IN THE NEWS

Through the keyhole

A large-scale study has shown that laparoscopic or 'keyhole' surgery for colon cancer is as safe and effective as conventional surgery, dispelling fears about a link with increased tumour recurrence.

Laparoscopic removal of colon tumours is less invasive than open surgery, requiring much smaller incisions, but its use has been held back by safety concerns. The first results of a randomized, controlled study comparing the two types of surgery now show that these fears are unfounded (*New England Journal of Medicine*, 13 May 2004).

The study reveals almost identical survival rates for both methods and shows that levels of recurrence are no higher in patients who have undergone keyhole surgery. "These findings will have a substantial and far-reaching effect and should remove some final obstacles to the use of laparoscopic colectomy", commented surgeons Theodore Pappas and Danny Jacobs in an accompanying editorial.

There were also important advantages for patients who had keyhole surgery — they needed shorter stays in hospital and less pain medication. "Now we can say it's safe, it's effective and it's beneficial for patients with colon cancer", said Heidi Nelson, the lead researcher in the team that carried out the study (*The New York Times*, 13 May 2004).

However, it could be some time before laparoscopic surgery is carried out routinely on patients with colon cancer: "…keyhole surgery needs well-trained surgeons", commented John Toy, Medical Director of Cancer Research UK (http://news.bbc.co.uk, 14 May 2004), and relatively few surgeons are trained to carry out the procedure. "The world of colorectal surgery will have to adapt," say Pappas and Jacobs.

Louisa Flintoft

cell lines resulted in 2–3-fold increased stimulation of the receptor by EGF and that activation of the mutant receptor lasted up to 12 times longer when compared with the wild-type receptor. The mutant EGFR proteins were also about 10 times more sensitive to inhibition by gefitinib than wild-type EGFR. Paez *et al.* investigated a cell line derived from a malignant pleural effusion from a Caucasian female non-smoker with lung adenocarcinoma — the cells had the L858R mutation in EGFR and were 50 times more sensitive to gefitinib than other adenocarcinoma cell lines.

The authors hypothesize that the mutations in EGFR stabilize the interaction between the drug and the kinase, thereby increasing the inhibitory effect of gefitinib. If these data are confirmed in prospective clinical trials, they will set a standard for approaches to the evaluation and use of targeted therapy for solid tumours.

Ezzie Hutchinson

References and links

ORIGINAL RESEARCH PAPERS Lynch, T. J. *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N. Engl. J. Med.* 29 April 2004 (doi:10.1056/NEJMoa040938) | Paez, J. G. *et al*. *EGFR* mutations in lung cancer: correlation with clinical response to gefitinib therapy *Science* 29 April 2004 (doi:10.1126/science.1099314)

SCREENING

Fishing for clues

A large-scale insertional mutagenesis screen in zebrafish has revealed the ability of ribosomal proteins to contribute to tumorigenesis.

Nancy Hopkins and colleagues have generated approximately 500 lines of zebrafish that are heterozygous for a recessive lethal mutation. As many tumour-suppressor genes cause recessive lethality, they searched for lines of fish with obvious tumours or short survival times, and identified 12 tumour-prone lines. These zebrafish mostly developed malignant peripheral-nerve-sheath tumours (81%), as well as some other tumour types.

One line carried a heterozygous mutation in a zebrafish paralogue of the human and mouse tumour-suppressor gene neurofibromatosis 2 (NF2) — so establishing the validity of this approach for identifying cancer genes. Surprisingly, all the other lines carried a heterozygous mutation in genes encoding different ribosomal proteins. All of these mutations reduced or eliminated expression of the genes, indicating that ribosomal proteins do not function as activated oncogene products. Loss of heterozygosity was not observed, so the authors conclude that a simple reduction in the amount of ribosomal protein is sufficient to lead to tumour formation.

How does loss of ribosomal proteins contribute to tumorigenesis? In each line, the authors observed a decrease in the overall amount of ribosomal RNA produced — primarily in the ribosomal subunit with which the mutant gene product was associated. A reduction in the level of protein synthesis could reduce the levels of a critical tumour suppressor, or signal the cell to produce more of the components required for ribosome biogenesis, leading to cell proliferation. Alternatively, a reduction in the number of ribosomes might alter the specificity of mRNAs recruited to the ribosome, changing the translation rate of mRNAs that encode proteins that promote proliferation. These proteins might also have undiscovered functions outside of their role at the ribosome, although it seems unlikely that there could be an important yet unknown function of so many ribosomal proteins.

It is only the loss of specific ribosomal proteins that causes cancer — loss of others had no effect. Hopkins and colleagues haven't identified any particular characteristic of those that were associated with cancer — the cancer-causing gene products could belong to either the small or large ribosomal subunit.

Further studies are needed to determine the reason that this screen resulted in such a high percentage of malignant peripheral-nerve-sheath tumours and why it led to disruption of ribosomal protein genes in particular. But it offers some interesting new genes to investigate in human tumours, which might also have alterations in ribosomal protein function.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Amsterdam, A. *et al*. Many ribosomal protein genes are cancer genes in zebrafish. *PLoS Biol.* **2**, 690–698 (2004)

FURTHER READING Stern, H. M. & Zon, L. I. Cancer genetics and drug discovery in the zebrafish. *Nature Rev. Cancer*. **3**, 533–539 (2003)

WEB SITE

Nancy Hopkins' lab: http://web.mit.edu/biology/www/facultyareas/facresearch/hopkins.shtml