IN THE NEWS

Brain drain

A year on from the successful merger of the Imperial Cancer Research Fund (ICRF) and Cancer Research Campaign (CRC), Cancer Research UK (CR-UK) has hit its first stumbling block. The chief executive, Sir Paul Nurse — former Director General of ICRF and 2001 Nobel Prize winner — is leaving to become President of Rockefeller University.

For Sir Paul, this will be a move back towards his first love, science, as running CR-UK — Britain's largest charity, with a US $400 million budget — obviously took up much of his time. Rockefeller are also delighted to have him on board — the board unanimously approved Nurse to the position following an international search. The Chairman of the board, Richard B. Fisher, said that he "is the ideal leader for Rockefeller University", being "an eminent scientist with an exceptional record as the CEO of a major research institution" (*Newsday.com*).

But what will become of CR-UK? The problem is that the position requires a unique combination of talents — scientific expertise and management skills. "The trouble is that great boffins don't usually make great managers and great managers are not known for their scientific prowess" (*The Guardian,* 3 February 2003).

Ian Gibson, former scientist and labour MP, has suggested that CR-UK should try to appoint Sir David Lane, Ninewells Hospital and Medical School, Dundee, but Delyth Morgan, Chief Executive of Breakthrough Breast Cancer, said that if he doesn't take it CR-UK might have to look to America.

Either way, "it's essential that it [CR-UK] has strong leadership, not just for them but for the whole cancer research community", said Delyth Morgan (*The Guardian*).

Emma Greenwood

GENOMIC INSTABILITY

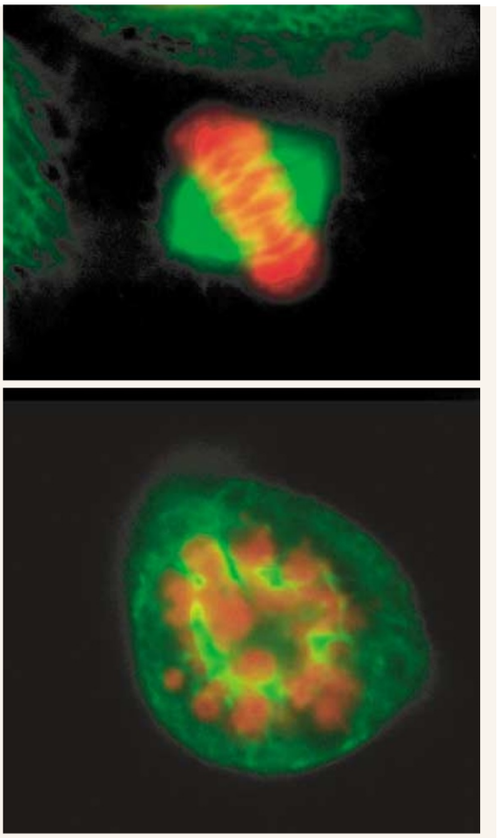
Dangerous division

Cell division is a dangerous business — every chromosome kinetochore must attach to the mitotic spindle for the two chromatids to be segregated correctly to opposite poles of the cell. The integrity of this process is carefully monitored by the spindle-assembly checkpoint, and it has been suggested that a defective checkpoint could lead to aneuploidy, as found frequently in human cancer. However, mutations in the checkpoint genes *BUB1*, *BUBR1* and *MAD2* are rarely found. Ashok Venkitaraman and colleagues now suggest that cancer cells might use an alternative mechanism for deregulating the checkpoint — amplification of *AURORA-A*.

The AURORA-A serine-threonine kinase is overexpressed in a significant number of epithelial cancers, often as a result of gene amplification. A similar protein in budding yeast — Ipl1 — regulates the attachment of chromosomes to the mitotic spindle. Reasoning that this process might become dysregulated if AURORA-A were overexpressed, the authors created mouse embryo fibroblasts or human HeLa cells in which AURORA-A was overexpressed to similar levels as found in human cancers. They found that this causes several abnormalities in mitosis that are consistent with defects in chromosome-spindle attachment. Chromosomes fail to align at the metaphase plate in 59% of mitoses, and 11% of cells have abnormal, often multipolar, spindles to which chromosomes do not properly attach (see figure).

Usually, problems with spindle attachment would be expected to activate the spindle checkpoint, leading to arrest at the metaphase–anaphase transition. The authors tested checkpoint activation by examining the localization of the MAD2 protein. This protein normally remains at the kinetochores as long as the checkpoint is active in metaphase, but is re-distributed when the checkpoint is switched off to let cells enter anaphase. However, the authors found that MAD2 behaves abnormally when AURORA-A is overexpressed in HeLa cells. It remains at the kinetochores in 80% of cells in anaphase, when it should have disappeared, indicating that anaphase occurs despite the continued activation of the spindle checkpoint.

As noted previously by several laboratories, one consequence of AURORA-A overexpression is the accumulation of polyploid cells. Could this be related to the spindle checkpoint problems that are induced by increased AURORA-A expression? The authors show that after passing through anaphase, cells that overexpress AURORA-A complete nuclear division, but not cytokinesis, leading to multi-nucleation and polyploidy. But co-expressing a mutant BUB1, which inactivates the spindle checkpoint, alleviated these defects, indicating that they are, indeed, linked to the ability of AURORA-A to 'override' the checkpoint at the metaphase–anaphase transition.



Spindle formation is defective when *AURORA-A* is overexpressed. The top panel is the control image; the bottom panel is with overepxression of *AURORA-A*. DNA is stained red and microtubules are stained green. Image provided with kind permission from © Cell Press (2003).

Cancer chemotherapeutics such as paclitaxel (Taxol) induce metaphase arrest and apoptosis because they interfere with microtubule dynamics and hence the mitotic spindle. So, does *AURORA-A* amplification affect the response to this drug? Interestingly, overexpression of AURORA-A causes an increase in the resistance to paclitaxel-induced apoptosis, indicating that it might contribute to drug resistance in cancer patients who have this amplification.

So, *AURORA-A* amplification — a frequent occurrence in human tumours — can contribute to genomic instability by interfering with correct kinetochore attachment to the spindle and activation of the spindle checkpoint. The mechanism by which this occurs is unclear at present, but the implication of this result for cancer treatment by paclitaxel certainly warrants further investigation.

Emma Greenwood

References and links

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FURTHER READING Jallepalli, P. V. & Lengauer, C. Chromosome segregation and cancer: cutting through the mystery. *Nature Rev. Cancer* **1**, 109–117 (2001)

WEB SITE

Ashok Venkitaraman's lab: http://www.hutchison-mrc.cam.ac.uk/Venkitaraman.html