “...granulin is required for accumulation of myofibroblasts at the metastatic site and growth of tumour cells”

New research published in *Nature Cell Biology* shows that recruitment of metastasis-associated macrophages (MAMs) is crucial for liver metastasis in pancreatic ductal adenocarcinoma (PDAC). Secretion of granulin by liver-infiltrating MAMs activates hepatic stellate cells (HSCs), which promote a tumorigenic fibrotic microenvironment.

PDAC is a highly lethal disease, in part due to aggressive metastatic spread to other organs, most commonly the liver. Research in the past decade has highlighted the role of non-cancer cells (stromal cells, fibroblasts and immune cells) in promoting PDAC tumorigenesis. Non-cancer cells, including stromal cells and macrophages, are also known to promote metastasis in other cancer types; however, the role of these cells in metastasis to the liver in PDAC has not been investigated before.

By analysing liver biopsy samples from patients with advanced metastatic PDAC, the researchers showed that metastatic tumour cells are surrounded by a stromal compartment, with abundant macrophages and myofibroblasts and extensive connective tissue deposition. In a mouse model of PDAC induced by intrasplenic implantation of cancer cells, a number of immune cell types were increased in tumour-bearing livers; of these cells, infiltrating macrophages were the predominant cell population. Furthermore, the authors found that metastasis-associated myofibroblasts, which only accumulate in established metastatic sites, originate primarily from HSCs.

After showing that MAMs were infiltrating macrophages derived from circulating monocytes, the researchers assessed liver metastasis in a mouse model of PDAC deficient in monocyte recruitment. Accordingly, metastatic sites in mice with impaired ability to recruit monocytes had a decreased number of MAMs, a finding accompanied by reduced frequency and size of metastatic lesions, and fewer tumour-associated activated myofibroblasts than control mice. Depletion of MAMs (using clodronate liposomes) led to fewer myofibroblasts at metastatic sites than untreated mice, and decreased the size of metastatic lesions.

“We then performed unbiased proteomic secretome analysis to identify factors secreted by macrophages that activate HSCs,” explains author Michael Schmid. Granulin, a secreted glycoprotein known to stimulate fibroblast migration, was identified as being highly expressed by MAMs. Importantly, activation of HSCs exposed to media conditioned by MAMs was dependent on the presence of granulin — media conditioned by MAMs deficient in granulin secretion did not activate HSCs.

Schmid and colleagues confirmed that granulin is highly expressed in the stroma of hepatic metastatic lesions in mice and in human samples. Next, using mice lacking granulin expression only in bone-marrow-derived cells (including macrophages and monocytes), the researchers showed that granulin is required for accumulation of myofibroblasts at the metastatic site and growth of tumour cells. Further secretome analysis of human fibroblasts stimulated with media conditioned by macrophages showed that periostin, an extracellular matrix component, was upregulated in activated cells. Periostin has previously been found to promote metastatic growth in other cancers; Schmid and colleagues found that neutralization of periostin abolished the tumorigenic effects of media conditioned by myofibroblasts on PDAC cancer cells *in vitro*. Notably, granulin was required for the induction of periostin expression in HSCs *in vitro* and in mouse models.

“In summary, we were able to demonstrate that granulin secretion by MAMs transdifferentiates resident HSCs into myofibroblasts that secrete periostin, resulting in a fibrotic microenvironment that sustains metastatic tumour growth,” concludes Schmid. “Thus, blockade of granulin functions might be of great benefit for patients with metastatic PDAC.”

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ORIGINAL ARTICLE Nielsen, S. R. *et al.* Macrophage-secreted granulin supports pancreatic cancer metastasis by inducing liver fibrosis. *Nat. Cell Biol.* http://dx.doi.org/10.1038/ncb3340 (2016)