News in brief

Cancer Targets and Mechanisms

Targeting TRP2

Tyrosine-related protein-2 (TRP2), an immunogenic antigen in melanoma, has now been detected in highly aggressive brain tumours known as gliomas, and could be a target for monitoring or developing immunotherapeutic strategies.

Immunotherapy techniques have been used in clinical trials for several years to battle glioma. A dendritic cell (DC) vaccine is created when foreign proteins extracted from the tumour are introduced to DCs taken from the patient's blood. The resulting DCs, when re-injected into the patient, recognize and destroy any lingering malignant tumour cells. TRP2 is also seen as foreign by the immune system and therefore appears to be a target for anti-tumour immunotherapy [1].

A new study, by researchers at Cedars-Sinai's Maxine Dunitz Neurosurgical Institute (http://www.leadingthequest.com/mdnsi/home.asp) and the National Cancer Institute (http://www.nci.nih.gov/), found that TRP2 could be a potential target in primary glioma [1].

TRP2 has proved to be an excellent target for immunotherapies in mouse and human studies of melanoma. The new study found that the TRP2 antigen is also expressed at significant levels in glioma cells and a strong immune response can be triggered against it. Certain cytotoxic T lymphocytes (CTLs) recognize TRP2 as a target when it is expressed at significant levels. The degree of recognition correlated with the level of TRP2 expression in the genetic material, which is important because TRP2 is expressed at low levels in normal brain tissue.

Therefore, the identification of TRP2 as a brain tumour-associated antigen appears to offer not only a new target for immunotherapy but also a way to monitor the related immune response. Keith Black, an author of the study, comments; '… the immune system appears to have the potential to destroy glioma cells and contribute to longer periods of patient survival…' He added, 'Therefore we are always looking for new ways to target and boost the immune response'.

1 Liu, G. *et al.* (2003) Molecular and functional analysis of tyrosinase-related protein (TRP)-2 as a cytotoxic T lymphocyte target in patients with malignant glioma. *J. Immunother.* 26, 301–312

BRCA2 linked to childhood brain cancer

New results indicate that mutations in BRCA2, which are best known for increasing susceptibility to breast cancer, can also lead to childhood brain tumours [2]. These findings provide important information on the origin of such brain tumours and have implications for prospective parents who carry BRCA2 mutations.

The link between BRCA2 and childhood brain cancer was made by Kenneth Offit, of the Memorial Sloan-Kettering Cancer Center (http://www.mskcc.org/mskcc/html/44.cfm), and colleagues. The team made use of an international registry, based at the Rockefeller University (http://www.rockefeller.edu/), of those with Fanconi anaemia, a rare genetic disorder characterized by bone marrow failure, congenital malformation and cancer susceptibility. In all four families studied, Offit and colleagues found that children who had both Fanconi anaemia and brain tumours had inherited a mutant copy of BRCA2 from each parent.

Although BRCA2 mutations have already been implicated in some cases of Fanconi anaemia, Offit points out; 'these findings are the first to establish childhood brain cancers, predominantly medulloblastoma,

Viral Targets and Mechanisms

A viral trigger for multiple sclerosis

A common debate among researchers is whether or not there is a link between virus infection and multiple sclerosis (MS). Many believe that an apparently harmless virus, harboured perhaps from childhood, could be the crucial trigger that causes development of MS. An animal model has now been produced that can test this theory.

Claude P. Genain and his colleagues at the University of California, San Francisco (http://www.ucsf.edu/), have reported producing an MS-like condition in an animal model by exposing marmosets to a common virus that is suspected to have a link with MS [3].

Evidence suggests that MS is an autoimmune disorder, where the immune system acts destructively towards its own essential nervous system cells. However, the mechanisms behind this remain unclear and could be a result of numerous genetic and environmental factors, such as viruses or other infectious agents.

Genain and colleagues discovered that marmosets are susceptible to infection with human herpesvirus 6 (HHV-6), which has been proposed by numerous studies to be linked to MS. Marmosets infected with HHV-6 remained asymptomatic following primary inoculation, but developed clinical symptoms resembling an MS-like illness following a second inoculation with HHV-6 variant A.

These findings indicate that HHV-6 acts as a trigger for disease development. It is hoped that this model can be used to determine the mechanisms involved in virus-induced CNS autoimmune demyelination and to suggest therapeutic approaches that could be used to combat this disease. 'This is an unprecedented opportunity to understand how infection with a common human virus could lead to MS in a model system that resembles young humans,' says Genain.

3 Research presented at the *128th Annual Meeting of the American Neurological Association*. 18–22 October 2003, San Francisco, CA, USA (http://www.aneuroa.org/).

 1359-6446/03/$ – see front matter PII: S1359-6446(03)02931-3

as among the diseases that can occur if both parents carry BRCA2 mutations'. The study recommends that those carrying a heritable BRCA2 mutation consider genetic counselling if they plan to have children with someone who might also be a carrier.

The team is now looking at whether BRCA2 mutations are involved in other cases of brain tumours among children on the Fanconi register. 'Our goal is to translate these findings regarding cancers of the brain and breast into better prevention and treatment strategies for these malignancies', says Offit.

2 Offit, K. *et al*. (2003). Shared genetic susceptibility to breast cancer, brain tumors and Fanconi anemia. *J. Natl. Cancer Inst.* 95, 1548–1551

Genomics and Proteomics

Scientific evidence for 'fragile' regions

Genome scientists have now confirmed that 'fragile' regions exist in the human genome and these are more susceptible to gene rearrangements [4].

Researchers at the University of California, Santa Cruz (UCSC; http://www.ucsc.edu), led by scientists Jim Kent and David Haussler, have now confirmed with scientific evidence an earlier theory posited in June 2003 that predicted the existence of evolutionary 'fault zones' – hotspots where gene rearrangements were more likely to occur and change the architecture of genomes.

One of the original proponents of the theory, Pavel Pevzner from the University of California, San Diego (UCSD; http://www.ucsd.edu/), says that 'it took only three months to go from theory to hard scientific evidence that there are regions of the genome that are subject to evolutionary 'earthquakes' over and over again'.

This 'fragile breakage' theory, which was presented in a recent publication by Pevzner and Tesler [5], departed from the prevailing 'random breakage' theory of evolution that had been held for nearly two decades.

Kent and Haussler's latest findings confirm 'fragile breakage' and for the first time explicitly pinpoint the location of some of the faults in the human genome. Further support is offered in an accompanying commentary by Nadeau and Sankoff [6]. This support is most notable because it was Joseph Nadeu who, in 1984, first originated the 'random breakage' theory that Pevzner and Tesler later rebutted.

Taking the theory further, Pevzner is currently collaborating with biologists from UCSF to see if the new theory can yield potentially life-saving insights into diseases such as breast cancer, in which chromosomal rearrangements are implicated.

4 Kent, W.J. *et al.* (2003) Evolution's cauldron: Duplication, deletion and rearrangement in the mouse and human genomes. *Proc. Natl. Acad. Sci. U. S. A.* 100, 11484–11489

5 Pevzner, P. and Tesler, G. (2003) Human and mouse genomic sequences reveal extensive breakpoint reuse in mammalian evolution. *Proc. Natl. Acad. Sci. U. S. A.* 100, 7672–7677

6 Sankoff, D. and Nadeau, J.H. (2003) Chromosome rearrangements in evolution: From gene order to genome sequence and back. *Proc. Natl. Acad. Sci. U. S. A.* 100, 11188–11189

Gene Therapy

Muscular dystrophy and the Gene Team

New gene therapy techniques could produce an effective treatment for muscular dystrophy. Scientists traditionally used viruses to transport genes into cells. Viruses penetrate cells easily and encourage them to produce viral proteins. Conversely, because of their small size, viruses can not carry larger, therapeutic genes, and are subject to attack by the body's immune system.

It was reported recently [7] that scientists at Stanford University (http://www.stanford.edu) and the Palo Alto VA Medical Center, had devised another approach. They tested the use of plasmids, alongside integrase, which facilitated the integration of the plasmid genes into the host cell.

'The advantage of integrase-mediated gene therapy is that it delivers normal healthy genes into specific sites within the genome, allowing for sustained protein production' explained lead author Thurman M. Wheeler.

Scientists discovered that, unlike viruses, the plasmids are able to carry the larger disease-combating genes. They also do not provoke attack from the immune system.

Muscular dystrophy is an inherited disease caused by a missing or mutated gene, which triggers progressive weakness in the muscles. This gene normally expresses a protein called dystrophin, which gene therapy seeks to replace or repair. Although in its early stages, this research could prove invaluable to the advancement of gene therapy techniques.

7 Research presented at the *128th Annual Meeting of the American Neurological Association*. 18–22 October 2003, San Francisco, CA, USA (http://www.aneuroa.org/)

The genetics of Cayman ataxia

Cayman ataxia has been explained at the genetic level [8]. The rarity of this neurological disorder might appear to render the findings of limited importance. However, the results could lead to an improved understanding of more common forms of ataxia, and reinforce the value of comparative genetics studies.

Cayman ataxia occurs only in the population of Grand Cayman Island in the Caribbean. Those afflicted suffer from poor muscle coordination, mental retardation and difficulties with speech. The genetic cause of the disorder had previously been narrowed to a 50–100 gene region of chromosome 19.

Now, a team led by Margit Burmeister of the University of Michigan Medical School (http://www.med.umich.edu/medschool/), have pinpointed the gene responsible. A mutant strain of mouse, called 'jittery', showed similar neurological symptoms to those of Cayman ataxia sufferers.

Burmeister compared overlapping DNA sequences between the human chromosome 19 region, and part of mouse chromosome 10 that is known to cause the jittery phenotype. This narrowed the region of chromosome 19 down to seven genes. One of these genes, named *ATCAY*, contained both a point mutation and a splice mutation that expresses an inactive form of caytaxin protein, thought to be responsible for the ataxia.

Burmeister and a team from several organizations tested these promising results by analyzing DNA from Cayman Island residents. All DNA from subjects with Cayman ataxia carried both mutations, whereas DNA from people without the disorder contained neither mutation. The team is now carrying out structure–function experiments that will hopefully lead to the development of inhibitors of caytaxin. Burmeister also plans research to see whether the ATCAY mutations might be responsible for other forms of ataxia.

8 Bomar, J. M. *et al.* (2003) Mutations in a novel gene encoding a CRAL-TRIO domain cause human Cayman ataxia and ataxia/dystonia in the jittery mouse. *Nat. Genet.* (published online: doi:10.1038/ng1255; http://www.nature.com)

Microarray analysis lights the way for lung cancer treatment

The retinoblastoma gene *RB2/p130* suppresses the progression of lung cancer cells, however, the molecular mechanisms involved were unknown until now. New research has now identified specific genes that are regulated by *RB2/p130* [9].

The current research builds on a previous study that demonstrated an independent role for the reduction or loss of *RB2/p130* expression in the formation and/or progression of lung carcinoma. The *RB2/p130* gene was discovered in the 1990s and, when over-expressed in cancer cells, caused the murine tumours to completely regress. 'In this study we wanted to understand the molecular mechanisms behind *RB2/p130* tumour growth inhibition,' says Guiseppe Russo, first author of the study from Temple University's Sbarro Institute for Cancer Research and Molecular Medicine (http://www.temple.edu/).

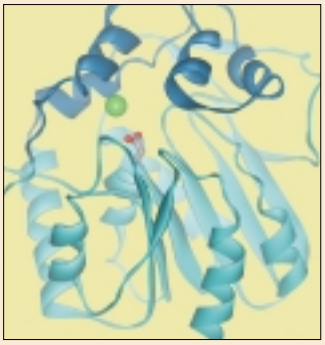
A viral shuttle system was used to introduce correct copies of RB2 into H23 lung cancer cells. Then, customized microarray analysis was used to examine the simultaneous expression of thousands of genes within the cancer cell. '… we were able to see which genes were over-expressed or under-expressed because of the enhanced *RB2* gene expression,' says Antonio Giordano, lead author of the paper.

Nearly 70 genes were identified, confirming previous data because some of them were previously known to be involved in lung cancer progression. The leading cause of cancer death worldwide is lung cancer, which is usually diagnosed at an incurable stage because of an absence of effective therapies as well as standard diagnostic procedures for early tumoural stages compared to other cancer types, such as colon, breast and prostate cancers. It is hoped that this new research, identifying these genes regulated by *RB2*, will contribute to identifying novel therapeutic biomarkers and developing new gene therapies to diagnose and treat lung carcinoma.

9 Russo, G. *et al.* (2003) pRB_2/p130 target genes in non-small lung cancer cells identified by microarray analysis. *Oncogene* 22, 6959–6969

Miscellaneous

Protein research comes into the fold



A collaboration between the University of California, Santa Barbara (UCSB; http://www.ucsb.edu/) and the National Institutes of Health (http://www.nih.gov/) have developed a way of observing how proteins fold [10].

The technique relies on the detection of the Forster energy resonance transfer between two dye molecules; one photon donor, which fluoresces green, and a photon acceptor, which fluoresces red. When the protein is in its folded state, the two molecules lie close to each other so that when the green dye molecule is excited by a laser it transfers a photon of energy to the red dye causing it to light up. However, as the protein gradually unfolds, the distance between the two dye molecules increases and so less energy transference occurs resulting in more green light being emitted. By taking a sequence of measurements as the protein folds, scientists are able to envisage how the protein folds into its final state.

At present, the process by which a protein adopts its shape is poorly understand. A limitation with previous studies was their inability to discriminate the states of single proteins. Everett Lipman, an Assistant Professor at the UCSB, commented; 'Once we have more understanding of the folding process, it will fill in a huge gap in our knowledge of how biological systems work.'

A protein's shape determines how it interacts with other molecules. Incorrectly folded proteins are the cause of diseases such as Alzheimer's, the prevalence of which is set to almost double by 2025 (http://www.alz.co.uk/alzheimers/faq.html). The need to elucidate disease causing protein configurations is obviously of great value now but will prove even more so in the future.

10 Lipman, E.A. *et al.* (2003). Single-Molecule Measurement of Protein Folding Kinetics. *Science.* 301. 1233–1235 (http://www.sciencemag.org)

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