Nature Reviews Cancer | AOP, published online 9 February 2012; doi:10.1038/nrc3229

METASTASIS

Navigating uncharted territory

> Two papers … now challenge us to think more carefully about how metastasis occurs in pancreatic cancer

Pancreatic cancer is often diagnosed at an advanced stage, and previous genetic studies have indicated that metastasis occurs late in pancreatic tumour evolution. However, other data support the model that metastasis is an early event. Two papers published in *Cell* now challenge us to think more carefully about how metastasis occurs in pancreatic cancer, and the implications this may have for the treatment, prevention or early detection of this deadly disease.

Rhim *et al.* used the expression of yellow fluorescent protein (a *Rosa*^{YFP} allele) to label only pancreatic epithelial cells in a Cre–*lox*-based mouse model of pancreatic ductal adenocarcinoma (PDAC) with *Kras* and *Trp53* mutations. Importantly, control experiments indicated that only the pancreatic epithelium was labelled with YFP. The authors first investigated whether these labelled epithelial cells underwent an epithelial-to-mesenchymal transition (EMT) *in vivo*, as the relevance of EMT to metastasis is unclear. Using YFP expression combined with expression of mesenchymal markers and/or lack of expression of E-cadherin, they found that 42% of YFP$^+$ cells within tumours in these mice had undergone EMT. Looking at an earlier stage of tumorigenesis, premalignant pancreatic intraepithelial neoplasia (PanIN), they saw EMT in a small proportion of the PanIN2 and PanIN3 lesions, but not in earlier stage PanIN1. In addition, some YFP$^+$ cells in mice with PanIN had crossed the basement membrane and had dissociated from the epithelium ('delaminated' cells). Circulating YFP$^+$ cells were observed in both mice with PDAC and in mice with PanIN. Furthermore, most PDAC mice had YFP$^+$ liver micrometastases, and four of 11 PanIN mice had YFP$^+$ cells in the liver (but no micrometastases), indicating that these cells can disseminate and seed the liver prior to PDAC formation. However, it is not known whether these cells can eventually form metastases. Additional experiments demonstrated that the circulating YFP$^+$ cells in both PDAC and PanIN mice are primarily mesenchymal, and have features associated with stem cell-like activity. These data may be relevant to human tumours, as delaminated cells were observed in sections from human PanINs.

GETTY

To improve our understanding of the formation of clinically relevant metastases, Haeno *et al.* developed a mathematical model describing the growth and dissemination of pancreatic cancer, based on patient data. Autopsy data from one cohort of 101 patients provided extensive information on metastatic burden and tumour size. Based on these data, the authors estimated the mutation rate and metastasis rate, and established that an exponential growth model best represented the growth of primary and metastatic tumours. They then used this information to develop a mathematical model that could indicate the probability that metastases exist within a patient at a given time point. This model predicted that, at the time of diagnosis, even when a primary tumour is small, all patients are expected to harbour cells that are capable of metastasis (but not necessarily metastatic disease). The autopsy patient data fit the predictions of this model accurately, as did data from an independent cohort of patients with pancreatic cancer. Interestingly, the model also predicts that reducing the growth rate of both primary and metastatic lesions will be more effective than surgical resection of the primary tumour in extending patient survival, supporting a role for neoadjuvant chemotherapy in pancreatic cancer.

These papers have provided interesting insights and raised new questions about the nature of pancreatic cancer dissemination and metastasis.

Sarah Seton-Rogers

ORIGINAL RESEARCH PAPERS Rhim, A. D. *et al.* EMT and dissemination precede pancreatic tumor formation. *Cell* **148**, 349–361 (2012) | Haeno, H. *et al.* Computational modeling of pancreatic cancer reveals kinetics of metastasis suggesting optimum treatment strategies. *Cell* **148**, 362–375 (2012)