IN THE NEWS

The 'kiss of death' prize
Aaron Ciechanover, Avram Hershko and Irwin Rose have been awarded the Nobel Prize in Chemistry 2004 for "…helping to understand how the human body gives the 'kiss of death' to rogue proteins to defend itself from diseases like cancer" (*Reuters*, 6 October 2004).

These scientists — the former two from Israel, the latter from the US — discovered ubiquitin-mediated protein degradation, a process in which 'doomed' cellular proteins are marked for destruction by the addition of a ubiquitin tag.

"What the three scientists found 'started out as a simple biochemical curiosity,' said Keith Wilkinson, an Emory University biochemist. 'It has turned out to be of profound importance in understanding the regulation of the cell.'" (*The Seattle Times*, 7 October 2004).

"The protein-destroying process the scientists discovered was completely unexpected, because scientists had thought such destruction was not regulated, said Lars Thelander, a member of the Nobel Committee for Chemistry. Thelander said researchers now hope they will be able to manipulate the protein degradation system in two different ways — either to prevent it from destroying proteins that boost the immune system, or to get rid of proteins that help cause diseases." (*The Washington Post*, 6 October 2004).

This is the first time that a Nobel science prize has been awarded to Israeli scientists. Ciechanover said, "It is more the honor for Israel, for myself, that a small country can make it." And, as for the prize money, "I have never thought of money; we earn very small salaries in Israel," he said (*Reuters*, 6 October 2004).

Rachel Smallridge

EPIGENETICS

Nuclear reprogramming

The gene-expression pattern of a somatic cell nucleus undergoes a marked change when it is injected into growing *Xenopus laevis* oocytes, and this change occurs in the absence of DNA replication or cell division. So, how, exactly, is a somatic cell nucleus reprogrammed? Simonsson and Gurdon asked whether DNA demethylation might be involved, as DNA methylation is epigenetically stable and is reversed only during gametogenesis, in early embryos and other specific situations. They report their results in *Nature Cell Biology*.

They started out by injecting mouse thymus nuclei into *X. laevis* oocytes, and found that it was four days before murine *oct4* — a gene that is usually only expressed in pluripotent cells — was transcribed. By contrast, injecting deproteinized nuclei resulted in *oct4* expression within two days, and *oct4* transcription occurred immediately after the injection of unmethylated DNA. So, in the absence of repressive proteins, *oct4* transcription is still delayed, which indicates that DNA demethylation — or some other modification — might be required for transcription to proceed.

Simonsson and Gurdon obtained direct evidence for DNA demethylation by analysing the *oct4* promoter region. They found that when mouse thymus nuclei were injected into *X. laevis* oocytes, specific sites within the *oct4* promoter were selectively demethylated. Furthermore, they showed that this demethylation preceded *oct4* transcription.

To simplify further analyses, the authors created plasmid DNA constructs that contained different regions of the *oct4* promoter, plus a reporter gene. They methylated these constructs at specific sites *in vitro* and, after their injection into *X. laevis* oocytes, tested how this methylation affected demethylation and transcription. They found that the demethylating activity of *X. laevis* oocytes modified these plasmids in the same way that it modified whole nuclei and genomic DNA, which indicates that this activity functions locally and independently of the rest of the mouse genome. In addition, they showed that demethylation occurred when DNA replication and RNA/protein synthesis were inhibited.

Next, Simonsson and Gurdon examined the sequence requirements for DNA demethylation. First, they found that mutating known transcription-factor-binding sites in the *oct4* promoter disrupted both the demethylation and transcription of *oct4*, which indicates a requirement for transcription-factor binding. Second, they fortuitously discovered an unusual methylation site at position –166 that must be demethylated for transcription to proceed. When this was the only methylated site on the plasmid, it could not be demethylated and transcription could not proceed. Demethylation of this site required the presence of other methylated sites on the same DNA, which might be needed to recruit the demethylating activity that then functions in *cis*.

The demethylating activity identified here is interesting because it is selective, and functions in the absence of DNA replication and RNA/protein synthesis. So, although the significance of this activity of *X. laevis* oocytes is not yet clear, this work indicates that "…the selective demethylation of promoter DNA may be a general mechanism required for the reprogramming of somatic cell nuclei."

Rachel Smallridge

References and links

ORIGINAL RESEARCH PAPER Simonsson, S. & Gurdon, J. DNA demethylation is necessary for the epigenetic reprogramming of somatic cell nuclei. *Nature Cell Biol.* **6**, 984–990 (2004)
FURTHER READING Fujita, N. & Wade, P. A. Nuclear transfer: epigenetics pays a visit. *Nature Cell Biol.* **6**, 920–922 (2004)
WEB SITE
John Gurdon's laboratory: http://www.welc.cam.ac.uk/groups/gurdon.html