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News in brief

Targets and mechanisms

Halting the spread of bowel cancer: a new target

Although Src has long been known as a cancer-causing molecule, until now, scientists were unsure how it was involved in the disease. While studying colon cancer, a research team from the Cancer Research Campaign Beatson Laboratories in Scotland (http://www.vet.gla.ac.uk/beatson/) has discovered how this molecule helps cancer to spread through the body. Their work was recently published in *Nature Cell Biology* [1].

The scientists report that in colon cancer cells Src becomes over-active and causes the normal tissue structure to break down. Src sends out signals for the removal of E-cadherin – a molecule that is required to hold cells together – and also works with integrins to form a looser type of tissue structure that allows cancer cells to move and spread. 'We've now found that the molecule triggers several different chemical signals in a variety of ways', said Professor Margaret Frame who headed the research team, 'Designing drugs to intercept these signals could be an important way of preventing bowel cancer from spreading'.

1 Avizienyte, E. *et al*. (2002) Src-induced de-regulation of E-cadherin in colon cancer cells requires integrin signalling *Nat. Cell Biol*. 4, 632–638

Burning off those extra calories

Excessive calorific intake can lead to obesity, but scientists at Beth Israel Medical Center (BIMC; http://www.bethisraelny.org) have provided a new explanation as to how the brain can adjust the body's metabolic rate to prevent extra calories from turning into extra pounds.

When the body takes in more calories than it needs, the excess can be either stored as fat – leading to weight gain – or converted to heat, which is subsequently dissipated. This diet-induced thermogenesis (or heat production) is controlled by the brain and has been assumed to have an important role in preventing obesity. A new study published in *Science* [2], researchers have been able to provide an explanation as to how this happens.

It was thought that diet-induced thermogenesis takes place via the sympathetic nervous system when the β-adrenoceptors (βARs) act on thermogenically active target tissues to prevent weight gain. By creating a group of knockout mice lacking all three known βARs (β-less mice), the authors tested the hypothesis that βARs have a key role in diet-induced thermogenesis. A comparison of β-less mice and control mice fed on identical diets showed that those lacking the βARs grew massively obese when fed on a high-fat diet. Both the β-less and wildtype mice ate the same amounts, but because the β-less group could not expend the extra calories they grew fat. The authors conclude that βARs are not only necessary for the process of diet-induced thermogenesis, but that this process has a crucial role in preventing obesity. Using this approach it should be possible to discern other parts of the system, which could lead to the identification of mutations that cause obesity in humans and could aid the search for anti-obesity drug targets.

2 Bachman, E.S. *et al*. (2002) βAR signaling required for diet-induced thermogenesis and obesity resistance. *Science* 297, 843–845

New protein linked to aggressive breast cancers

Scientists have discovered a new form of a protein that is associated with aggressive forms of cancer, including breast cancer [3]. This naturally occurring, short form of metastatic tumour antigen 1 (MTA1s) is an important discovery that could improve the prognosis of cancer patients.

Approximately 60% of breast cancers are classified as estrogen receptor (ER)-positive, responding to signals from estrogen through its receptor. These patients typically respond well to hormonal treatment such as tamoxifen, which blocks the estrogen signals responsible for cancer cell growth. However, most tumours eventually stop responding to hormone therapy and become more aggressive. When ERs can no longer be found in the nucleus of cancer cells, the cancer is termed 'hormone independent' and alternative therapies must be tried.

MTA1 is known to contribute to the transformation of breast cancer tumours to more aggressive forms by interacting with the ER in the nucleus. However, MTA1s was found to intercept the ER in the cytoplasm and prevent it from making its way to the nucleus.

A team at M.D. Anderson Cancer Center (http://www.mdanderson.org/) found that MTA1s levels are fourfold higher in tumours classified as ER-negative by conventional methods. Moreover, they found that these cells actually contain ERs, but that they are trapped in the cytoplasm by MTA1s. 'Currently, pathologists look for ER in the nucleus of cancer cells,' said Rakesh Kumar, who led the research team. 'If they don't find it there, they classify the tumour as ER negative. However, some percentage of those tumours actually may have the functional ER that is being sequestered in the cytoplasm by MTA1s. Currently, there is no way to distinguish between cells with no or low ER in the nucleus and those with ER sequestered in the cytoplasm'.

It has been impossible, so far, to restore estrogen responsiveness to breast cancer cells once it is lost. However, the new protein, MTA1s, contains a previously unknown sequence of 33 amino acids with an ER-binding motif. Deleting this motif was found to restore nuclear localization of the ER.

'The finding demonstrates that it may be possible to restore ER responsiveness to breast cancer cells. Since we have defined at least one of the mechanisms that is responsible for retaining the ER in the cytoplasm, it should be possible to find a small molecule to compete it out,' says Kumar. The discovery holds great promise for longer effective treatment of breast cancer in the future.

3 Kumar, R. *et al.* (2002) A naturally occurring MTA1 variant sequesters oestrogen receptor-α in the cytoplasm. *Nature* 418, 654–657

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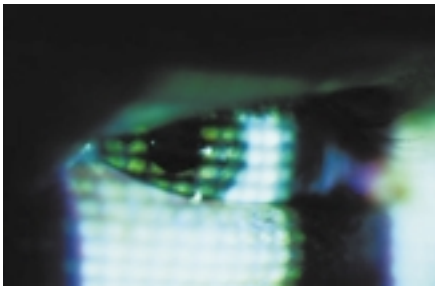
Miscellaneous

One in the eye for angiogenesis



Researchers have found how to form new blood vessels in the eye using adult bone marrow stem cells [4]. This technique could be used to deliver chemicals into the eye that could prevent the formation of new blood vessels and could also stimulate vessel growth and treat ocular diseases resulting from abnormal angiogenesis.

The study, at The Scripps Research Institute (TSRI; http://www.scripps.edu), involves injecting stem cells into the eye. Martin Friedlander, leader of the study at TSRI, said: 'We have shown that the cells can incorporate into the [degenerating] vasculature and make it normal. And when loaded with antiangiogenics, they can selectively wipe out the formation of new blood vessels.'

The group selected pluripotent stem cells that differentiate into endothelial cells. Vascularization in both age-related macular degeneration and diabetic retinopathy involves the concerted action of endothelial cells and astrocytes, which act as a template for vessel formation. Friedlander and colleagues found that they could target activated astrocytes with stem cells *in vivo*, and then tested the stem cells in a mouse model of ocular disease. In the disease model, the stem cells differentiated into endothelial cells and proliferated, forming new blood vessels that were actually able to rescue the vessels that were degenerating.

The team also discovered that angiogenesis could be shut down by transfecting stem cells with an angiogenesis inhibitor – a fragment of human tryptophanyl-tRNA synthetase (T2-TrpRS). These cells expressed the protein at the back of the eye and prevented development of new retinal blood vessels without affecting vessels that were already present. This could lead to a therapeutic approach to treat a variety of ocular diseases.

4 Otani, A. *et al.* (2002) Bone marrow-derived stem cells target retinal astrocytes and can promote or inhibit retinal angiogenesis. *Nat. Med.* 10.1038/nm744 (epub ahead of print; http://www.nature.com/nm/)

Morphine: no pain *and* no gain?

Morphine might actually promote tumour growth [5], according to researchers at the University of Minnesota (UMN) Cancer Center (http://www.cancer.umn.edu/). They have found that the drug can stimulate signals in endothelial cells, causing tumours to grow in mice. Morphine is routinely given to cancer patients to manage severe pain, but before this study, little was known about how it might affect blood vessels or cancer.

Kalpna Gupta, an Assistant Professor at UMN's Department of Medicine, and colleagues found that doses of morphine similar to those given to cancer patients activate the mitogen-activated protein kinase (MAPK) signalling pathway in human endothelial cells, which has a key role in cell proliferation and angiogenesis. Furthermore, morphine was found to activate the survival signal PKB/Akt, inhibit apoptosis, and promote cell cycle progression by increasing the amount of cyclin D1. These effects of morphine were proven to actually promote tumour neovascularization in a human breast tumour xenograft model and led to tumour progression.

These findings suggest that the clinical use of morphine could be potentially harmful in patients with angiogenesis-dependent tumours, and further studies will be needed to see whether morphine and other opiates lead to increased tumour growth in humans.

5 Gupta, K. *et al.* (2002) Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. *Cancer Res.* 62, 4491–4498

Can bananas reduce the risk of stroke?

A low intake of potassium in your diet could increase your susceptibility to stroke, according to a US study [6].

Researchers followed 5600 men and women from four different communities for a period of four to eight years. They were all over the age of 65 years and were free of stroke when the study began. The number and types of stokes that occurred were recorded.

Bananas are a good source of potassium, as are avocados, citrus fruits and green leafy vegetables. Individuals with low intakes of potassium in their diet (defined as <2.4 g per day) were 1.5-times more likely to have a stroke than those with high intakes of potassium (defined as >4 g per day).

The study also looked at the role that diuretics (used to treat illnesses such as high blood pressure, congestive heart failure and kidney disease) had on the risk of stroke because they can rob the body of potassium. Individuals with low blood

potassium levels also taking diuretics were 2.5-times more likely to have a stroke than those taking diuretics with high blood potassium levels.

'Diuretics clearly help prevent stroke by controlling high blood pressure, but we wanted to see whether their effect on potassium levels would affect the isk of stroke,' said Deborah Green from the Queen's Medical Center (http://www.queens.org) and one of the study authors. She went on to stress that the results of the study do not imply that diuretics increase the risk of stroke. 'The question is whether diuretics would be even more effective with adequate potassium intake.'

The researchers say that further study is needed to determine whether increasing potassium intake can prevent strokes.

6 Green, D. *et al.* (2002) Serum potassium level and dietary potassium intake as risk factors for stroke. *Neurology* 59, 314–320

Better treatment for breast and prostate cancers

A potent experimental drug has been identified that slows tumour growth in both breast and prostate cancer tumours, even when only low levels of HER-2/neu are expressed [7]. The discovery of 2C4, which is more effective than Herceptin, could lead to improved treatment for breast and prostate tumours.

Herceptin, a drug currently used to treat breast cancer, targets HER-2/neu, a cell-surface protein expressed in cancer cells; growth factors signal the protein to stimulate tumour growth. However, Herceptin is less effective in patients whose cancer cells over-express HER-2/neu.

The team at the Cedars-Sinai Comprehensive Cancer Center (http://www.csccc.com) evaluated the effectiveness of 2C4 both in cell lines established in culture and in human tumours grown in mice. Unlike Herceptin, 2C4 disrupts communication between members of the HER family of proteins, HER-2 and HER-3, and between epidermal growth factor receptors (EGFR) and HER-2.

'We found that 2C4 not only targeted HER-2/neu, but that it disrupted cell signalling among the entire HER family of proteins,' said David Agus, Research Director at the Cedars-Sinai Prostate Cancer Center, and leader of the study.

Mice with tumours expressing both high and low levels of HER-2/neu were injected with either Herceptin or 2C4. Results showed that Herceptin and 2C4 are equally effective when high levels of HER-2/neu are expressed, reducing tumour growth by 77% and 80%, respectively. However, Herceptin failed to slow cancer growth in tumours expressing low levels of HER-2/neu, whereas 2C4 inhibited growth by 59%.

'These findings suggest that 2C4 may work in breast cancers that do not express large amounts of HER-2/neu, which may ultimately mean that we can treat more patients with breast cancer,' said Agus.

The research team also investigated the effectiveness of 2C4 in testosterone-independent prostate tumours. These tumours become resistant to treatment, but still express low levels of HER-2/neu. Results showed that 2C4 reduced tumour growth by 82%, whereas no reduction in tumour size was achieved in mice treated with Herceptin. 'The potential of a biological agent, such as 2C4, to treat advanced prostate cancer is exciting, as there are presently few alternatives for treatment in these patients,' said Agus.

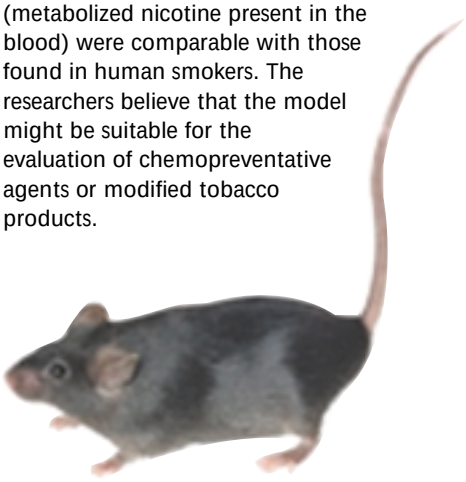
A Phase I clinical trial is currently under way at Cedars-Sinai Medical Center to evaluate the safety and tolerability of 2C4 in patients with advanced cancers of the prostate, breast, ovary, lung and colon, and other solid tumours.

7 Agus, D.B. *et al.* (2002) Targeting ligand-activated ErbB2 signaling inhibits breast and prostate tumor growth. *Cancer Cell* 2, 127–137

Mice with a vice

Research into the carcinogenic properties of tobacco smoke has been hampered by the lack of an effective animal model. Now, a new study has reported results from a mouse model that compare well with data from humans [8].

Hanspeter Witschi of the Center for Health and Environment (http://che.ucdavis.edu) and co-workers used Balb/c and SWR mice in their studies. The animals were exposed to tobacco smoke for 6 h per day, 5 days per week for five months, at an average concentration of 122 mg m^{-3} of total suspended particles. After a four month recovery period, both strains showed an increase in lung tumour multiplicities, with the data from the SWR mice being statistically significant. Combined with previous data from A/J mice, a good correlation was found between exposure and lung-tumour multiplicities. Levels of plasma cotinine (metabolized nicotine present in the blood) were comparable with those found in human smokers. The researchers believe that the model might be suitable for the evaluation of chemopreventative agents or modified tobacco products.



8 Witschi, H. *et al.* (2002) A mouse tumour model of tobacco smoke carcinogenesis. *Toxicol. Sci.* 68, 322–330

Kamikaze cancer cells

New research has shown that cancer cells can be induced to 'commit suicide', thus preventing their spread [9]. This research, by scientists at the Hebrew University of Jerusalem (http://www.huji.ac.il), involves using an engineered virus that 'tricks' the cancer cells into behaving in a way that is similar to those under attack.

In normal cells that are attacked by a virus, the replication of RNA results in the activation of a protein. This protein is a double-stranded RNA-dependent protein kinase (PRK), which is a potent growth inhibitory protein that causes cell destruction and prevents viruses from spreading. Graduate student Alexei Shir and his supervisor Alexander Levitzki devised a strategy to trick the cancer cells into activating PKR without activating it in non-cancerous cells.

This was achieved by the engineering of a virus from the same family as HIV, which was then introduced into cancer cells. The virus triggers PKR activation in cancer cells and induces them to die without harming normal cells when directed against a virulent form of brain tumour. This represents a breakthrough compared with current chemotherapy treatments, which are not specific for cancer cells alone.

Levitzki said that other students of his are now adapting this strategy to lymphoma and leukaemia but stresses that a great deal of laboratory and clinical work still remains to be done before this technique can be used in the treatment of cancer.

9 Shir, A. and Levitzki, A. (2002) Inhibition of glioma growth by tumor-specific activation of double-stranded RNA-dependent protein kinase PKR. *Nat. Biotechnol.* DOI 10.1038/nbt730 (epub ahead of print: http://www.nature.com)

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