IN THE NEWS

Max Perutz 1914–2002

Max Perutz, one of the great figures in molecular biology, died of cancer on 6 February 2002 at the age of 87. The importance of his work in the development of molecular biology can never be overestimated and his discoveries still remain the foundation of current research.

Perutz pioneered the use of X-ray crystallography to study the structure of proteins, and he shared the Nobel Prize for Chemistry in 1962 with John Kendrew for his work on identifying the structure of haemoglobin. He was Chairman of the Laboratory of Molecular Biology in Cambridge, which has been home to nine Nobel prize-winners since the 1950s, perhaps the most famous being James Watson and Francis Crick.

"Not only have his colleagues lost a great co-worker and friend, but Britain and the world will be mourning the loss of one of the 20th Century's scientific giants", said Professor Sir George Radda, Chief Executive of the UK's Medical Research Council (BBC News Online, 7 February 2002). "He has inspired countless young scientists. He will be sorely missed, but his life and work will continue to shape science", Radda added. (The New York Times, 7 February 2002).

Although he officially retired in 1979, Perutz's appetite for research never waned. He still worked almost every day in the lab, and submitted his last scientific paper for publication just before Christmas 2001. This work, on the structure of the glutamine repeats in Huntington's disease, is now in press in the *Proceedings of the National Academy of Sciences*.

Simon Frantz

APOPTOSIS

Grim, reaper and the sickle of death

In 1994, a fly strain was discovered that is essentially defective in developmental cell death. This strain bears a homozygous genomic deletion (called H99). Three genes — *reaper*, *hid* and *grim* — were subsequently identified that map to this deletion, and regulate programmed cell death by similar mechanisms. Now, reporting in *Current Biology*, three laboratories have identified Sickle, a fourth homologue in *Drosophila melanogaster*, that seems to act in parallel with Reaper and Grim.

Reaper, Hid and Grim not only map close together, but they are also structurally related. The homology is limited to the amino-terminal 10–15 amino acids, and to a 30-amino-acid region called the 'Trp block'. The three proteins also function by a similar mechanism — they regulate the activity of caspases, the effector enzymes of cell death, by relieving the repression of caspases by the 'inhibitor of apoptosis' (IAP) proteins. It seems that Reaper, Hid and Grim compete with

caspases for binding to IAPs; a function that requires the presence of the conserved amino terminus.

sickle was identified on the basis of its homology to reaper-family genes with respect to sequence, chromosomal location and expression. The *sickle* gene maps to chromosome 3L, just proximal to the *reaper* gene, and it is responsive to γ -radiation, as is the case for *reaper*. *sickle* expression is essentially restricted to specific regions of the head and central nervous system in developing *Drosophila* embryos, in areas where *reaper* and *grim* have been reported to be expressed. This suggests that Sickle might functionally interact with Reaper and Grim to regulate cell death in the central nervous system.

All three groups found that Sickle can induce cell death when overexpressed in mammalian or insect cells, and the Alnemri lab saw

ectopic cell death when Sickle was overexpressed in *Drosophila* embryos. But as *sickle* is expressed in H99 mutants, which are largely defective in programmed cell death, it seems that its expression at physiological levels is not sufficient to induce cell death in most cell types. Indeed, unlike Reaper or Grim, when ectopically expressed in the *Drosophila* eye, Sickle alone was unable to induce cell death, but it did enhance Reaper- or Grim-induced cell death. Like other Reaper-family proteins, however, the Sickle gene product has a conserved amino-terminal end and a Trp block. Induction of apoptosis by Sickle is dependent on this conserved amino terminus, and it is inhibited by caspase inhibitors and IAPs.

How does Sickle regulate Reaper- and Grim-induced death? Does it simply contribute to titrating out

Image courtesy of E. Lalli and K. Ohe.

RNA SPLICING

New feat for Sox

DNA-binding Sox (SRY box) proteins are important during development; many are expressed in a tissue-specific manner. Sassone-Corsi and colleagues now report that Sox proteins are also involved in pre-messenger RNA (pre-mRNA) splicing.

The authors showed that SOX6 is expressed diffusely in the nucleoplasm, but is concentrated in nuclear speckles. Such localization resembles that of components of the pre-mRNA splicing machinery. Moreover, the authors showed that SOX6 co-localizes with splicing factors and U small nuclear RNAs in the speckles, and that blocking splicing caused SOX6 and SRY to redistribute in the

IAPs? And what is Sickie's actual function *in vivo*? More insight into the genetic interaction between *sickle* and other cell-death-regulating genes in *Drosophila* is required to address these questions.

Two proteins that seem to be functional homologues of Reaper-like proteins have recently been identified in mammals. These proteins — Smac/DIABLO and Omi/HtrA2 — also bear the conserved amino-terminal motif. However, their expression pattern and subcellular localization seem to be different from those of the *Drosophila* Reaper-like proteins, so further work is needed to establish whether they are true homologues.

Valerie Ferrer, Associate Editor,
Nature Cell Biology

References and links

ORIGINAL RESEARCH PAPERS Srinivasa, M. *et al.* *sickle*, a novel *Drosophila* death gene in the reaper/hid/grim region, encodes an IAP-inhibitory protein. *Curr. Biol.* **12**, 125–130 (2002) | Wing, J. P. *et al.* *Drosophila* sickle is a novel grim-reaper cell death activator. *Curr. Biol.* **12**, 131–135 (2002) | Christich, A. *et al.* The damage-responsive *Drosophila* gene sickle encodes a novel IAP binding protein similar to but distinct from reaper, grim, and hid. *Curr. Biol.* **12**, 137–140 (2002)

WEB SITES

Emad Alnemri's laboratory:
<http://www.kcc.tju.edu/staff/alnemri/>
John Nambu's laboratory:
<http://www.bio.umass.edu/biology/faculty/jnambu.phtml>
John Abrams' laboratory:
http://www.swmed.edu/home_pages/cellbio/dw/abrams%20people.html

enlarging speckles.

This indicated that Sox proteins might be directly involved in splicing, which the authors then showed to be the case — splicing was inhibited and spliceosomal complexes failed to form in SOX6-depleted nuclear extracts. However, adding back recombinant SOX6, SRY or SOX9 restored splicing in a dose-dependent manner, confirming a role in pre-mRNA splicing.

As Sox proteins have unusual DNA-binding properties, there is every possibility that they can bind and bend RNA too. By doing so, they could then facilitate the rearrangements that occur during splicing.

Katrin Bussell

References and links

ORIGINAL RESEARCH PAPER Ohe, K., Lalli, E. & Sassone-Corsi, P. A direct role of SRY and SOX proteins in pre-mRNA splicing. *Proc. Natl Acad. Sci. USA* **99**, 1146–1151 (2002)

ONCOGENES

Dancing the two-step

Regulation by protein degradation has become a recurring theme in cancer biology: several oncoproteins, including β -catenin, are controlled by being targeted for degradation. But biological control is seldom as simple as it seems. In *EMBO Reports*, Frank Staal and colleagues reveal that phosphorylation, not degradation, might be the key to regulating β -catenin's activity.

β -catenin leads a double life: it's a component of epithelial junctions but also a coactivator of the TCF family of transcription factors. Cell proliferation is stimulated by β -catenin-mediated induction of TCF's targets, and β -catenin levels are normally kept in check by a 'destruction complex' containing the APC tumour-suppressor protein and GSK3 β . The accepted view is that phosphorylation of β -catenin by GSK3 β allows it to be recognized by a second complex that conjugates β -catenin with ubiquitin. The physiological switch that blocks β -catenin's destabilization is the extracellular signalling molecule Wnt, which indirectly prevents β -catenin from being phosphorylated by GSK3 β .

But is simply increasing the level of β -catenin sufficient to drive transcription of TCF-target genes? To find out, the authors blocked β -catenin degradation using a proteasome inhibitor and measured the transcription of TCF-target genes using a reporter construct. Surprisingly, stabilizing β -catenin did not increase transcription of the reporter gene.

The authors reasoned that dephosphorylation of β -catenin might be needed not just to protect it from destruction, but also to activate its function as a transcriptional coactivator. So they measured levels of dephosphorylated β -catenin under four different conditions, and found that dephosphorylation of β -catenin was indeed required for its activation.

Cath Brooksbank, Editor,
Nature Reviews Cancer

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ORIGINAL RESEARCH PAPER Staal, F. J. T. *et al.* Wnt signals are transmitted through N-terminally dephosphorylated β -catenin. *EMBO Rep.* **3**, 63–68 (2002)

ENDOCRINOLOGY

Time to relax

The hormone relaxin favours the growth and remodelling of reproductive tissues during pregnancy. But despite the fact that relaxin was one of the first reproductive hormones to be identified, its receptor has remained undiscovered. Hsu and colleagues now report in *Science* that they have matched up the lonely hormone with the orphan receptors LGR7 and LGR8.

Although relaxin is structurally related to insulin, some data indicated that it might bind to a G-protein-coupled receptor (GPCR) instead of a tyrosine-kinase receptor. So, the authors tested whether any of the orphan leucine-rich GPCRs (LGRs) might be the missing relaxin receptor.

They expressed LGR7 or its relative LGR8 (which was discovered based on GenBank searches for genes with similar structure to glycoprotein hormone receptors) in cells and found that relaxin could indeed increase cyclic AMP levels in these cells in a dose-dependent manner, whereas it had no effect on cells that did not express these receptors. Crosslinking analysis showed that relaxin can bind to the extracellular domain of LGR7. Moreover, the soluble extracellular domain of LGR7 inhibited the effect of relaxin on cells. This inhibition was also observed *in vivo*, as pregnant mice treated with the extracellular domain of LGR7 had a delayed birth and reduced nipple size.

But the two receptors are expressed in many tissues, indicating that relaxin is far more versatile than just a pregnancy hormone. This is consistent with studies in humans, which have shown that, among other functions, relaxin is also important for cardiac function and for the formation of new blood vessels.

In rats, mice and other model organisms, relaxin functions during late pregnancy, when it promotes growth and dilation of the cervix, growth and quiescence of the uterus, and growth and development of the mammary gland and nipple. So, the authors suggest that the development of agonists and antagonists for its newly discovered receptors might help to solve problems related to preterm labour and delivery. In humans, however, as Richard Ivell points out in an accompanying Perspectives article, relaxin peaks during the first term of pregnancy, and is probably involved in implantation of the fetus. Whatever the exact function of relaxin, it is safe to say that the discovery of its receptors is bound to accelerate research on this versatile hormone.

Raluca Gagescu

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FURTHER READING Ivell, R. This hormone has been relaxin' too long. *Science* **295**, 637–638 (2002)