WEB WATCH

Meeting of minds

- http://www.cancer-researchuk.org/

Those of us in the United Kingdom cannot have failed to notice that its two leading cancer research charities — the Imperial Cancer Research Fund and the Cancer Research Campaign — have merged to form Cancer Research UK. The merging of their web sites is proof that two heads are better than one.

The front page is aimed squarely at the general public, with news, information on fundraising events and prominent links to patient resources. But a large 'science and research' button at the top of the page takes cancer researchers straight to the information that's most relevant to them.

Navigation within this 'science wing' is through five tabs. The 'researchers' section is a simple directory, searchable by name, keyword or free text. Information on individual researchers and their projects varies in detail; it would be useful to have key publications for all of them. There's also a clickable map that takes you to Cancer-Research-UK-funded institutes and labs around the United Kingdom. The 'research institutes' section is presented as a hypertext-linked list, each institute taking you to a list of group leaders; clinical centres are presented similarly but, unfortunately, are not yet clickable.

Cancer Research UK now awards an almost bewildering array of grants; these are organized into broad categories in the Grants application section, and sufficient information is given for you to work out whether you're eligible and when you should apply; forms are not available on the web, but there is information on how to send for application packs.

Finally, in the enigmatic 'other sites' section, don't miss the links list; this tracks cancer research across the globe, making it a useful resource for all cancer researchers.

Cath Brooksbank

GENOMIC INSTABILITY

Defective division

Centrosomes are frequently amplified in cancer cells, and this amplification has been proposed to contribute to tumorigenesis because cells with several spindles are genomically unstable. But what is the mechanism of amplification? Patrick Meraldi *et al.* report in *The EMBO Journal* that centrosome amplification is a consequence, rather than a cause, of defective division.

Overexpression of the mitotic kinase Aurora-A — which occurs in many cancers — causes centrosome amplification. Both wild-type Aurora-A and a kinase-dead (KD) mutant caused an increase in centrosome number when overexpressed in CHO cells, indicating that the kinase activity is not required for centrosome duplication. Addition of hydroxyurea (HU) — a drug that blocks cells in S phase, thereby allowing multiple rounds of centrosome duplication without DNA replication — also increased the percentage of cells with more than two centrosomes, but Aurora-A expression did not enhance this number above that of wild-type CHO cells.

So does Aurora-A induce centrosome amplification by mimicking HU and blocking cells in S phase? Overexpression of Aurora-A in HeLa cells — which are unable to duplicate their centrosomes during S-phase arrest — still increases centrosome number, but only in the absence of HU, indicating that Aurora-A overexpression does not induce S-phase arrest and that cells must pass through mitosis to increase their number of centrosomes.

Closer examination of the Aurora-A-overexpressing HeLa cells revealed that most cells (75%) with multiple centrosomes were also multinucleate, so could the increase in centrosome number be an indirect consequence of aberrant cell division? The number of multinucleate and tetraploid cells increases as Aurora-A is overexpressed, indicative of a cytokinesis defect. So can other defects that lead to an aberrant cytokinesis also cause centrosome amplification? Overexpression of the Aurora-B and PLK-1 mitotic kinases, which also result in multinucleate cells, leads to centrosome amplification, as does addition of the cytokinesis-inhibitory drug cytochalasin D.

TUMOUR SUPPRESSORS

More than meets the eye

Although most people don't think much of mucus, its important functions, such as lubricating the epithelia and protecting against infection, are undisputed. Recent findings, reported in the 1 March issue of *Science*, reveal a new function for this underappreciated substance — preventing the development of colorectal cancer.

A family of high-molecular-weight secreted glycoproteins known as mucins are a primary component of the mucus layer. So far, 13 different mucins have been discovered (MUC1–13), and found to be expressed in different tissues. Alterations in mucin expression and glycosylation pattern have been observed in human colon cancer samples, and MUC2 — the most abundant gastrointestinal mucin — is reportedly downregulated in human colorectal carcinomas. Little is known, however, about MUC2 function at the molecular level.

To evaluate the role of MUC2 in tumorigenesis, Anna Velcich *et al.* created *Muc2*-null mice. *Muc2* is highly expressed by the mucus-producing goblet cells of the intestine. The authors found that *Muc2*-null mice did not develop recognizable goblet cells in any region of the intestine, and were therefore defective in mucus production. *Muc2*-null mice are able to digest food and absorb nutrients, as they gained weight at the same rate as their heterozygous and wild-type littermates. But 65% of *Muc2*-null mice developed gastrointestinal tumours by the time they are 1 year old. These tumours were found in the small and large intestine and rectum, but not in the stomach, where *Muc2* is not normally expressed.

So what is the function of Muc2 in the intestinal epithelium? Velcich *et al.* believe that Muc2 is involved in regulating cell proliferation and migration, as intestinal epithelial cells of *Muc2*-null mice had a higher proliferation:apoptosis ratio than those of wild-type epithelium, resulting in elongated crypts. *Muc2*-null epithelial cells also migrated faster in the intestinal mucosa than did wild-type cells — in mice injected with bromodeoxyuridine, labelled epithelial cells of *Muc2*-null mice migrated more rapidly to proximal regions of intestinal villi. Tumours

Loss of the tumour suppressor p53 is frequently associated with centrosome amplification, so how might this be related to the proposed mechanism of a defect in cell division? Perhaps centrosomes accumulate in p53-null cells because they are unable to respond appropriately — by arrest or apoptosis — to a defective division. Consistent with this, a 66% correlation was observed between the frequency of multinucleation and centrosome amplification in *Trp53*$^{-/-}$ mouse embryo fibroblasts (MEFs). Many of the mononucleate cells with more than two centrosomes also had large nuclei, indicating that they might be polyploid. Multinucleate *Trp53*$^{-/-}$ MEFs were also more likely to proceed through to S phase than multinucleate wild-type cells, and overexpression of the mitotic kinases caused centrosome amplification in 80% of *Trp53*$^{-/-}$ MEFs, compared with 25% of wild-type MEFs.

So defective cell division can result in tetraploid cells with a concomitant amplification of centrosomes. What is left to discover is whether this is the only mechanism of centrosome amplification in cancer cells, and the impact that centrosome amplification has on genomic instability and tumorigenesis.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Meraldi, P. M. *et al*. Aurora-A overexpression reveals tetraploidization as a major route to centrosome amplification in p53$^{-/-}$ cells. *EMBO J.* **21**, 483–492 (2002)

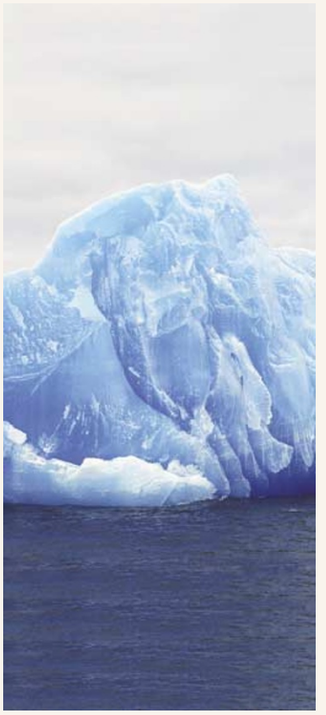
WEB SITE

Erich Nigg's lab:
http://www.biochem.mpg.de/nigg/projects.shtml

that developed in *Muc2*-null cells overexpressed c-*Myc*, a known regulator of cell proliferation, so Muc2 might somehow regulate the expression of this oncogenic transcription factor.

Inactivation of Muc2 therefore causes intestinal tumour formation, and is also required for normal goblet-cell formation and mucus production. Further experiments are required to determine whether tumour development in these mice is due to the absence of the lubricating effect of mucus, or alterations in the epithelial-cell signalling pathways that regulate cell proliferation.

Kristine Novak



References and links

ORIGINAL RESEARCH PAPER Velcich, A. *et al*. Colorectal cancer in mice genetically deficient in the mucin Muc2. *Science* **295**, 1726–1729 (2002)

WEB SITE

Leonard Augenlicht's lab:
http://sequence.aecom.yu.edu/bioinf/Augenlicht/default.html

IN BRIEF

THERAPEUTICS

Small-molecule antagonists of Myc/Max dimerization inhibit Myc-induced transformation of chicken embryo fibroblasts.

Berg, T. *et al*. *Proc. Natl Acad. Sci. USA* **99**, 3830–3835 (2002)

MYC–MAX heterodimers drive oncogenic transcription, so Thorsten Berg and colleagues searched for molecules that block this partnership, using a simple *in vitro* assay. The authors screened 7,000 compounds for a drop in energy transfer (FRET) between fluorescently labelled MYC and MAX proteins. Two compounds inhibited the transformation of chick fibroblasts, as well as blocking MYC–MAX interaction.

GENOMIC INSTABILITY

Disruption of *Brca2* increases the spontaneous mutation rate *in vivo*: synergism with ionizing radiation.

Tutt, A. N. J. *et al*. *EMBO Rep.* **3**, 255–260 (2002)

Do mammography and radiotherapy pose an additional cancer risk for women with *BRCA2* mutations? A mouse model that combines a *Brca2* truncation mutation (*Brca2*^{Tr}) with a reporter gene that allows measurement of spontaneous mutation has been used to show that *Brca2*$^{Tr/Tr}$ mice have more spontaneous and ionizing-radiation-induced mutations than wild-type mice. Mutation rates in *Brca2*$^{Tr/+}$ mice and wild-type mice are similar, indicating that *BRCA2*-mutation carriers are not at increased risk from radiation exposure.

TUMOUR SUPPRESSORS

Induction of p57^{KIP2} expression by p73β.

Bálint, E. *et al*. *Proc. Natl Acad. Sci. USA* **99**, 3529–3534 (2002)

The transcription factor p73 acts similarly to its homologue p53 in its ability to induce cell-cycle arrest and apoptosis. But, despite their ability to activate expression of many of the same genes, their functions are distinct — only p73 is involved in normal growth and development. Éva Bálint *et al.* now show that the p73β isoform activates *CDKN1C*, which encodes the cyclin-dependent kinase inhibitor KIP2, and *KvLQT1*, both of which reside in an imprinted region of the genome and are involved in development.

SIGNALLING

Vascular endothelial growth factor (VEGF)-C signaling through FLT-4 (VEGFR-3) mediates leukemic cell proliferation, survival, and resistance to chemotherapy.

Dias, S. *et al*. *Blood* **99**, 2179–2184 (2002)

Leukaemia cells release pro-inflammatory cytokines and pro-angiogenic factors in autocrine loops that promote leukaemic-cell growth and migration. A vascular endothelial growth factor family member, VEGFC, has similar effects: VEGFC treatment induces receptor phosphorylation, proliferation and increased survival in leukaemia cells *in vitro*. Moreover, VEGFC protects the cells against the apoptotic effects of three chemotherapeutic agents, so it might be involved in cancer-drug resistance.