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News

'Normal' genes key to cancer growth

Shutting off genes stops cancer cells from growing but leaves healthy cells unharmed.

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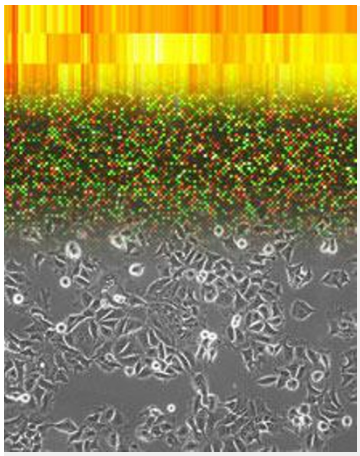
Geneticists have identified genes that are normally present and that seem to be key to the growth and survival of specific cancers. The finding, from a 'functional-genomics' screen of human cells, could offer new drug targets for blitzing tumours.



Gene signatures (top) result from multi-gene analysis (middle) of cancer-cell survival (bottom).

SCIENCE

In an alternative approach to the traditional search for oncogenes (rogue genes that can turn normal cells into tumours), two teams of US scientists publish support this week for what they call the "non-oncogene addiction" idea: that a tumour relies heavily on certain normal cell pathways, and that drugs disabling gene products in those pathways could be deadly to cancer. The teams, led by Stephen Elledge of Brigham and Women's Hospital in Boston, Massachusetts, and Greg Hannon of Cold Spring Harbor Laboratory in New York, designed a method to knock down thousands of genes relatively cheaply and quickly.

The method uses 'short hairpin RNAs' (shRNAs) — pieces of RNA that can be designed to target and shut off specific genes. In two papers[1,2], the teams describe how they introduced thousands of shRNAs that target normal genes into colon cancer cells, breast cancer cells and healthy breast cells. Dozens of the shRNAs slowed or stopped the cancer cells from growing, but didn't impair the healthy cells, which could point the way to new cancer drug targets.

"It will take time and money to sort out which of these are the best drug targets, but the important thing is that we are finding them," Elledge says.

'Welcome advance'

Oncologists say that drugs against oncogene products, such as Novartis' Gleevec (imatinib) and Genentech's Tarceva (erlotinib), have been a welcome advance for patients with cancer. But because patients often develop resistance to the drugs, they are not cures, says Gary Schwartz of New York's Memorial Sloan-Kettering Cancer Center. "Everyone's looking for the next Gleevec, but even though these targeted drugs have been exciting, they have not had the overwhelming impact we would have hoped for," says Schwartz, who is trying to find funding for a clinical trial of a drug that inhibits a normal cell-cycle pathway[3]. Early clinical trials of the drug indicate that it may operate best in a 'therapeutic window' in which it is more harmful to cancer cells than to healthy cells, Schwartz says.

Elledge and Hannon say that their work will complement two large projects aiming to spur development of more drugs like Gleevec and Tarceva, which target mutations involved in certain blood and lung cancers. Both projects involve sequencing the genomes of cancer cells to find more oncogenes and help scientists understand the biology of cancer. One — the The Cancer Genome Atlas — began in December 2005, and is expected to cost $1.35 billion over 9 years. The other is led by scientists at the Wellcome Trust Sanger Institute in Cambridge, UK.

The team has long contended that the sequencing studies have a low "bang for the buck" — they are quite costly and will require detailed follow-up studies to sort out the mutations that drive cancers from those that are merely along for the ride. Their work is, by contrast, cheap and easy enough to be done in a single laboratory. And they that say their "functional" approach, which looks at the behaviour of cancer cells in response to certain triggers, might be a quicker path to new drugs.

> **"The sequencing becomes the easy part — the longer road is going to be to figure out what it all means in functional studies."**

Elledge and Hannon have found growing support for their argument, even among scientists using the sequencing approach. Bert Vogelstein, co-director of the Ludwig Center at Johns Hopkins School of Medicine in Baltimore, Maryland, says that his own studies highlight the need for the cancer atlas to fund some functional-genomics work. "What's clear now that wasn't clear at the beginning of The Cancer Genome Atlas is the complexity and heterogeneity of the mutational signatures that are going to be found in most cancers," says Vogelstein, who demonstrated such complexity in a 2006 study on breast and colorectal cancers[4].

"The sequencing becomes the easy part — the harder and longer road is going to be to figure out what it all means in functional studies," Vogelstein says. "I believe some well-thought-out combination of those two approaches is likely to be the best way to progress."

References

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