News in brief

Targets and Mechanisms

Art imitating life

Researchers at the University of Texas Southwestern Medical Center (UTSWMC; http://www.swmed.edu) have validated novel proteins that block the activity of tumour necrosis factor (TNF; the major molecule involved in inflammation onset) and decrease swelling in a rodent model of rheumatoid arthritis (RA) by 25% [1].

Created by Xencor (http://www.xencor.com), the structure and sequence of these synthetic molecules are similar to natural proteins and, thus, have a reduced probability of rejection by the immune system.

As Malú Tansey, co-author of the report, explains, 'the inhibitors are actually modified versions of the TNF protein'; but they have mutations that prevent binding to receptors while enabling binding to TNF itself, thus, sequestering the active TNF away from the receptors that mediate inflammatory responses.

TNF is not only implicated in the painful inflammation of RA, but also in the underlying joint destruction. Over 2 million Americans suffer from this autoimmune disease, which is characterized by swelling, loss of joint function and deterioration of the affected cartilage and bone. Current treatments target TNF inhibition and are effective in reducing pain but not always joint destruction. Some patients develop antibodies against these drugs and, thus, require higher doses.

The dominant-negative TNFs represent a 'promising new avenue' in the treatment of RA, according to David Karp, Chief of Rheumatic Diseases and Associate director of the Harold C. Simmons Arthritis Research Center at the UTSWM. They could also be used to treat other autoimmune diseases, such as multiple sclerosis and systemic lupus erythematosis, as well as neurodegenerative diseases like Alzheimer's and Parkinson's disease.

1 Steed, P.M. *et al.* (2003) Inactivation of TNF signaling by rationally designed dominant-negative TNF variants. *Science* 301, 1895–1898

Neuronal gridlock on the highway to Huntington's

A team from the University of California, San Diego, School of Medicine (UCSD; http://www.ucsd.edu) has discovered that the reduced expression of the *Drospohila* neuronal protein, huntingtin, is linked to a disruption in protein transport within the brain and, as a result, neurodegeneration [2].

The mutated form of huntingtin is detrimental to axonal transport, forming aggregates that block the neurone. Although the mutated huntingtin protein has been previously linked to Huntington's, this study provides the first real evidence for its role in axonal obstruction.

Previous work by two members of this research group had found that, using the same animal model, expressing proteins known to cause Alzheimer's in humans led to reduction in axonal transport and neuronal cell death [3].

It has also been observed that the aggregation of the huntingtin mutant causes a severe dysfunction in the mechanosensory neurones of the nematode, *Caenorhabditis elegans* [4].

The ramifications of these discoveries could be far reaching. The senior lead author of the paper, Lawrence S.B. Goldstein, said: 'These findings support our hypothesis that blockage of neuronal transportation is related to several neurodegenerative diseases.'

Huntington's disease is an incurable neural disorder leading to a loss in the abilities to walk, talk and reason. The finding that the huntingtin mutant is present in several neurodegenerative diseases could provide the basis for a cure for Huntington's, and a plethora of other, debilitating neural disorders.

2 Gunawardena, S. *et al.* (2003) Disruption of axonal transport by loss of Huntingtin or expression of Pathogenic PolyQ Proteins in *Drosophila*. *Neuron* 40, 25–40

3 Gunawardena, S. and Goldstein, L.S. (2001) Disruption of axonal transport and neuronal viability by amyloid precursor protein mutations in *Drosophila*. *Neuron* 32, 389–401

4 Parker, J.A. *et al.* (2001) Expanded polyglutamines in *Caenorhabditis elegans* cause axonal abnormalities and severe dysfunction of PLM mechanosensory neurons without cell death. *Proc. Natl. Acad. Sci U. S. A.* 98, 13318–13323

When chromosomes reach breaking point…

An unstable region on chromosome 15 has been identified as the source of several inherited neurological diseases [5]. Researchers at the University of Pennsylvania (http://www.upenn.edu) have identified two known (*CYFIP1* and *GCP5*) and two novel (*NIPA1* and *NIPA2*) genes in a breakpoint region that, when lost, might contribute to Prader-Willi and Angelman syndromes.

Murine studies have revealed that these genes are located in a domain that shows asynchronous replication; as Robert Nicholls, co-author of the report, explains, 'disease can be caused by re-arrangements such as occurs in Prader-Willi and Angelman. These are simply good genes in a bad neighbourhood'.

A second report by this group reveals that a mutation in one of these genes might also be linked to hereditary spastic paraplegia (HSP) [6].

Prader-Willi and Angelman syndromes occur in one in 12,000–15,000 births. The former is characterized by mild cognitive impairment and morbid obesity, whereas, the latter is associated with seizures, movement disorders and severe mental retardation. HSP is marked by progressive development of leg paralysis.

The researchers collaborated with John Fink, a neurologist with the University of Michigan Health System (http://www.med.umich.edu), who provided DNA samples from several individuals of two unrelated families with HSP. The same mutation in the *NIPA1* gene was identified in both families.

Elucidation of the function of, and ligands for, this gene will help researchers

  PII: S1359-6446(03)02872-1

Cancer Targets and Mechanisms

Hsp90 inhibitors: selectivity explained

What is the difference between a normal chaperone protein and one from a tumour cell? The answer has now been posited [9], potentially clearing the way towards novel cancer therapeutics with broad utility.

Heat-shock protein 90 (Hsp90) is a molecular chaperone that maintains the stability and shape of many oncogenic signaling proteins. It is therefore a much-investigated target of anti-cancer drugs. However, Hsp90 is also widely expressed in normal tissue, and questions have been raised regarding the specificity of drugs that target the chaperone. Despite this, inhibitors do seem to be selective for tumour Hsp90, and have potent anti-tumour activity. But the molecular reasons underpinning this specificity have remained obscure. Now, a group of researchers from Conforma Therapeutics (http://www.conformacorp.com/) have proposed a mechanism.

The researchers identified a difference in form between Hsp90 samples from normal cells and tumour cells. The latter harbour Hsp90 in an activated, high-affinity form that is sufficiently different from the normal form to enable inhibitors to block the tumour Hsp90 with up to 100-fold greater affinity. The authors speculate that overexpressed mutant proteins are stabilized by tumour Hsp90. Bound co-chaperone proteins induce the tumour Hsp90 to adopt the high-affinity form.

Because of the ubiquity of Hsp90, the technique might be applicable to a variety of tumours. 'The activation of Hsp90 chaperones has been found in every tumour type we have investigated,' commented Francis Burrows, the senior author of the paper. 'Accordingly, we are optimistic that Hsp90 antagonists will have broad activity against diverse human cancers.'

9 Kamal, A. *et al.* (2003) A high-affinity conformation of Hsp90 confers tumour selectivity on Hsp90 inhibitors. *Nature* 425, 407–410

Could anti-diabetics make effective anti-cancer agents?

Researchers at the University of Dundee (http://www.dundee.ac.uk) believe that drugs used to treat Type 2 diabetes might also have the potential to be effective as anti-cancer therapies [10]. While looking into targets for treating diabetes, an unexpected link was forged to Peutz-Jeghers syndrome (PJS), a hereditary disease that increases the risk of developing malignant tumours in other tissues by 15-fold.

The finding came from a search for a protein that would activate the enzyme AMPK, which functions to reduce blood glucose levels and inhibit cell proliferation. The protein that was found to behave as an AMPK activator was another enzyme, LKB1, the reduced expression of which is a known cause of PJS.

Dario Alessi, a research team leader, said: 'LKB1 was thought of as a tumour suppressor gene, and AMPK was involved in diabetes. No one thought that there could be a link between the two.' Grahame Hardie, who led a second research team, added: "The idea that LKB1 might be the key was a genuine 'Eureka' moment."

People suffering from Type 2 diabetes commonly possess high blood glucose levels. Active AMPK induces muscles to take up glucose from the bloodstream and inhibit blood glucose production. Some common drugs target AMPK for these reasons and one such drug, metformin, was ineffective in cells that contained no LKB1.

Although not present in PJS, LKB1 is active in nearly all other cancers. The realization of anti-diabetics as cancer treatments still requires much future work, however, it remains a sweet prospect nonetheless.

10 Hawley, S.A. *et al.* (2003) Complexes between the LKB1 tumour suppressor, STRADα/β and MO25α/β are upstream kinases in the AMP-activated protein kinase cascade. *J. Biol.* 2, 28 (http://jbiol.com/content/2/3/28)

to understand the process of axonal neurodegeneration in HSP. In addition, all of the findings will help to improve the genetic diagnosis of these diseases but, as Nicholls warns, 'these are complex disorders that do not play by the normal rules of genetics'.

5 Chai, J-H. *et al.* (2003) Identification of four highly conserved genes between breakpoint hotspots BP1 and BP2 of the Prader-Willi/Angelman syndromes deletion region that have undergone evolutionary transposition mediated by flanking duplicons. *Am. J. Hum. Genet.* 73, 898–925

6 Rainier, S. *et al.* (2003) *NIPA1* gene mutations cause autosomal dominant hereditary spastic paraplegia (SPG6). *Am. J. Hum. Genet.* 73, 967–971

No job too big or too small for the immune system

A role for the immunological synapse (IS) has been suggested and its potential use as a target for treating diseases highlighted by new research. These include diseases in which the body attacks itself, such as arthritis, and those in which the body does not recognize the attacker, such as tumours.

The research team, from the University of California, Berkeley (http://www.berkeley.edu/), Washington University School of Medicine (http://medschool.wustl.edu/), Genentech (http://www.gene.com/gene/index.jsp) and New York University (http://www.nyu.edu/), brought together results from genetically altered mice and a computer model to show that the IS, which forms between an antigen-presenting cell (APC) and T cell, enables the immune system to detect signs of infection of virtually any size [7].

Although researchers initially thought that the IS simply amplified signals between cells, this new research found that, at the height of IS formation when the signalling should be strongest, there was only a low signal because most of the T-cell receptors (TCRs) were being degraded [7].

'The [computer] model predicts that if you could turn off this degradation process,' says author Michael Dustin, 'the T cell would probably over-respond, and it would have a hard time attenuating these signals'.

The genetically altered mice were missing proteins that are involved in forming the IS central cluster and degrading TCRs; therefore, their T cells over-responded to strong antigen signals. Enabling these cells to form an IS but not degrade TCRs decisively confirmed the computer model prediction that the signals at the centre of the IS are strong instead of weak. The IS can therefore either augment or decrease signals.

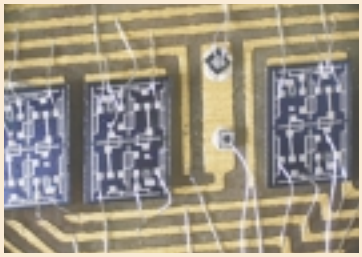
This wide range of sensitivity is necessary for the immune system because pathogens that are trying to evade the immune response can generate few antigenic structures, whereas some pathogens try to swamp the immune system with one antigenic structure with a large system. The IS therefore enables the immune system to adapt to strong signals by reducing the TCR density and then arrive at a uniform signalling rate in any situation.

The next research phase will attempt to determine what causes the TCR degradation. If involved in intense signaling, they are degraded; if not, they are returned to the surface. However, what controls these processes is still unknown.

7 Lee, K-H. *et al.* (2003) The immunological synapse balances T cell receptor signaling and degradation. *Sciencexpress* 10.1126/science.1086507 (http://www.sciencexpress.org)

Bioinformatics

Protein network software gets interactive



With the continuing gush of genomics data comes the much-talked-about need for digging out the useful information. A new piece of software offers one such application by comparing the genomes of different organisms and identifying differences in protein interaction networks [11].

The new software tool, called PathBLAST, was designed by workers at the Whitehead Institute (http://www.wi.mit.edu/) in collaboration with scientists at the International Computer Science Institute (http://www.icsi.berkeley.edu/).

The algorithm uses knowledge derived from previous microarray experiments to hunt for interaction networks in genomic data. These networks are captured mathematically and translated into linear code. The program can then compare interaction networks from different organisms.

To demonstrate the approach, the team analyzed the entire genomes of the yeast *Saccharomyces cerevisiae* and the bacterium *Helicobacter pylori*. According to a database on interacting proteins, the bacterium contains 1465 known interactions among 732 proteins, and the yeast contains 14,489 interactions among 4688 proteins. Running this and other genomic information in PathBLAST took only a few seconds.

The results revealed two networks that are conserved between these two different species: a pathway that is crucial for DNA replication and one that is crucial for protein degradation. One possible application of this work is the comparison of viral and human genomes for cellular pathways unique to the virus. Such knowledge could provide fresh targets for drug development.

11 Kelley, B.P. *et al.* (2003) Conserved pathways within bacteria and yeast as revealed by global protein network alignment. *Proc. Natl. Acad. Sci. U. S. A.* 100, 11394–11399

Viral Targets and Mechanisms

Beat retroviruses the natural way

Retroviruses can cause damage by inserting into host genes and altering their expression. A new study shows how a naturally occurring mutation can counter these effects, suggesting new ways in which the actions of retroviruses might be controlled [8].

Bruce Hamilton (University of California at San Diego; http://www.ucsd.edu/) and colleagues have previously shown that the mouse modifier-of-vibrator 1 (*Mvb1*) allele suppresses neurodegeneration and early death that are caused by vibrator (*vb*), an allele formed by retroviral insertion.

The team has now worked out how *Mvb1* has this effect: they found that *Mvb1* increases the production of normal mRNA from *vb*, and realized that *Mvb1* encodes mRNA nuclear export factor 1 (Nfx1).

By controlling export of mRNA from the nucleus to cytoplasm, Nfx1 forms part of a checkpoint that can block expression of genes disrupted by retroviruses. By contrast, the variant of Nfx1 encoded by *Mbv1* seems to enable export of normal mRNA that is produced from disrupted genes.

The researchers found *Mvb1* in wild-type mouse populations, suggesting that the beneficial mutation occurred spontaneously and has been retained by natural selection.

'The properties of this gene could be used to engineer a system for controlling mutations caused by retroviruses', said Hamilton. 'This could be particularly useful for creating mouse models of human disorders.' Hamilton and colleagues are already looking more closely at the molecular mechanisms involved and hope to adapt Nxf1 for use as a research tool.

8 Floyd, J.A. *et al*. (2003). A natural allele of Nfx1 suppresses retrovirus insertional mutations. *Nat. Genet*. doi:10.1038/ng1247 (http://www.nature.com)

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