Glucose uptake was measured in all subjects at the beginning and end of the study. Those randomized to the chromium supplement had a mean increase in insulin sensitivity of 8.9%, whereas the placebo group showed a mean decrease of 3.6%.

Importance of the findings

The researchers tied in their results to recent findings about the molecular biology of chromium picolinate. Previously, it had been suggested that the supplement increases the phosphorylation of the protein Akt. This intracellular enzyme is activated by insulin and facilitates the uptake of insulin into cells. The researchers found that insulin-stimulated Akt activation was significantly increased at the end of the study compared with placebo measurements. No adverse side effects were observed. Cefalu commented on the relevance of this finding. 'As this intracellular pathway is implicated in contributing to insulin resistance, this represents a possible mechanism to explain chromium picolinate's beneficial effect on insulin sensitivity as observed in several clinical studies,' he said.

Despite the small number of patients in the study, the findings could be important. John Vincent, an expert on chromium biology from the University of Alabama (http://www.ua.edu) and not connected with this study, commented on the significance. 'Any information on the mechanism by which chromium may positively affect metabolism is potentially quite valuable, both in terms of the scientific community in understanding the role of this poorly understood potential nutrient and in attempting to develop therapeutic agents for the treatment of type 2 diabetes.' However, he called attention to the fact that the study did not address whether the effects are unique to chromium picolinate, or whether other chromium supplements, for example, chromium chloride, might also be effective.

References

1 Anderson, R.A. *et al.* (1997) Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes. *Diabetes* 46,1786–1791

2 Cefalu, W.T. *et al.* (1999) Effect of chromium picolinate on insulin sensitivity *in vivo*. *J Trace Elem. Exp. Med.* 12, 71–83

3 Anderson, R.A. (1998) Chromium, glucose intolerance and diabetes. *J. Am. Coll. Nutr.* 17, 548–555

4 Cefalu, W.T. *et al.* (2003) Chromium picolinate supplementation increases insulin-stimulated Akt phosphorylation *in vivo* in skeletal muscle from subjects with Type 2 diabetes. *18th International Diabetes Federation Congress* 24–29 August, Paris, France (Abstract No. 154)

News in brief

Targets and Mechanisms

Survival tactics

Two cell types have been found to adapt in the absence of oxygen, enabling them not only to survive but also to become 'tougher' [1,2]. Researchers at the Medical College of Georgia (http://www.mcg.edu/) removed the oxygen supply from tubular cells of the kidney (through which the body's entire fluid volumes flows) and found that some of these cells appear to adapt by up-regulating two genes, IAP-2 and Bcl-xL. When the genes are knocked out, the sensitivity of the cells to injury returns.

Zheng Dong, co-author of the reports, believes that this response enables the cells to survive ischaemic stress, giving them a chance to repair the injured kidney. He explains that some cancer cells show similar adaptation, as a tumour grows too big for its oxygen supply, although probably not via the same route; as Dong explains, 'they simply become stronger, tougher and more resistant to injury, and for those in tumours, more resistant to cancer therapies'.

The work details how a poorly understood protein, Bax – which is usually found in the cytosol – moves into mitochondria in a hypoxic cell, where it perforates the membrane and, thus, acts pro-apoptically. However, in resistant cells, membrane accumulation of this molecule is suppressed and IAP-2 was induced in the cytosol.

The work could ultimately lead to gene therapy, where survival genes, such as IAP-2 and Bcl-xL, can be up-regulated in ailing cells (e.g. in cardiovascular disease or diabetes) and down-regulated in proliferating cells, such as cancer cells. Dong is optimistic; 'hopefully, we can identify some therapeutic tool that is either genetic or pharmaceutical, to switch these as needed'.

1 Dong, Z. *et al.* (2003) Apoptoisis-resistance of hypoxic cells. *Am. J. Pathol.* 163, 663–671

2 Yi, X. *et al.* (2003) Inhibition of Bid-induced Apoptosis by Bcl-2. tBid insertion, Bax translocation and Bax/Bak oligomerization suppressed. *J. Biol. Chem.* 278, 16992–16999

New turn-ons for T-cells

A newly developed retroviral gene-delivery system has been implemented in the discovery of novel immunoregulators [3]. Researchers from Rigel Pharmaceuticals (http://www.rigel.com/) observed that, when transfected with certain lymphoid-derived genes, T-cells failed to activate. This could aid in the development of drugs that target the immune response.

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The T-cell constitutes an important arm of the immune response. Their roles stretch from stimulating antibody production from B-cells and playing an integral part of the inflammatory response, to directly eliminating infected cells. Although T-cell functions are initiated through the T-cell receptor, it is the downstream signalling elements that determine the final immune response. The team, led by Charlene Liao, found that proteins possessing previously unknown immunomodulatory properties were those encoding signalling molecules for other pathways, such as EDG-1 and PAK-2. In addition, a newly characterized protein, TRAC-1, was found to be expressed specifically within lymphoid and haematopoietic tissues.

Up until now, finding these signalling molecules has been a slow process. This new technique has the power to highlight possible signalling molecules where no prior sequence information has been recorded, meaning that searches are not biased towards previously known components of signalling pathways. The authors are confident that their approach, 'provides a tool for functional cloning of regulators in numerous signal transduction pathways'.

The identification of the molecules that regulate T-cell activation is an important step in understanding how immune responses are regulated and, ultimately, towards the development of therapeutic agents to target this process.

3 Chu, P. *et al* (2003) Systematic identification of regulatory proteins critical for T-cell activation. *J. Biol.* 2, 21 (http://jbiol.com/content/2/3/21)

Kamikaze pathogens: a new resistance to antibiotics

Researchers at the University of Wisconsin-Madison (UW-M; http://www.pharmacy.wisc.edu/) have discovered a new way in which harmful pathogens can resist destruction by antibiotics – by self-sacrifice [4].

Scientists have long known that harmful bacteria have been able to resist antibiotic treatment by employing a variety of defence mechanisms. This latest discovery, however, which suggests that some pathogens are also capable of self-sacrificing to resist antibiotics, is a further blow for scientists. Jon S. Thorson, Professor of Pharmacy at UW-M and senior author of the paper, suggests that: 'It is a new paradigm for resistance, it points to the fact that bacteria continue to find new routes to evade drugs'.

This discovery was made while investigating a class of anti-tumour antibiotics known as enediynes, which work by shredding DNA and disrupting the ability of a cell ,such as a cancer cell, to function and reproduce. With only a few molecules required to destroy a cell, these are considered as one of the most potent forms of naturally occurring antibiotics.

Soil bacteria can secrete a protective buffer of enediyne that is inhospitable to

Cancer Targets and Mechanisms

How aggressive tumours keep the blood flowing

An important feature of aggressive melanomas is the ability to mimic vasculogenic cells and build an intra-tumour vascular network. Cancer biologists and a cardiologist have now joined forces to look at the mechanisms behind this vasculogenic mimicry. They have identified genes involved in initiating tumour vasculogenesis and in ensuring that the resulting vessels are kept blockage-free [5], suggesting new ways in which aggressive tumours could be treated.

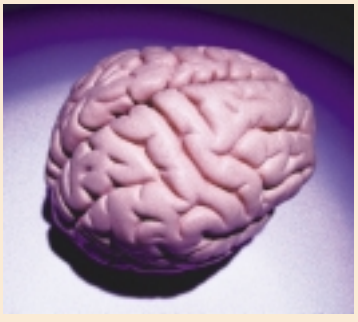
Cancer biologists led by Mary Hendrix at the University of Iowa (UI; http://www.uiowa.edu/) and cardiologist Robert Weiss, also at UI, began by comparing the gene and protein expression profiles of highly and poorly aggressive melanomas. They found that aggressive cells specifically upregulate three factors that are active in normal vasculogenic endothelial cells: the pro-coagulant tissue factor (TF), and the TF-pathway inhibitors (TFPI) 1 and 2.

Using function-blocking antibodies, the team showed that TFPI-2 is necessary for vasculogenic mimicry *in vitro*. When poorly aggressive melanoma cells were cultured on a matrix containing TFPI-2, they became more like vasculogenic, aggressive melanoma cells. TPFI-1 inhibited the pro-coagulant activity of TF in aggressive melanomas, suggesting that it acts after initial vasculogenesis to ensure that blood can flow freely through the intra-tumour networks.

'This is yet another example of the plasticity of aggressive melanoma tumour cells in that they can mimic other cell types, such as endothelial cells, and our study provides a mechanistic example of how they do it', says Hendrix. '…it also provides new insights on how we might target them more effectively.'

5 Ruf, W. *et al*. (2003) Differential role of tissue factor pathway inhibitors 1 and 2 in melanoma vasculogenic mimicry. *Cancer Res.* 63, 5381–5389

From brain to breast



New research has highlighted a neural survival factor, dermcidin (DCD), as a candidate oncogene in breast cancer. This could explain how certain breast cancers grow rapidly and tenaciously – they could be borrowing a survival strategy from brain cells.

DCD encodes a secreted protein that is normally only expressed in the pons of the brain and the sweat glands (not the breast), enhancing the survival and growth of certain brain cells while shielding them from damage. New research from Kornelia Polyak's group at the Dana-Farber Cancer Institute (http://www.dfci.harvard.edu/) has found that DCD is overexpressed in ~10% of invasive breast carcinomas and that its expression is associated with advanced clinical stage and

competing microbes. However, this toxic environment can also overwhelm the host bacteria itself. In these situations, it has been observed that bacterium releases a

protein that deflects the harmful enediyne before it can locate and destroy the DNA of the organism.

Instead of cleaving DNA, the enediyne cleaves the protein and thereby inactivates itself, 'says Thorson. 'By detonating its 'warhead' to cleave the protein instead of the DNA, the cell is preserved. It is somewhat inefficient, but at least the cell survives.' Thorson argues that this new mechanism might not be unique to the enediyne-producing bacteria and suggests that this mechanism will also most likely be found in other organisms.

This finding could shed light into a different mechanism of antibiotic resistance and, with further research, could aid in the quest to fight these harmful microorganisms.

4 Biggins J.B. *et al.* (2003) Resistance to enediyne antitumour antibiotics by CalC self-sacrifice. *Science* 301, 1537–1541

Viral Targets and Mechanisms

Protecting women from HIV

A potentially novel way to prevent HIV infection in women has recently been highlighted. Commensal bacteria, primarily lactobacilli, which colonize the cervico–vaginal mucosa, have been genetically enhanced to provide potent antiviral activity. 'Enhancing bacteria that already colonize humans is a completely new strategy to combat viral invasion', says Peter Lee, main researcher in the study.

Heterosexual contact is the predominant mode of HIV transmission worldwide and the cervico–vaginal mucosa is the main portal of entry in women. Therefore, this new research by a team at Stanford University School of Medicine (http://www-med.stanford.edu/school/) could prove to be

poor prognosis [6]. In some cases, this overexpression is also coupled with a focal copy number gain of its locus at 12q13.1.

DCD expression in breast cancer cells promotes cell growth and survival, and putative high- and low-affinity receptors for DCD are present on the cell surface of breast carcinomas and neurons of the brain [6]. The DCD protein also contributes to cachexia, which is a muscle-wasting and weight-loss condition that afflicts many cancer patients. 'It appears that the same substance that is beneficial in the case of nerve cells can play a harmful role in the development of certain breast cancers', says Polyak.

The response to DCD, whether in the brain or in the breast, is triggered when a chemical signal docks at receptors on the surface of cells. Current research is assessing the ways of blocking these receptors in breast cancer, which might slow tumour growth, or, in the case of Alzheimer's disease or stroke patients, might stimulate them to protect nerve cells from death. 'DCD's role in a variety of different disorders makes it an attractive target for new therapies', says Polyak.

6 Porter, D. *et al.* (2003) A neural survival factor is a candidate oncogene in breast cancer. *Proc. Natl. Acad. Sci. U. S. A.* 100, 10931–10936

Killer protein helps breast cancer prognosis

New research has shown that the protein EZH2, which has already been linked to prostate cancer, is also involved in breast cancer. Furthermore, it could also help us identify just how dangerous the tumours might be.

In this new study, led by researchers from the University of Michigan Comprehensive Cancer Center (http://www.umich.edu/), it was observed that EZH2 appears to help cancer cells invade adjacent tissue and form colonies [7]. This makes the protein crucial for aggressive, metastatic forms of breast and prostate cancer, both of which are regulated by steroid hormones.

However, copies of this protein can easily be detected in cancerous tissue. The researchers found that the levels of EZH2 in a patient's tumour were consistent with the severity of the tumour; the more EZH2 that was present, the more severe the cancer and the worse the outcome for the patient.

Celine G. Kleer, Assistant Professor of Pathology at the U-M Medical School and lead author of the paper, says: 'EZH2 may serve as an excellent biomarker for determining a breast cancer patient's prognosis more precisely than current methods.' The use of an EZH2 test as a clinical tool is still years away; however, the U-M team are planning a prospective clinical trial to test its use in breast cancer patients.

If things go well, the EZH2 test could join other tests that physicians currently use to determine how aggressively to treat breast cancer patients. However, like all previous tests that have been considered, these tests do not give a precise prognosis.

Kleer says: 'If our work is confirmed through carefully controlled clinical trials, testing for EZH2 would be a relatively straightforward and feasible way to judge a patients prognosis and help determine her best course of treatment. She suggests that, 'for tens of thousands of women a year, that could mean a lot'.

7 Kleer, C.G. *et al.* (2003) EZH2 is a marker of aggressive breast cancer and promotes neoplastic transformation of breast epithelial cells. *Proc. Natl. Acad. Sci. U. S. A. 10.1073*/pnas.1933744100 (http://www.pnas.org)

crucial in providing an urgently needed female-controlled approach to blocking HIV transmission [8].

The researchers have engineered natural human vaginal isolates of *Lactobacillus jensenii* to secrete two-domain CD4 proteins [x]. Lactobacillus provides some protection against vaginal HIV transmission because those women with little or no lactobacillus have a higher risk of contracting HIV and other sexually transmitted diseases than those with high levels of the bacteria. The two-domain CD4 proteins also give the bacteria an extra boost because HIV attaches first to CD4 on the target cell and could prevent virus entry.

The genetically engineered strain significantly inhibited the ability of HIV to infect cells [8]. However, the bacteria produce acid that kills cells, which makes testing this strategy in cell models difficult. There is also not a good animal model of vaginal HIV transmission, although initial studies using monkeys showed that the engineered bacteria grew well and were safe. Future research is obviously required to test the therapy in humans.

Eventually this research could lead to the creation of a small vaginal suppository that could be used regularly by women, providing ongoing protection. The technology could also be applied to other viruses, such as the herpes virus or the common cold. 'It would be as discreet as can be,' added Lee, Assistant Professor of Medicine at Stanford.

8 Chang, T.L-Y. *et al.* (2003) Inhibition of HIV infectivity by a natural human isolate of *Lactobacillus jensenii* engineered to express functional two-domain CD4. *Proc. Natl. Acad. Sci. U. S. A.* 10.1073/pnas.1934747100 (http://www.pnas.org/)

Miscellaneous

Antimicrobial strategy inspired by nature

Scientists have developed many clever ways to destroy bacteria, but nature beat them to it billions of years ago in the form of the bacteriophage. New research has examined the mechanisms that bacteriophage use to inhibit bacterial growth, and exploited the findings to identify new small-molecule inhibitors [9].

Bacterial resistance to drugs is one of the most pressing problems for the pharmaceutical industry. To stay one step ahead of the pathogen, researchers are constantly on the lookout for new bacterial proteins, and novel drugs to block such targets. Now, researchers from PhageTech (http://www.phagetech.com/) have disclosed a fresh source of ideas, homing in on the bacterial proteins that are targeted by bacteriophages.

The team sequenced the genomes of 43 phages that target three human pathogens, *Streptococcus pneumonias*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. By using functional genomics strategies, they identified various antimicrobial proteins produced by the bacteriophages. These proteins were then used as 'bait', to screen for their cognate bacterial targets. The screen revealed several novel bacterial proteins that are important for microbial growth. Small molecules that can block these proteins might form the basis of effective antibiotics.

The team has identified candidates and are preparing to evaluate these in animals. Jinzi Wu, Vice President of PhageTech, summed up the findings; 'By taking advantage of what we have learned from nature, we have developed a technology platform that should enable PhageTech to play an important role in the battle against increasing antibiotic resistance worldwide.'

9 Research presented at the *43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy*. 14–17 September 2003, Chicago, Illinois, USA (http://www.icaac.org)

From tiny libraries, great leads grow

At 2036 molecules, it is not the largest library in the world. But a new collection of biologically active compounds punches above its weight, thanks to its trenchant annotation [10].

Whereas many libraries are no more than the sum of their parts, a concept from researchers at the Whitehead Institute (http://www.wi.mit.edu/) adds much greater depth. An algorithm annotates every biological activity that each of the molecules is experimentally verified to undertake – up to 12,000 per compound. According to the leader of the research team, Brent Stockwell, the technique 'gives scientists greater and more immediate insight into the molecules they study'.

To test the concept, the library was screened for compounds that could inhibit or prevent tumour growth in a line of cells derived from lung cancer tumour samples. A surprisingly high number, 85, showed some such capability. By cross-referencing the annotated information for each of these compounds, the team was able to identify common features of the inhibitors.

This cache of shared properties pointed to 12 new inhibitory targets that could be of interest in cancer research. Impressively, the results took just over a week to acquire, as opposed to the several years of study that would have been needed with traditional methods.

The system is highly flexible; David Root, a co-author of the paper, outlined the possibilities for expansion. 'Our annotation system automatically culls the literature,' he said. 'As more information is published, the profile of the compound will be adjusted.'

10 Root, D.E. *et al.* (2003) Biological mechanism profiling using an annotated compound library. *Chem. Biol.* 10, 881–892

News in brief was written by *Matt Brown, Anthony Li, Morag Robertson, Karl Smart, Georgina Smyth* and *Heather Yeomans*