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)

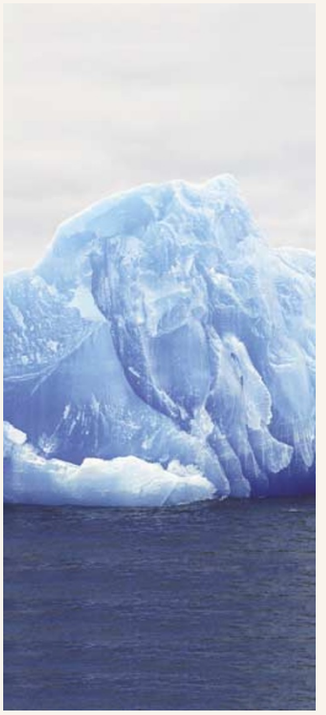
WEB SITE

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.