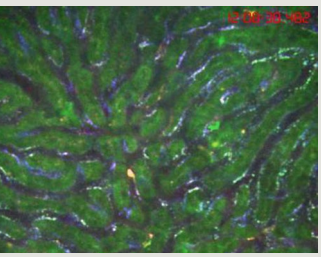
> Pharmacological ERK inhibition was found to phenocopy KRAS suppression

with concurrent treatment with an ERK MAPK inhibitor, inhibition of autophagy will be even more effective," explains Bryant. "Our current work is focused on improving either arm of the combination with more specific inhibitors of autophagy or by targeting pathways to make PDAC cells more reliant on autophagy."

In a similar study published alongside this work, Kinsey et al. examined combined inhibition of autophagy and MEK, which directly activates ERK. This approach resulted in anti-proliferative effects on PDAC cells in vitro and regression of patient-derived PDAC tumours in mice. Furthermore, treatment of a single patient with PDAC using this combination substantially reduced the tumour burden, highlighting the potential of this strategy for pancreatic cancer.

Iain Dickson

ORIGINAL ARTICLES Bryant, K. L. et al. Combination of ERK and autophagy inhibition as a treatment approach for pancreatic cancer. *Nat. Med.* https://doi.org/10.1038/s41591-019-0368-8 (2019) | Kinsey, C. G. et al. Protective autophagy elicited by RAF→MEK→ERK inhibition suggests a treatment strategy for RAS-driven cancers. *Nat. Med.* https://doi.org/10.1038/s41591-019-0367-9 (2019)



Intravital imaging showing sinusoidal accumulation of neutrophils (red), platelets (blue) and extracellular DNA (green) after partial inferior vena cava ligation. Image courtesy of T. Sehrawat, Mayo Clinic, USA.

> genetic disruption or pharmacological inhibition of NET formation decreased portal hypertension

Finally, the investigators explored the mechanisms by which mechanical stretch promotes prothrombotic LSEC responses using in vitro models. "We demonstrated that LSECs transduce mechanical forces through a unique molecular pathway that involves Notch and piezo-type mechanosensitive ion channels," explains Shah. "This signalling culminates in CXCL1 production." Notably, pIVCL mice with LSEC-specific *Notch1* knockout had reduced portal pressure compared with mice with intact LSEC *Notch1*, supporting the relevance of the in vitro findings. In the future, the team aim to build on their work to investigate CXLC1-related treatment targets in the context of cirrhosis and portal hypertension.

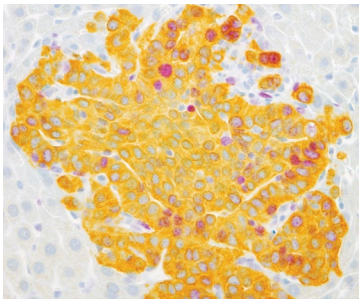
Hugh Thomas

ORIGINAL ARTICLE Hilscher, M. B. et al. Mechanical stretch increases expression of CXCL1 in liver sinusoidal endothelial cells to recruit neutrophils, generate sinusoidal microthombi, and promote portal hypertension. *Gastroenterology* https://doi.org/10.1053/j.gastro.2019.03.013 (2019)
FURTHER READING Gracia-Sancho, J. et al. Hepatic microcirculation and mechanisms of portal hypertension. *Nat. Rev. Gastroenterol. Hepatol.* **16**, 221–234 (2018)

PANCREATIC CANCER

IL-6 drives niche formation in pancreatic cancer liver metastasis

Pancreatic cancer promotes the formation of a pro-metastatic niche in the liver via secreted IL-6, reports a new study published in *Nature*.



Microscopy image showing a metastatic lesion in the liver. Image courtesy of J. Lee, University of Pennsylvania, USA

The liver is frequently affected by metastatic disease in pancreatic cancer. In addition to a rich blood supply and mechanical trapping of tumour cells, studies have indicated that the liver can form a pro-metastatic niche to support metastasis. However, the mechanisms underlying the formation of this niche have been poorly understood.

To investigate the role of the hepatic niche in pancreatic cancer metastasis, the Beatty Laboratory at the University of Pennsylvania, USA, and colleagues used mouse models to recapitulate human disease. "We developed a two-tumour model system in which mice had either precancerous lesions (KPC mouse model) or a primary pancreatic tumour in place prior to injection of pancreatic cancer cells into the blood stream," explains Gregory Beatty, senior author. "This model better reproduced biology that we detected in liver samples collected from patients with pancreatic cancer."

Livers from KPC mice with either pancreatic tumours or precancerous lesions had increased numbers of myeloid cells and more extensive fibrosis than livers from control mice, a finding consistent with other studies investigating the hepatic metastatic niche. The authors also showed that the hepatic metastatic burden was markedly higher in KPC mice than in control mice, indicating increased liver susceptibility to metastases in the presence of pancreatic tumours or precursor lesions.

Hepatic gene expression analysis revealed that genes involved in immune-related processes, including myeloid cell chemoattraction and the IL-6–JAK–STAT3 signalling pathway, were upregulated in KPC mice versus control mice. Activation of STAT3 protein was also increased in KPC mice, leading the investigators to examine the role of IL-6 and STAT3 signalling in metastatic niche formation. Using a number of methods, they found that IL-6, produced by non-cancer cells within pancreatic tumours, activates proinflammatory STAT3 signalling in hepatocytes. In turn, these hepatocytes release myeloid cell chemoattractant proteins (serum amyloid A1 and A2, together known as SAA), which recruit myeloid cells and increase fibrosis deposition by promoting hepatic stellate cell activation. Extending these findings to humans, patients with pancreatic cancer had high circulating SAA levels, which were correlated with poor clinical outcomes.

Notably, the researchers found similar results in a mouse model of colon cancer and in patients with colon, lung and pancreatic cancer, suggesting the mechanisms underpinning pro-metastatic niche formation in the liver are applicable to multiple cancer types.

"General inflammation induced by IL-6, even in the absence of cancer, was sufficient to establish a niche environment in the liver that was supportive of cancer cell spread," summarizes Beatty. "This finding implies that any inflammatory process involving IL-6 (including obesity and cardiovascular disease) might alter the liver and increase its susceptibility to cancer spread."

The findings reported by Beatty and colleagues hold promise for the development of approaches to prevent pro-metastatic niche formation. "This work is particularly relevant to preventing cancer recurrence and spread after surgery or in patients with localized disease that has not spread," Beatty concludes.

Hugh Thomas

ORIGINAL ARTICLE Lee, J. W. et al. Hepatocytes direct the formation of a pro-metastatic niche in the liver. *Nature* **567**, 249–252 (2019)