IN THE NEWS

Collaborative effort

A newly developed partnership between five pharmaceutical companies and the National Cancer Institute (NCI) will provide US \$6 million of funding to increase enrollment in early-phase clinical trials (<http://www3.cancer.gov/cancercenters/announcements/PA-03-501.pdf>).

In this unique public-private collaboration, the National Institutes of Health (NIH), along with the pharmaceutical companies, will provide selected cancer centres with funding to design and implement new approaches to increase patient participation in Phase I and Phase II cancer trials. NCI-funded cancer centres can apply for up to US \$600,000 of funding per year for two years. Half of the funding will be provided by the NCI and half will be provided by the industrial partners. The NCI expects to make 5–8 awards.

The funds are to be used by the cancer centres to develop new approaches for overcoming barriers to enrolling patients in early-phase trials. Some of these obstacles include inadequate understanding of the importance of clinical trials by the public and health-care professionals, inadequate compensation for participation, increasing regulatory requirements and over-burdened institutional review boards. Public wariness to clinical research, geographical barriers and inadequate peer recognition of physicians that conduct early-phase trials also prevent the enrollment of cancer patients.

The NCI plans to use what it learns from this pilot study to develop models that can be disseminated to other cancer centres and research institutions. The five pharmaceutical partners that will provide funding are Aventis, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline and Novartis.

Kristine Novak

TUMORIGENESIS

Hang on tight!

Helicobacter pylori infects the gastric mucosa of more than half of all people worldwide, and infection with these bacteria is an early risk factor for gastric cancer. Both *H. pylori* and the host inflammatory response that it elicits are believed to contribute to tumorigenesis, but this interaction is not well understood. Ironically, according to Thomas Borén and colleagues, this antibacterial inflammatory response promotes gastric-cell synthesis of sialylated glycoconjugates, which the bacteria exploit for adherence to the surface epithelium.

In *Science*, Borén's group reported that epithelial cells of inflamed gastric mucosa have sialylated glycosphingolipids (GSLs) on their surface, and they isolated a repetitive sialyl-di-Lewis x GSL (sLex/a) from human adenocarcinoma cells. The authors showed that *H. pylori* expresses an adhesin protein called sialic-acid-binding adhesin (SabA), which binds to sLex/a antigens and allows the bacteria to cling to the surface of the

GENOMIC INSTABILITY

Chromosome crisis

Crisis ensues when telomeres become critically short — the chromosome ends fuse with other chromosomes, which sets the stage for chromosomal breakage at cell division. These double-strand breaks provide a site for amplifications and deletions in the genome, which can result in tumorigenesis. Mice have much longer telomeres than humans and do not normally undergo significant telomere shortening — which occurs in premalignant cells and ageing tissues in humans — and crisis. However, engineered mice that do not possess *mTerc* — the RNA subunit of telomerase — display more gross chromosomal aberrations and have a shift in tumour spectrum to one that resembles that of aged humans. So which genes are affected by these chromosomal rearrangements, and are homologous genes affected in humans?

Rónán O'Hagan and colleagues, reporting in *Cancer Cell*, used array-comparative genomic hybridization (array-CGH) to investigate the mechanism by which loss of telomerase promotes genomic instability. To perform the analysis, arrays of bacterial artificial chromosomes (BACs) that spanned the mouse genomes were differentially hybridized with normal and tumour-cell DNA. Tumours from late-generation telomerase-deficient mice (*mTerc*^{-/-}, *Trp53*^{+/-}) showed alterations in 20.5% of the arrayed BACs, compared with only 2.5% from early-generation telomerase-deficient mice. A direct comparison between the amount of genomic instability in specific tumour types was difficult because of the different tumour spectrums of the early- and late-generation mice; however, an examination of osteosarcomas, lymphomas and breast carcinomas revealed that

late-generation mice have more chromosomal alterations than early-generation mice. So, this increase in genomic instability is independent of tumour type in those tumours that the mice have in common.

So where in the mouse genome do these alterations occur? Thirty-two alterations were recurrent — identified in more than 25% of the tumours examined — and the most common of these, which was observed in 8 out of 15 tumours, was an amplification of distal chromosome 6. A more careful analysis revealed that the minimal amplified region contained six genes — only one of which, *Kras*, is known to be involved in tumorigenesis. Although amplification of this region has been observed in viral-oncogene-induced skin tumours from late-generation telomerase-deficient mice, it has not been found in late-generation *mTerc*^{-/-} breast cancers that overexpress the *Wnt* oncogene, perhaps because *Wnt* expression can bypass the requirement for an activated *Kras*.

gastric cell. Interestingly, sLex/a was previously identified as a tumour antigen and a marker of gastric dysplasia. Boren's group showed that *H. pylori* infection causes formation of sLex/a antigens on the surface of human and monkey gastric epithelial cells.

SabA is not the only binding molecule that *H. pylori* possesses. Borén and colleagues previously showed that another bacterial adhesin protein, BabA, promotes attachment to the Lewis B (Leb) molecule on the gastric-cell surface. But bacteria could still adhere to these cells after the *babA* gene was deleted, so the sLex–SabA interaction is likely to be an important component of tumorigenesis.

So, what are the advantages of these adhesin proteins? They allow *H. pylori* strains to bind to gastric epithelial cells and they also protect the bacteria from being shed into the gastric lumen. The ability of these bacteria to cling tightly to gastric mucosal cells also ensures their access to the nourishing exudate from

gastric epithelium that is damaged by the infection. Their persistence in the gastric mucosa causes the host inflammatory response to be maintained.

This study not only sheds new light on the mechanism that allows *H. pylori* to take advantage of the host inflammatory response, but also opens the possibility of more effective treatment for *H. pylori* infection. These bacteria have developed increasing resistance to antibiotics, so the BabA and SabA proteins might be useful components of a gastric cancer vaccine.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Mahdavi, J. *et al.* *Helicobacter pylori* SabA adhesin in persistent infection and chronic inflammation. *Science* **297**, 573–578 (2002)

FURTHER READING Peek, R. M. & Blaser, M. *Helicobacter pylori* and gastrointestinal tract adenocarcinomas. *Nature Rev. Cancer* **2**, 28–37 (2002)

WEB SITES

An animated movie of *H. pylori* adherence: http://www.eurekalert.org/pub_releases/science/2002-07/mahdavi-7-26-02-public.html
Thomas Boren's web site: http://www.odont.umu.se/forskning/Oboren_proj_eng.html

The other recurrent alterations were mapped onto the human genome, and literature and database searches revealed that many of the homologous regions were also altered in human carcinomas. This type of analysis could therefore facilitate the identification of new genes that are involved in human cancer.

So, it seems that telomere dysfunction can drive tumorigenesis in mice, as it is thought to in aged humans. Among the remaining questions are the frequency with which this type of genomic instability causes tumour formation, the genes that are involved and how this determines the tumour types that develop.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER O'Hagan, R. C. *et al.* Telomere dysfunction provokes regional amplification and deletion in cancer genomes. *Cancer Cell* **2**, 149–155 (2002)

FURTHER READING Artandi, S. E. *et al.* Telomere dysfunction promotes non-reciprocal translocations and epithelial cancers in mice. *Nature* **406**, 641–645 (2000) | Maser, R. E. & DePinho, R. A. Connecting chromosomes, crisis, and cancer. *Science* **297**, 565–569 (2002)

WEB SITE

Ron DePinho's lab: <http://www.hms.harvard.edu/dms/bbs/fac/depinho.html>

IN BRIEF

GLIOBLASTOMA

Blockage of Ca^{2+} -permeable AMPA receptors suppresses migration and induces apoptosis in human glioblastoma cells.

Ishiyuchi, S. *et al.* *Nature Med.* 12 Aug 2002 (doi:10.1038/nm746)

Glioblastoma multiforme is highly invasive and difficult to treat. Glioblastoma cells express Ca^{2+} -permeable AMPA-type glutamate receptors that are involved in the migration response. Their overexpression resulted in migration and proliferation, and their conversion to Ca^{2+} -impermeable receptors inhibited cell migration and induced apoptosis. So, inhibition of these receptors might prevent glioblastoma invasion.

CELL MIGRATION

Src-induced de-regulation of E-cadherin in colon cancer cells requires integrin signalling.

Avizienyte, E. *et al.* *Nature Cell Biol.* **4**, 632–638 (2002)

Src activity is raised in colon cancer, but what is its effect? Increased Src activity results in the redistribution of components of adherens junctions to integrin–adhesion complexes in the presence of high calcium levels. E-cadherin remains internalized, so cannot assemble the correct intercellular contacts. A Src mutant that lacks the kinase domain does not deregulate E-cadherin. So, expression of catalytically active Src might facilitate cancer-cell migration.

EPIDEMIOLOGY

Risk of cancer in patients with human pituitary growth hormone in the UK, 1959–85: a cohort study.

Swerdlow, A. J. *et al.* *Lancet* **360**, 273–277 (2002)

Growth hormone raises serum concentrations of insulin-like growth factor 1 (IGF-1), and raised levels of growth hormone and IGF-1 might be associated with an increased risk of certain solid cancers. Follow-up of nearly 2,000 patients who were treated during childhood with human pituitary growth hormone showed a significant increase in the risk of developing colorectal cancer and Hodgkin's disease. This was based on very small numbers of cancer cases, but the findings are nevertheless of concern and warrant further investigation.

THERAPEUTICS

Inhibition of glioma growth by tumor-specific activation of double-stranded RNA-dependent protein kinase PKR.

Shir, A. & Levitzki, A. *Nature Biotechnol.* 19 Aug 2002 (doi:10.1038/nbt730)

A new antisense RNA strategy selectively targets tumour cells. Antisense RNAs that are complementary to sequences that flank a deletion or translocation bind the mutant RNAs to produce a double-stranded molecule. These molecules activate a double-stranded RNA-dependent protein kinase (PKR), which signals cells to undergo apoptosis. A lentiviral vector expressing a 39-nucleotide antisense RNA that is complementary to the flanking regions of an epidermal-growth-factor receptor (*EGFR*) gene deletion was shown to activate PKR, causing glioblastoma cells to undergo apoptosis.