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News in brief

Targets and Mechanisms

The role of serotonin in IBS

Scientists are a step closer to understanding the molecular mechanisms behind irritable bowel syndrome (IBS). The new findings show that alterations in serotonin signalling are present in patients with IBS [1].

Serotonin (also called 5-HT) is a neurotransmitter and signalling molecule, predominantly found in the gastrointestinal tract. It has a key role in regulating the motor, sensory and secretory functions of the gut. Consequently, alterations in serotonin levels are thought to contribute to abnormal gut conditions, such as those found in IBS. New findings from a team at the University of Vermont (http://www.uvm.edu/) reveal this biochemistry in more detail than was previously known.

The study examined gut tissue from IBS sufferers, patients with inflammatory bowel disorder and control samples. In tissue from IBS patients there was a significant decrease in the serotonin transporter. With fewer transporters, serotonin will persist in the gut for longer periods, causing changes in motility, secretion and sensitivity of the gut.

Peter Moses, one of the lead investigators, commented that the findings lend 'credibility to the notion that IBS is not simply a psychological or social disorder as was once thought, but is instead due to altered gut biochemistry and interactions between the gut and the brain'.

1 Moses, P. and Mawe, G. (2003) Oral presentation at the *68th Annual Scientific Meeting of the American College of Gastroenterology*. 12–15 October 2003, Baltimore, MD, USA

The obsessive-compulsive gene

Obsessive-compulsive disorder (OCD) is one of the 10 leading causes of disability worldwide, affecting 1–3% of the US population. It is a mental illness characterized by repetitive unwanted thoughts and behaviour, interfering strongly with daily life. Researchers have identified two genetic mutations that appear to be linked to the development of this disorder [2].

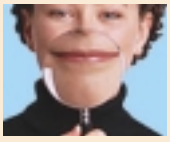
Researchers based at the US National Institute of Health (http://www.nih.gov/) in Washington and the Fujita Health University School of Medicine in Toyoake, Aichi, Japan (http://www.fujita-hu.ac.jp/english/university/medicine.html) analyzed DNA samples from 170 unrelated individuals, including patients with OCD, eating disorders, seasonal affective disorders and healthy individuals. They used single strand conformational polymorphism (SSCP) to scan the coding sequence of the serotonin transporter (SERT) gene. This gene, located on chromosome 17, is involved in regulating the neurotransmitter serotonin, a major target of anti-depressant drugs.

Two uncommon gene variants were detected. One of these mutations, which resulted in a valine to isoleucine substitution at position 425, was found in two unrelated families. Six out of seven members of the same family, who were found to carry this mutant gene, had OCD or OC personality disorder, and some also suffered from Asperger's syndrome (autism), social phobia, anorexia nervosa, tic disorder and alcohol or substance abuse. Although rare, it is concluded that the mutation probably exists in other families with OCD and related disorders, and it is suggested that it might contribute to an uncommon familial form of OCD that is associated with autism, anorexia and many other neuropsychiatric disorders.

2 Ozaki, N. *et al.* (2003) Serotonin transporter missense mutation associated with a complex neuropsychiatric phenotype. *Mol. Psychiat.* 8, 933–936

Viral Targets and Mechanisms

Looking AIDS in the mouth



The finding that peptides in the mouth can inhibit the HIV virus [6] could serve as a fountainhead for AIDS research. As well as suggesting new lines of enquiry for the development of drugs, the discovery could also be applied to preventing secondary infections during surgical procedures.

The work is being led by a team from Case Western Reserve University (http://www.cwru.edu/). Aaron Weinberg, a dentist and microbiologist at the Case School of Dentistry, had been curious about why AIDS is so rarely contracted orally. Research pointed to a group of peptides found in the lining of the mouth, known as human β-defensins 2 and 3 (hBD2 and hBD3). These small cationic peptides prevent infections in the mouth and promote rapid healing from food abrasions and accidental bite wounds. Weinberg and his colleagues studied the effects of the HIV-1 virus on epithelial cells that harbor hBD2 and hBD3.

The levels of hBD2 on a monolayer of human oral epithelial cells increased almost 80-fold in the presence of HIV-1. The response lasted for 72 hours – longer than the virus could survive in the mouth. Electron microscopy confirmed that the defensins inhibit virus replication and infectivity by direct binding. In addition, both defensins induced down-modulation of the HIV-1 co-receptor CXCR4.

According to Weinberg, the information could be used to create new drugs based on extractions from 'good oral bugs' that induce the defensin response. Such natural products could also be used to coat surgical equipment and implants, thus limiting secondary infections.

6 Quiñones-Mateu, M.E. *et al.* (2003) Human epithelial β-defensins 2 and 3 inhibit HIV-1 replication. *AIDS* 17, F39-F48

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Cancer Targets and Mechanisms

Findings at the checkpoint control

A new study by researchers from the Mayo Clinic and Foundation in Minnesota (http://www.mayoclinic.org/) provides important information about the molecular mechanisms of BRCA-1 action both in healthy cells and when the gene encoding this protein is mutated [3].

The C-terminal domain of BRCA-1 (BRCT) has an essential role in interaction between BRCA-1 and its binding partners. The key finding of the study is that BRCT recognizes and binds to only phosphorylated proteins. BRCT, which is evolutionarily conserved, acts similarly in other proteins. However, of particular interest to a molecular understanding of the pathology of familial breast cancer is the BRCT-mediated interaction between BRCA-1 and another protein called BRCA-1-associated C-terminal helicase (BACH1).

In healthy cells, DNA damage causes cell-cycle arrest before mitosis, which continues until the damage is repaired. This checkpoint control is absent in BRCA-1-deficient cells. The research team from Mayo Clinic, led by Junjie Chen, report that, in cells containing a truncated form of BRCA-1 that lacks BRCT domain, BRCA-1–BACH1 interaction does not occur. A similar checkpoint defect was observed in cells expressing lower levels of BACH1. This suggests that phosphorylation-dependent interaction between BRCA-1 and BACH1 is essential for the tumour-suppressing function of BRCA-1.

Mutations in the gene encoding BRCA-1 are responsible for approximately 50% of familial breast-cancer cases. The findings of Chen and colleagues are an important step towards devising anti-cancer treatments. By exploiting phosphorylation bonds between key proteins, therapeutical regulation of the cell cycle might be possible.

3 Yu, X. *et al.* (2003) The BRCT domain is a phospho-protein binding domain. *Science* 302, 639–642

Miscellaneous

New antibiotic to fight resistant bacteria?

A new class of synthetic antibacterial chemicals has been found, which inhibits the ability of a cell to express genetic material, one of the most fundamental processes of life, and hence prevents bacterial reproduction. This new class of antibiotic might now be developed into a new drug to fight increasingly drug-resistant bacteria.

The CBR703 series inhibits RNA polymerase, the key enzyme involved in gene expression and protein generation [7]. Although many bacterial inhibitors act in this way, these new compounds use a unique, and previously unknown, mechanism to inhibit RNA polymerase [7]. Importantly, the researchers from the University of Wisconsin (http://www.wisc.edu/) and Cumbre (http://www.cumbre.net/) also outline a proposed mechanism of action of the compounds, which is key to designing an actual drug. 'When we find something that inhibits a particular process, it's easier to make targeted drugs,' says Irina Artsimovitch, lead author of the study.

CBR703 compounds were tested on *Escherichia coli,* which can become toxic and cause food poisoning. The inhibitors prevented RNA polymerase in *E. coli* from performing crucial catalytic functions, such as nucleotide addition, pyrophosphorolysis and Gre-stimulated transcript cleavage. However, they had no effect on RNA or DNA translocation when it is uncoupled from catalysis. The CBR703 compounds affect the RNA polymerase by binding to a specific point on the enzyme, which results in a hindrance of active site structure movement, which is linked to the CBR703 binding site through a bridge helix. The compounds therefore killed the *E. coli* but did not harm human cells, making them an exciting option for drug development.

'Knowing how a new antibiotic acts on its target takes the process of making new drugs to a new level, allowing for better understanding of a drug's direct- and side-effects,' says Artsimovitch. It is hoped that these compounds will enable drugs specifically targeted to major bacterial pathogens, such as those causing pneumonia and tuberculosis, to be developed.

7 Artsimovitch, I. *et al.* (2003) A new class of bacterial RNA polymerase inhibitor affects nucleotide addition. *Science* 302, 650–654

Ginger snaps colorectal cancer cells

Plants from the ginger family have been used for thousands of years and have been reported to have anti-cancer properties. New research now suggests that ginger, the key ingredient in Asia's culinary triangle, could contain a powerful component to combat the growth of human colorectal cancer cells [4].

The main active compound of ginger, [6]-gingerol, which also provides the flavour, inhibits the growth of human colorectal cancer cells that have been injected into athymic nude mice [4]. Researchers from the University of Minnesota (http://www1.umn.edu/twincities/index.php) presented findings, at the *American Association for Cancer Research* meeting, of slower rates of cancer growth in mice given thrice weekly feedings of [6]-gingerol.

Half a milligram of [6]-gingerol was fed to mice before and after injecting human colorectal tumour cells into their flanks. Mice consuming [6]-gingerol developed smaller tumours in a smaller number of mice than the control group. 'These results strongly suggest that ginger compounds may be effective chemopreventive and/or chemotherapeutic agents for colorectal carcinomas,' says Ann Bode, co-author of the study.

The preliminary data also suggest that tumours in the control mice had metastasized more than tumours in the [6]-gingerol mice. However, because mice were euthanized once their tumours grew larger than 1 cm^3, 'it's difficult to know if the ginger-treated mice would have lived longer if left to die of their tumours, but it looks that way,' Bode says.

The researchers next round of experiments should be more clinically relevant because ginger will only be fed to mice after they have grown tumours to a certain size. 'They will get at the question of whether a patient could eat ginger to

slow the metast of a non-operable tumour,' says Bode.

4 Bode, A. and Dong, Z. (2003) Research presented at the *American Association for Cancer Research* meeting, 28 Oct 2003, Phoenix, AZ, USA, (http://www.aacr.org/)

Neuroscience

Atlas of light guides neuroscientists

Scientists have taken a major step towards understanding the remarkable complexity of the mammalian CNS. The Gene Expression Nervous System Atlas (GENSAT) project has published details of a new technique for studying where and when genes are active in the mouse CNS, and has established libraries of research tools that should greatly benefit those looking at how the CNS develops, functions and responds in disease [5].

The GENSAT team modified bacterial chromosomes (BACs) to include regulatory sequences of a gene of interest along with a reporter gene. Mouse eggs containing the BACs were allowed to develop, and fluorescence from the reporter protein revealed which cells expressed the gene of interest in mice of different ages. By repeating this experiment with different genes and different cells, researchers can build up an 'atlas' of the locations and timings of CNS gene expression, and infer functional information.

Gong *et al.* confirmed that their BACs could report true expression patterns by comparison with patterns from the conventional methods of immunohistochemistry and *in situ* hybridization, which require greater disruption to tissue and are often less sensitive. The researchers went on to demonstrated how their approach can generate new information on CNS gene function, cell migration and anatomy. They predict that use of their BACs to identify cells will also facilitate studies of CNS physiology, pathophysiology and responses to drugs.

Various institutions are involved in the initiative, which is spearheaded by Nathaniel Heintz of the Howard Hughes Medical Institute (http://www.hhmi.org/) and Mary Hatten of Rockefeller University (http://www.rockefeller.edu/). As a bonus, the technique provides experimental materials for other neuroscientists. The library of BAC vectors and the transgenic mice could prove very useful to the field, as Heintz explained. 'This access to mice with precisely labelled cell populations will stimulate the whole area of neurobiology that studies cell physiology and connections,' he said.

The atlas will help neurobiologists who are studying the cellular and molecular mechanisms of neurological disorders. For example, although many mice models of diseases are available, in most cases the cells responsible for the primary effects of the disease have not been located.

Data from the project, including high-resolution images of gene expression, are available at the GENSAT website (http://www.gensat.org) and will be updated as the project continues. In addition, scientists will have access to the BACs and transgenic mice generated, guaranteeing that the project will stimulate and accelerate research throughout the neuroscience community.

5 Gong, S. *et al.* (2003) A gene expression atlas of the central nervous system based on bacterial artificial chromosomes. *Nature* 425, 917–925

News in brief was written by *Matt Brown, Michelle Doherty, Morag Robertson, Sadaf Shadan and Heather Yeomans*

People

Appointments

SWITCH Biotech appoints Stefan Schulze as CEO

Stefan Schulze has been appointed as Chief Executive Officer of SWITCH Biotech (http://www.switch-biotech.com), a company involved in dermatological research and development. Previous to his appointment as CEO, Schulze was Chief Financial Officer and Speaker of the Management Board at the company. Schulze is a trained economist and prior to joining SWITCH Biotech worked for McKinsey & Company as a management consultant.

On his appointment, Schulze commented: 'It is an honour for me to serve SWITCH Biotech as CEO. We have the tremendous opportunity to emerge as the market leader for innovative research and drug development in dermatology.' Marc Guyader, Chairman of the Board of Directors, added: 'The appointment of Stefan Schulze as new CEO will consolidate the company's development. His background in economics, his expertise in financial matters, his experience in the medical-scientific environment, as well as his pro-active and positive attitudes to significant managerial and environmental moves will be of great benefit to SWITCH.'

BioTrove announces new President and CEO

BioTrove (http://www.biotrove.com) has announced the appointment of Robert Ellis, formerly the company's Chief Operating Officer, as President and Chief Executive Officer. Colin Brenan, founding CEO of BioTrove, becomes Chief Technology Officer and Senior Vice President, Research and Engineering Development.

Ellis has more than 29 years of experience in analytical and biotechnology instrumentation and prior to joining BioTrove held senior executive positions at Affymetrix and Applied Biosystems. While at Applied Biosystems, he led the marketing of the first automated DNA sequencer, which has generated over US$1 billion dollars in sales since its introduction. His new role will involve guiding the commercialization of BioTrove's micro- and nano-scale products in molecular biology.

Enrico Petrillo, a member of BioTrove's Board of Directors, commented: 'As BioTrove transitions from an R&D focus to commercializing its core technologies, Bob is an ideal person to lead the process.'

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