How do mutations in the various insulin signalling pathways contribute to increased longevity? The papers discuss the possible connections between fertility and life span and also between environmental stress and life span. The conservation of these insulin signalling pathways means that these connections can now be investigated further in not one, but at least three, model systems.

Alison Mitchell

References and links
ORIGINAL RESEARCH PAPERS Clancy, D. J. *et al.* Extension of life-span by loss of CHICO, a *Drosophila* insulin receptor substrate protein. *Science* **292**, 104–106 (2001) | Tatar, M. *et al.* A mutant *Drosophila* insulin receptor homolog that extends life-span and impairs neuroendocrine function. *Science* **292**, 107–109 (2001) | Fabrizio, P. *et al.* Regulation of longevity and stress resistance by Sch9 in yeast. *Science* **292**, 288–290 (2001)
FURTHER READING Strauss, E. Growing old together. *Science* **292**, 41–43 (2001)
Guarente, L. & Kenyon, C. Genetic pathways that regulate ageing in model organisms. *Nature* **408**, 255–262 (2001)

synthesized DNA after ultraviolet treatment of the cells. They then narrowed down the reason for this association, and showed that p300 is involved in DNA repair. This role was supported by the observation that p300 also binds XPA, another DNA repair factor.

The authors propose that, as an acetyltransferase, p300 "might change the structure of the chromatin adjacent to DNA lesions, inducing chromatin changes that facilitate PCNA function and DNA repair synthesis, although the p300 complex is unlikely to affect DNA synthesis directly".

Together, these papers add to the transcriptional repertoire of p300 and CBP, indicating that they have more diverse functions in the cell, including DNA repair and protein stability, both of which might contribute to their role as tumour suppressors.

Alison Schuldt

References and links
ORIGINAL RESEARCH PAPERS
Ito, A. *et al.* p300/CBP-mediated p53 acetylation is commonly induced by p53-activating agents and inhibited by MDM2. *EMBO J.* **20**, 1331–1340 (2001) | Hasan, S. *et al.* Transcription coactivator p300 binds PCNA and may have a role in DNA repair synthesis. *Nature* **410**, 387–390 (2001)

PROTEOLYSIS

Cleavage mystery comes to N-end

In 1986, Alexander Varshavsky and colleagues proposed the 'N-end rule', according to which a protein can be earmarked for degradation by the nature of the amino-acid residue at its amino-terminal (N) end. Fifteen years on, Varshavsky and collaborators now describe the first physiological substrate of the N-end rule pathway. Reporting in *Nature* they show that cleavage of SCC1 — a subunit of the cohesin complex, which holds sister chromatids together — generates a fragment that is degraded in an N-end-dependent manner.

The defining feature of an N-end rule substrate is a 'destabilizing' residue at its amino terminus. In yeast and other eukaryotes, the substrate is then recognized by a component of the ubiquitin-conjugating machinery, Ubr1, and destroyed by the ubiquitin–proteasome system. Arginine — a strongly destabilizing residue — is found at the amino terminus of the main SCC1 cleavage fragment, leading Varshavsky and colleagues to investigate the fate of this fragment.

Dipeptides bearing a destabilizing amino-terminal residue can block degradation by the N-end rule pathway *in vivo* — this is just what the authors saw for the SCC1 fragment.

They next engineered in a stabilizing residue at the amino terminus of the SCC1 fragment, and found that overexpression of this variant was toxic to the cell. Given that cleavage of SCC1 is normally required for sister-chromatid separation, might the failure to destroy the SCC1 fragment lead to chromosomal instability? To test this the authors studied *ubr1Δ* cells, which lack the N-end rule pathway, and observed a much higher than normal frequency of chromosome loss. And finally, they confirmed that this effect was indeed due to stabilization of the SCC1 cleavage fragment.

Alison Mitchell

References and links
ORIGINAL RESEARCH PAPER Rao, H. *et al.* Degradation of a cohesin subunit by the N-end rule pathway is essential for chromosome stability. *Nature* **410**, 955–959 (2001)

IN BRIEF

OXYGEN SENSING

HIF-α targeted for VHL-mediated destruction by proline hydroxylation: implications for O_2 sensing.

Ivan, M. *et al. Science* **292**, 464–468 (2001)

Targeting of HIF-α to the von Hippel–Lindau ubiquitylation complex by O_2-regulated prolyl hydroxylation.

Jaakkola, P. *et al. Science* **292**, 468–472 (2001)

Hypoxia-inducible factor (HIF) is a transcriptional complex that regulates gene activity in response to levels of O_2 — when O_2 is present, HIF is destroyed by a complex involving the VHL protein. These papers show that the HIF–VHL interaction is regulated by hydroxylation of a proline residue on the HIF-1α subunit, suggesting that proline hydroxylation could be key in cellular responses to O_2.

DEVELOPMENT

Drosophila Rho-associated kinase (Drok) links Frizzled-mediated planar cell polarity signaling to the actin cytoskeleton.

Winter, C. G. *et al. Cell* **105**, 81–91 (2001)

The Frizzled (Fz)/Dishevelled (Dsh) pathway mediates planar cell polarity. But how does it regulate cytoskeletal reorganization? Winter and colleagues now report that *Drosophila* Rho-associated kinase acts downstream of Fz/Dsh to phosphorylate nonmuscle myosin II and restrict F-actin bundle formation.

TECHNIQUE

Attomole level protein sequencing by Edman degradation coupled with accelerator mass spectrometry.

Miyashita, M. *et al. Proc. Natl Acad. Sci. USA* **98**, 4403–4408 (2001)

The limit for amino-terminal sequencing has just been pushed down to the low attomole level. The authors have increased the sensitivity of Edman sequencing by introducing accelerator mass spectrometry — a tandem spectrometry tool that counts rare atoms — as a detection system.

EXTRACELLULAR MATRIX

Extracellular matrix composition determines the transcriptional response to epidermal growth factor receptor activation.

Yarwood, S. J. & Woodgett, J. R. *Proc. Natl Acad. Sci. USA* **98**, 4472–4477 (2001)

Integrins transduce signals from the extracellular matrix (ECM) and modulate receptor tyrosine kinases. The authors used DNA arrays to monitor EGF-induced gene expression after attachment of cells to either laminin or fibronectin. Although expression of most genes was not influenced by the type of ECM, certain gene clusters responded differentially. This survey should be valuable for further analysis of the crosstalk between ECM and growth factor signalling.