IN THE NEWS

Nobel achievement

The 2001 Nobel Prize for Physiology or Medicine has been awarded to three scientists for their "seminal discoveries at the molecular level of how the cell is driven from one phase to the next in the cell cycle," (CNN.com, 8 October 2001).

The joint winners of this prestigious award are Leland H. Hartwell, professor of medicine at the University of Washington, Seattle for his discovery of checkpoints; and R. Timothy Hunt and Sir Paul M. Nurse from the Imperial Cancer Research Fund, UK, for their discoveries of cyclins and cdc2, respectively.

"Findings from their research are about to be applied to the development of tests for cancer and may lead to new cancer therapies, according to the Nobel Assembly," reported *The New York Times* (9 October 2001).

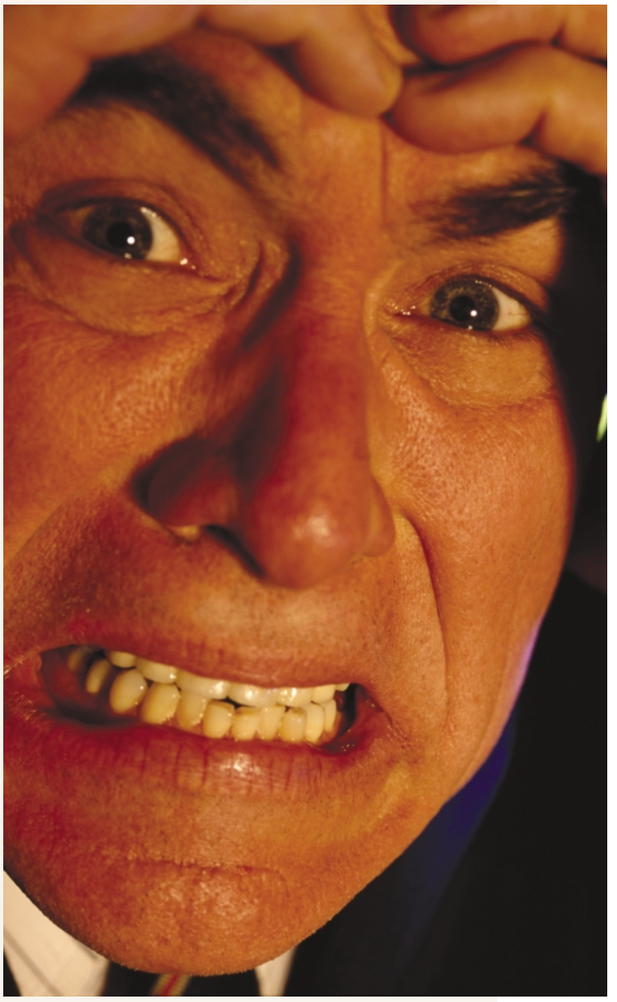
But this is also a victory for 'blue-sky' research, wrote *The Guardian*. "It is yet another justification for spending money on pure research which doesn't have any obvious outcome when it is embarked upon. Practically every major breakthrough, from Darwin's discovery of evolution to X-rays, lasers and microwaves has been sparked by curiosity-driven research without pecuniary motives," (10 October 2001).

The scientists will receive their award plus a share of the $943,000 prize in a ceremony in December, which marks the 100th anniversary of the first prizegiving. As to how he will spend the money, Nurse revealed to *Reuters* that he plans to research another kind of cycle. "I know it's the male menopause — but I do have my eye on a motorbike," (8 October 2001).

Simon Frantz

CHAPERONES

Stress relief



Being a chaperone is all about escorting your charges away from any sign of trouble before you can administer your tender, loving care. And it seems this might also be the case for the biochemical equivalent, according to a study by Nollen and colleagues in *Proceedings of the National Academy of Sciences.*

They found that the molecular chaperone Hsp70 is not only involved in the holding and refolding of heat-unfolded nuclear proteins but it also drives them to the nucleolus during stress. Escorting damaged proteins to one location in the nucleus might prevent random aggregation of thermolabile proteins, which will allow their refolding under the permissive conditions and prevent indirect damage to other nuclear components, say the authors.

Under normal growth conditions, molecular chaperones and proteases are responsible for the quality control of protein structure and function. Molecular chaperones prevent the aggregation — and enable refolding — of unfolded proteins, whereas proteases eliminate irreversibly damaged proteins.

However, if cells are subjected to stress, such as heat shock, the amount of unfolded proteins increases markedly, and this can lead to the formation of protein aggregates if the chaperone levels are not raised too. In response to this, cells rapidly activate the synthesis of heat-shock proteins, which function as molecular chaperones to repair the protein damage and also to provide protection against any subsequent stress.

One of the major heat-shock proteins is Hsp70. Much effort has gone into studying the biochemical activity and action of Hsp70 but very little is known about exactly where unfolded proteins are processed by Hsp70.

To investigate the whereabouts of Hsp70 during heat stress, the authors fused the heat-sensitive protein model luciferase (adapted for expression in the nucleus of mammalian cells) to the traceable fluorescent protein EGFP and followed its fate during and after heat stress by time-lapse analysis.

As expected, heat stress led to the accumulation of heat-unfolded luciferase. This occurred at multiple small foci throughout the nucleus, and was reduced by coexpression of Hsp70 during heat shock.

But interestingly, Nollen *et al.* found that the heat-unfolded N-luc-EGFP translocates to form large, insoluble foci during heat stress when Hsp70 was co-expressed; and immunofluorescence analysis showed that these foci colocalized with the nucleoli. Time-lapse analysis showed that when the cells were returned to the physiological growth temperature, protein translocation to the nucleolus returned to normal and was reactivated in an Hsp70-dependent manner. Abolishing chaperone activity in a carboxy-terminal deletion mutant of Hsp70(1–543) had no effect on the localization of N-luc-EGFP, which showed that the Hsp70 chaperone activity is needed for translocation.

Storage of unfolded proteins in the nucleolus during ongoing stress could have many advantages, say the authors. "Concentration of unfolded proteins at one locus in the nucleus will reduce damage because it will prevent their random aggregation with other nuclear proteins and macromolecular structures. Storage of unfolded proteins in the nucleolus will interfere with the assembly of ribosomes essential for protein synthesis. However, during ongoing stress, this may be beneficial because it will inhibit protein synthesis at its earliest step and, hence, limit the number of thermolabile nascent chains that could damage the cell further," they write.

Simon Frantz

References and links

ORIGINAL RESEARCH PAPER Nollen, E. A. A. *et al.* Dynamic changes in the localization of thermally unfolded nuclear proteins associated with chaperone-dependent protection. *Proc. Natl Acad. Sci.* USA 2001 Sep 25 [epub ahead of print]

FURTHER READING Pirkkala L. *et al.* Roles of the heat shock transcription factors in regulation of the heat shock response and beyond. *FASEB J.* **15**, 1118–1131 (2001)

WEB SITE Harm Kampinga's laboratory: http://www.oprit.rug.nl/kampinga/webpage7.htm