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News in brief

Targets and mechanisms

Netrin-1 directs the way in MS treatment

An estimated 50,000 people have multiple sclerosis (MS). The devastating effects of this condition last a lifetime and can include problems in seeing or speaking, difficulty with balance and coordination, and even paralysis. A new discovery by scientists at the Montreal Neurological Institute at McGill University (http://www.mcgill.ca) could provide new insights into MS.

Tim Kennedy and colleagues [1] have discovered that a protein called netrin-1 directs the normal movement of the cells that become oligodendrocytes in the developing spinal cord. Oligodendrocytes are the cells that provide crucial support for the nerve cells – they make myelin, the electrical insulation of the CNS. They are also the cells that degenerate and die in MS. Although oligodendrocytes have an essential role in the nervous system, many aspects of their basic cell biology are not well understood, which is one of the reasons why MS is such a mystery. 'Understanding the basic biology of oligodendrocytes is very important for MS. If we can understand what stimulates them to function, then perhaps we can develop new targets for therapy,' explained Jack Antel, a Neurologist at the Montreal Neurological Institute. This new research identifies a fundamental mechanism that directs migrating oligodendrocyte precursor cells. The researchers showed that netrin-1 acts as a repellent cue for migrating oligodendrocytes – directing them to move away from sources of netrin.

Understanding how proteins function is a key step in developing an effective treatment against any disease. This study of netrin-1 is important for understanding the root causes of MS and might enable the development of a new generation of drugs to combat this condition.

1 Jarjour A.A. *et al*. (2003) Netrin-1 is a chemorepellent for oligodendrocyte precursor cells in the embryonic spinal cord. *Neuroscience* 23, 3735–3744

New promise for tuberculosis prevention

A gene controlling susceptibility to tuberculosis in mice has been discovered by researchers at McGill University Health Center (http://www.muhc.mcgill.ca) [2].

The infectious disease is caused by the virulent *Mycobacterium tuberculosis* bacteria and affects 1.9 billion people worldwide but a large proportion of individuals do not develop symptoms. Similarly, in this study, two different strains of mice – DBA/2 (D2) and C57BL/6 (B6) – show tuberculosis susceptibility and resistance, respectively.

Both strains of mice, which were infected with air-borne bacteria, showed rapid bacterial growth in the lungs during the first three weeks. Beyond this point, replication stopped in B6 mice, but progressed to fatal pulmonary disease in D2 mice. Using the extent of bacterial replication as a quantitative measure of susceptibility to infection in a whole-genome scan, quantitative trait locus mapping revealed a common gene variant on chromosome 19 of disease susceptible mice.

The gene variant, Trl4, is believed to control the growth of bacteria in the lung. In the more resistant strain of mice (B6), alleles at this locus are inherited in an incompletely dominant fashion, and associated with reduced bacterial replication. An additional effect of locus Trl3 might also interact with Trl4 in regulating replication of *M. tuberculosis*.

Philippe Gros, Professor of Biochemistry and Medicine at McGill, said: 'We have identified a gene that controls *M. tuberculosis* growth in the lung. This is an important step toward understanding why some infected individuals are able to fight off the infection and others are not.' He added, 'This discovery may lead to innovative prevention and treatment strategies for the two million patients who die from tuberculosis yearly'.

2 Mitsos, L.M. *et al.* (2003) Susceptibility to tuberculosis: A locus on mouse chromosome 19 (Trl-4) regulates *Mycobacterium tuberculosis* replication in the lungs. *Proc. Natl. Acad. Sci. U. S. A.* May 9/epub ahead of print http://www.pnas.org)

Humanin interferes with Bax to block apoptosis

Humanin, a 24-amino-acid protein, which was recently discovered in studies of Alzheimer's disease, has been found to suppress activation of the apoptosis-inducing protein Bax (Bcl2-associated X protein) [3]. Bax triggers cell death in Parkinson's disease, stroke, heart attack and in the degeneration of ovaries during the menopause, and recent results suggest inhibiting the apoptotic activity of Bax could be a novel therapeutic target.

Bax promotes apoptosis in cells by attacking the mitochondria of the cell. Bax resides in an inactive form in the cytosol of many cells and in response to death stimuli, it undergoes conformational changes, exposing membrane-targeting domains and resulting in its translocation to mitochondrial membranes. Here, Bax inserts and causes the release of cytochrome *c* and other apoptogenic proteins.

It is unknown what controls the conversion of Bax from the inactive to active conformation, however, recent results from The Burnham Institute (http://www.burnham-inst.org/), have found that Bax interacts with humanin [3], which prevents the translocation of Bax from the cytosol to mitochondria. Humanin therefore blocks Bax from causing apoptosis.

'Our results demonstrate that Bax is the target of humanin, and they suggest at least three novel ways of designing therapeutics that could prevent or arrest diseases associated with activation of Bax,' says John C. Reed, lead investigator in the study. Because humanin can readily enter cells, it could be synthesized and developed as an injectable drug for acute situations, such as heart attack or stroke. Reed also envisages gene therapy that exploits the ability of humanin to translocate from cell to cell, thus protecting cells in the vicinity of gene injection.

3 Guo, B. *et al.* (2003) Humanin peptide suppresses apoptosis by interfering with Bax activation. *Nature* 10.1038/nature01627 (www.nature.com)

Miscellaneous

Multidrug resistance: pumping out solutions

The first crystal structures of a bacterial efflux protein have been solved in complex

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with a variety of ligands. The structures provide a more detailed insight into the workings of this versatile pump and suggest a new strategy for combating the scourge of bacterial multidrug resistance [4].

Antibiotic resistance in bacteria is a well-known yet serious threat to public health. The problem is chiefly caused by molecular pumps that can capture and expel a variety of structurally unrelated molecules, including drugs. Because of the indiscriminate nature of the binding site it is difficult to create a drug that is able to selectively block these pumps. Elucidating how these remarkable protein complexes accommodate such a broad spectrum of molecules would be an important step in finding ways to prevent their action.

One example is AcrB: this multi-protein complex, housed in the inner membrane of *Escherichia coli*, has the widest substrate specificity of all known efflux pumps. Sequestered in animal intestines, the normal function of AcrB is to expel toxic bile salts that enter the bacterium. However, a mutated form can cause food poisoning, which can be tricky to cure as AcrB also expels drugs.

A team from the Lawrence Berkeley National Laboratory (http://www.lbl.gov/) and the University of California, Berkeley (http://www.berkeley.edu/) have studied AcrB in the greatest detail yet. The team obtained 3.5–3.8 Å resolution X-ray crystallography structures of AcrB with four different ligands: an antibiotic, a dye, a disinfectant and a DNA-binding molecule. All ligands bound within a previously discovered cavity, but the exact binding sites were different in each case. The researchers believe the cavity might contain further binding sites able to capture a large variety of other ligands, and will now turn their attentions to a more thorough exploration of the cavity. Because of the lack of specificity, tweaking existing drugs will probably be ineffective at blocking the pump. Instead, the researchers suggest a novel approach. The efflux pump works in conjunction with a funnel-shaped protein in the outer membrane, whose role is to eject molecules that have been captured by AcrB. Designing a drug to block this funnel might be a more successful strategy as AcrB is impotent without it. Such an approach could have wide use, as analogous pumps can be found in nearly all species of bacteria.

4 Yu, E.W. *et al.* (2003) Structural basis of multiple drug-binding capacity of the AcrB multidrug efflux pump. *Science* 300, 976–980

Cancer Targets and Mechanisms

Viral 'smart bomb'

Researchers in a team led by The University of Texas MD Anderson Cancer Centre (http://www.mdanderson.org) has tested a novel viral 'smart bomb' that can eradicate brain tumours in mice, while leaving normal tissue untouched [6].

The team looked at the retinoblastoma (Rb) protein that is seen to malfunction in nearly all malignant gliomas. This protein is found in all cells of the body and halts cell division by preventing other regulatory proteins from triggering DNA replication; if the Rb protein is missing or is not functioning, unregulated cell replication occurs leading to tumour development. In normal cells, the presence of Rb also prevents the replication of viruses that enter the cell; however, adenoviruses can counteract this by expressing the E1A protein, which binds to Rb and interrupts its protective function.

To create a viral therapy to target these molecular defects researchers developed a new virus with a 24-base-pair deletion in the adenovirus E1A gene that is designed to take advantage of mutant Rb; the malfunctioning E1A gene can not stop Rb from functioning and the virus can infect and spread through cells with mutant Rb – namely cancer cells. In this way, Delta-24-RGD is designed so that it can only replicate in cancer cells and if it enters a healthy cell the virus is prevented from replicating: when the cancer cells have been eradicated, the virus itself dies. The treatment is a new generation of 'replication-competent oncolytic' adenovirus therapy.

'Biological viral therapy like this may be just what we need to treat a complex disease like cancer' says Frederick Lang, Associate Professor in the Department of Neurology, and a primary investigator of the study 'In this experimental war between cancer and a viral therapy, the virus has won'.

The results show that in repeated experiments more than half of the mice that had human glioblastoma tumours implanted in their brains and were treated with Delta-24-RGD survived for more than four months, where untreated mice lived for less than three weeks. The mice in the studies were considered clinically cured of their brain tumours and the National Cancer Institute is providing financial support to produce a therapy for human clinical trials by late next year. Lang adds, 'Of course we hope to obtain similar results when patients are tested, but we can not predict such success based on animal studies'.

6 Juan Fueyo *et al.* (2003) Preclinical characterization of the antiglioma activity of a tropism-enhanced adenovirus targeted to the retinoblastoma pathway. *J. Natl. Cancer Inst*. 95, 652–660

Computers for genes

Much of the activity of a cell is organized as a network of interacting modules (for example, gene sets co-regulated to respond to different conditions). The first computational method that can identify clusters of genes responsible for controlling processes within a cell, when those clusters become active and, most importantly, how the clusters are regulated, has recently been developed by a multi-disciplinary team from the Hebrew University, Jerusalem (http://www.huji.ac.il/unew/

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Imaging

One-stop brain tumour diagnosis

Magnetic resonance imaging (MRI) is used routinely to identify potential brain tumours. Research now shows that MRI can simultaneously indicate whether lesions are malignant [7], removing the need to wait for biopsy results and paving the way for more rapid diagnosis and treatment of brain tumours.

Researchers led by Ronald Ouwerkerk, of the Johns Hopkins University School of Medicine (http://www.hopkinsmedicine.org/medicalschool/), used combined proton and sodium MRI to measure concentrations of sodium in tissues because features of malignancy, such as angiogenesis, rapid cell division and the death of normal cells, can all increase concentrations of this ion. Ouwerkerk and colleagues tried their technique on 20 patients with brain tumours and on nine healthy volunteers, testing cancerous and non-cancerous tissues. They found that sodium concentrations were on average 50% greater in cancerous tissues than in healthy ones.

Being able to distinguish a malignant tumour from a non-malignant one at the same time as the lesion is first detected should increase the efficiency of brain tumour diagnosis and treatment. As Ouwerkerk explains, 'determining precise sodium concentrations has been a problem, but MRI can do it at the same time it identifies possible malignant lesions. Using MRI non-invasively in a single examination to get information about tumour metabolism and physiology improves the identification of tumour malignancy and is a big step forward.'

7 Ouwerkerk, R. *et al.* (2003) Tissue sodium concentration in human brain tumors as measured with ^{23}Na MR imaging. *Radiology* 227, 529–537

CT assists physicians to diagnose SARS

A team of physicians from Hong Kong's Prince of Wales Hospital (http://www3.ha.org.hk/pwh/) have used computed tomography (CT) to assist their diagnosis of SARS and the study published in the journal *Radiology* [8] indicates that this imaging procedure can assist an accurate diagnosis of the infection.

Ahuja, Chairman of the Department of Diagnostic Radiology and Organ Imaging at the Chinese University of Hong Kong said, 'Until a reliable diagnostic test for SARS is available, physicians need a clear picture of its clinical presentation to be on the alert for the condition'. The Centres for Disease Control and Prevention (CDC) define the clinical appearance of SARS by high fever; pneumonia or respiratory distress syndrome; and travel within 10 days of onset of symptoms to an area with documented or suspected community transmission of SARS or close contact with such a person or a suspected SARS patient.

Physicians must therefore rely on the physical presentation of a suspected patient and can combine this with chest radiography to diagnose SARS. Ahuja's team determined that CT can be valuable in diagnosing SARS, especially in cases where patients had a normal chest X-ray but strong clinical signs of SARS because lung abnormalities more easily shown by the 3D cross sectional images produced by CT. It is hoped that CT will help physicians in diagnosing SARS as the CT scans were more likely to show abnormality in the lower and peripheral parts of the lung that were undetected by X-ray.

Ahuja added, 'Our study shows that CT can be used as a definitive investigation in questionable cases of SARS…this is extremely important because only with early recognition, prompt isolation and appropriate therapy can we combat this deadly infection'.

8 Wong,K.T. *et al.* (2003) Thin-section CT of severe acute respiratory syndrome: evaluation of 73 patients exposed to or with the disease. *Radiology* 10.1148/radiol.2283030541

main.html), Tel Aviv University, Israel (http://www.tau.ac.il/), and Stanford University, CA, USA (http://www.stanford.edu/) [5].

Although all cells in our body contain identical DNA molecules, their protein make-up dramatically differs. Precise regulation of gene expression is therefore crucial to ensure that the correct protein is made at the right time. Understanding the processes responsible for gene regulation, therefore, have important implications for understanding how cells function and how diseases that involve the breakdown in regulatory processes, such as cancer, can develop.

Usually, regulatory genes are identified experimentally, not computationally. However, the newly reported computational method makes the experimental process much more efficient. It extracts the regulatory circuits from large collections of gene expression measurements, being the first approach to incorporate data about known and putative regulatory clusters and the first to simultaneously predict which gene or genes regulate each cluster. The newly published method revealed several previously unknown control or regulatory genes from *Saccharomyces cerevisiae,* better known as baker's yeast.

'Revealing the control mechanism for gene clusters is crucial for understanding how cells respond to internal and external signals,' says team member David Botstein. 'This new computational method efficiently generates targets for testing and proposes hypotheses about their regulatory roles that can be experimentally confirmed'.

5 Segal, E. *et al.* (2003) Module networks: identifying regulatory modules and their condition-specific regulators from gene expression data. *Nat. Genet.* 10.1038/ng1165 (http://www.nature.com/genetics/)

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