IN THE NEWS

'Virtual' search finds polyps

Virtual colonoscopy — computed tomography (CT) imaging to build a three-dimensional representation of the bowel — can detect colon cancer as effectively as conventional methods, according to a study in *The New England Journal of Medicine* (4 December 2003). The procedure requires insertion of a small rectal catheter followed by a CT scan of the abdomen, and is cheaper, less invasive and less risky than conventional colonoscopy.

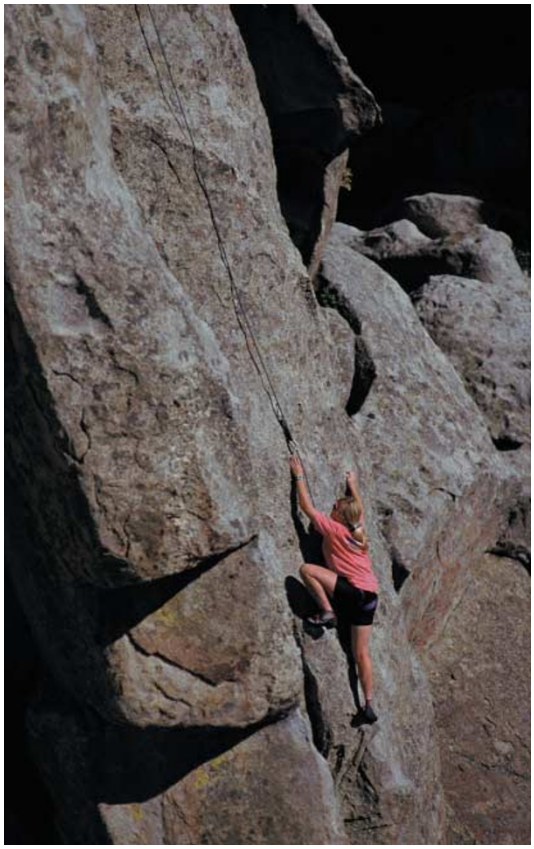
A team led by Perry Pickhardt of the University of Wisconsin screened 1,233 people aged 50–79 using the virtual method, then compared the results with conventional colonoscopy carried out on the same day. Both procedures detected over 90% of polyps that are at least 8 mm in diameter, but one of the two malignant growths found by the virtual technique was missed by the conventional method.

Chief Gastroenterologist at Beth Israel Medical School, Thomas Lamont, claims "It puts virtual colonoscopy right up there with the gold standard, optical colonoscopy" (*The New York Times*, 2 December 2003). Regular colonoscopy for the over 50s virtually eliminates the risk of colon cancer, but less than half of this population is screened. "If our methods are used, this will hopefully result in more widespread screening" suggests Pickhardt (*Associated Press*, 2 December 2003). But, conventional colonoscopy is still required to remove suspect polyps. "Since the patient has to go through the same preparation, which is the hardest part, they might as well do the conventional one" said Herman Kattlove, Medical Editor of the American Cancer Society (*Associated Press*, 2 December 2003).

Emma Croager

MOUSE MODELS

Pancreatic cancer: making progress



Pancreatic tumours are among the most lethal of human cancers and cause ~30,000 deaths each year in the United States alone. New progress in understanding the genetic and cellular origins of this type of cancer has now been made in two studies using transgenic mouse models. In one paper, Ronald DePinho, Nabeel Bardeesy and colleagues describe cooperative roles for lesions at the *Kras* and *Cdkn2a* loci in the development of pancreatic ductal adenocarcinoma, and in another, work from Harold Varmus's laboratory indicates that different oncogenic mutations give rise to distinct types of pancreatic tumour.

Although several genetic lesions are associated with pancreatic ductal adenocarcinoma, their contributions to disease progression are poorly understood. Activating mutations in *KRAS* are found in most cases of this type of cancer, as are loss-of-function mutations in *CDKN2A* — which encodes the tumour suppressors INK4A and ARF. To investigate the relative roles of these genes in tumour progression, DePinho, Bardeesy and colleagues generated mice that combined activation of an oncogenic *Kras* transgene and deletion of *Cdkn2a* specifically in the pancreas. All of the animals developed invasive tumours, which were very similar in terms of their histology and metastatic behaviour to human pancreatic ductal adenocarcinoma. In mice that carried only the activated mutant *Kras* transgene — with an intact *Cdkn2a* locus — pre-malignant lesions developed, but did not become invasive. No pre-malignant lesions or invasive tumours were seen in mice with the *Cdkn2a* deletion only. So, neither *Kras* nor *Cdkn2a* mutations are sufficient to give rise to pancreatic ductal adenocarcinoma. Instead, it seems that *Kras* activation is required to initiate tumorigenesis, but additional homozygous mutation of *Cdkn2a* is essential for progression to advanced malignancy.

But are mutations in *Kras* and *Cdkn2a* sufficient for full progression to malignancy? As invasive tumours developed rapidly without the known disruption of other loci, activated Kras in combination with loss of function of Ink4a and/or Arf might be sufficient for the development of metastatic tumours. Alternatively, other mutations could be required, but might occur at such a high frequency in this model that they do not limit the rate of progression to invasiveness. This possibility will need to be tested by genomic analysis of the tumours in these mice.

In a second study by Harold Varmus and colleagues, another mouse model was used to investigate how different types of pancreatic tumour arise. The pancreas contains acinar, ductal and endocrine cells, and different tumours develop that resemble each of these cell types. Whether these tumours arise from different cells or result from distinct effects of different genetic lesions in the same cells is unknown.

Varmus and co-workers used a retrovirus-based method to express oncogenes in the developing pancreas in a *Cdkn2a*-null background. Expression of the polyoma virus middle T antigen gene — which stimulates the Ras and PI3K pathways that are activated in pancreatic cancers — led to the formation of ductal and acinar tumours. By contrast, expression of the human c-*MYC* oncogene gave rise exclusively to endocrine tumours, indicating that specific oncogenes induce the formation of different types of pancreatic tumour.

Whether different oncogenes target distinct groups of cells to produce the various pancreatic tumour types or exert their effects in the same set of cells, which are then guided towards particular fates, remains to be determined.

Louisa Flintoft

References and links

ORIGINAL RESEARCH PAPERS Aguirre, A. J. *et al*. Activated $Kras^{G12D}$ and *Ink4a/Arf* deficiency cooperate to produce metastatic pancreatic ductal adenocarcinoma in the mouse. *Genes Dev.* 15 Dec 2003 (doi: 10.1101/gad.1158703) | Lewis, B. C., Klimstra, D. S. & Varmus, H. E. The c-myc and PyMT oncogenes induce different tumor types in a somatic mouse model for pancreatic cancer. *Genes Dev.* 15 Dec 2003 (doi: 10.1101/gad.1140403)

FURTHER READING Bardeesy, N. & DePinho, R. A. Pancreatic cancer biology and genetics. *Nature Rev. Cancer* **2**, 897–909 (2002)