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PANCREATIC CANCER

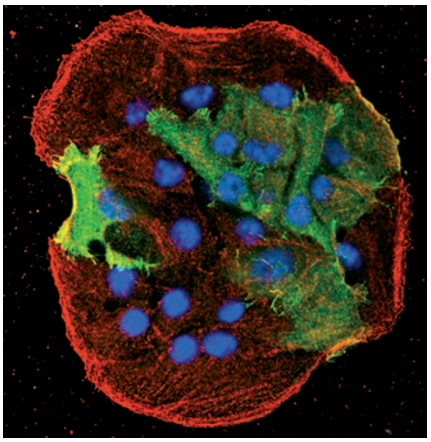
FASCINating insights into the metastatic nature of pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC)—the most common form of pancreatic cancer in humans—is highly invasive and metastatic and is associated with poor survival in patients. The actin-bundling protein fascin has previously been reported to be a biomarker of invasive and advanced PDAC, leading Professor Laura Machesky, Dr Ang Li and colleagues from the Beatson Institute for Cancer Research in Glasgow to investigate its potential role in the progression of pancreatic cancer.

"No treatments currently exist for preventing metastasis in patients with pancreatic cancer, so we sought to explore whether fascin was an interesting target for blocking PDAC metastasis," states Machesky. The team used a combination of *in vitro* and *in vivo* studies to demonstrate that fascin contributes to the metastatic nature of PDAC, and they also revealed underlying mechanisms that could explain how fascin promotes PDAC progression.

As an initial step, the effect of fascin deficiency was determined in KPC mice, a well-documented mouse model of pancreatic cancer. KPC mice have some of the most commonly mutated oncogenes and tumour suppressor genes found in human PDAC. Pancreatic cancer in these mice also progresses from pancreatic intraepithelial neoplasia (PanIN) to PDAC and then metastasis, in a manner similar to the stages observed in human disease.

"By studying KPC mice deficient in fascin [termed FKPC mice], we were able to determine how loss of fascin affects tumour spread from a primary pancreatic tumour that was genetically encoded," explains Machesky. FKPC mice had increased survival times (from 132 days to 189 days, 43%), delayed onset of PDAC and reduced tumour burden when compared with control (KPC) mice. An unexpected finding for the authors of this study is that FKPC mice had similar



PDAC cell line with staining of fascin (green), filamentous actin (red) and DNA (blue). Image courtesy of A. Li.

levels of PDAC invasion into the bowel and peritoneum as KPC mice. However, as expected, the level of tumour metastasis (to the liver, among other organs) was lower in FKPC mice than in control mice.

How could fascin promote pancreatic cancer metastasis? Fascin expression in KPC mice varied according to the stage of pancreatic cancer. Cells isolated from early stage PanINs were negative for fascin, but expression increased to 6% of cells taken from mice with PanIN stage 3 and to 100% in PDAC cells. Fascin was also shown to be expressed *in vitro* in PDAC cell lines and was found to be a direct target of the neural crest transcription factor slug, which regulates the epithelial–mesenchymal transition during tumour formation and is believed to be a key driver of tumour metastasis.

Fascin localization was concentrated in filopodia (finger-like protrusions that have a role in cell invasion) in both PDAC cell lines and in cells isolated from mice. Fascin expression was essential for filopodia assembly and turnover, and it promoted the intercalation of filopodia into mesothelial cell layers, driving PDAC cell transmigration.

The researchers then went on to correlate fascin expression levels with patient outcome. The majority of 122 resected PDAC samples from patients expressed fascin. Moreover, high fascin levels were associated with poor patient outcome, vascular invasion and a reduced time to recurrence.

"One of our most significant findings is that loss of fascin seems to delay the onset of PDAC and reduce early tumour formation," Machesky says. This point is echoed by Professor Anirban Maitra, an expert in the field from the MD Anderson Cancer Centre (USA) who was not involved in this study. "The role of fascin in this 'early' disease might be related to recent observations in mouse models of pancreatic cancer that metastatic programming (including the onset of epithelial–mesenchymal transition) occurs far earlier than previously believed," he comments.

"Although loss of fascin did not affect tumour invasion in mice, we saw a dramatic reduction in metastasis to the liver and diaphragm, indicating that fascin is potentially an interesting target against PDAC metastatic dissemination," Machesky concludes. Indeed, the researchers have now formed a drug discovery collaboration with colleagues at the Beatson Institute to try to develop fascin inhibitors as antimetastatic agents.

"As most patients with pancreatic cancer present with advanced disease, it might preclude the possibility of targeting fascin for its purported role in early disease," Maitra cautions. "But, as the authors have elegantly shown, there is continued requirement of fascin for metastatic colonization, providing a window of therapeutic opportunity," he adds.

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