CIRCADIAN RHYTHMS

Wrestling with time?

The relentless ticking of the clock leaves some of us struggling with our time keeping more than others, but, at the cellular level, our circadian clocks are finely controlled. Regulatory feedback loops that involve clock proteins preserve cellular circadian rhythmicity, and Paolo Sassone-Corsi and colleagues have now shown that regulation of a key clock protein, BMAL1 (brain and muscle aryl hydrocarbon receptor nuclear transporter (ARNT)-like protein-1), is likely to occur through modification with SUMO (small ubiquitin-like modifier).

BMAL1 and its binding partner CLOCK regulate the expression of genes that are involved in the circadian-clock mechanism, such as *PER1* (period homologue-1), through binding a regulatory DNA sequence known as the E-box. The BMAL1 protein has several lysine residues that are conserved among members of the same protein family as well as across species. And computer-modelling analysis shows that these residues closely match the consensus motif for sumoylation. Paolo Sassone-Corsi and colleagues found that BMAL1 is successfully sumoylated in COS1 cells, and showed by site-directed mutagenesis that K259 is the main *in vivo* sumoylation site.

Liver tissues were treated with an inhibitor of SUMO proteases to stabilize sumoylated proteins, and a sumoylated form of BMAL1 was detected, the abundance of which oscillates in a circadian manner. Phosphorylation of BMAL1 increases in parallel with its sumoylation and this also coincides with the induction of circadian-clock genes such as *PER1*.

Although CLOCK was known to mediate BMAL1 phosphorylation, the authors found that it also mediates BMAL1 sumoylation. But what is the function of BMAL1 sumoylation? In contrast to wild-type BMAL1, the levels of BMAL1(K259R) do not oscillate in a circadian manner. Moreover, BMAL1(K259R) is more than twice as abundant as its wild-type counterpart. So protein degradation is likely to have an important function in the control of BMAL1.

Bmal1$^{-/-}$ mouse embryonic fibroblasts have altered circadian oscillation of an E-box-controlled gene (*Dbp*). Virally expressed BMAL1 rescues the circadian oscillation of this gene, but expressing BMAL1(K259R) generates an altered, shorter period of *Dbp* rhythmicity.

So it seems that sumoylation has an important role in the circadian expression and function of BMAL1, which reveals a previously unknown facet of circadian-clock regulation. The authors suggest that future studies should look at identifying elements of the SUMO pathway that might be selective for circadian-clock components.

Lesley Cunliffe

References and links

ORIGINAL RESEARCH PAPER
Cardone, L. *et al.* Circadian clock control by SUMOylation of BMAL1. *Science* **309**, 1390–1394 (2005)

WEB SITE
Paolo Sassone-Corsi's lab: http://www.igbmc.fr/recherche/Dep_Trans/Eq_PSass/index.html

IN BRIEF

TELOMERES

The yeast Pif1p helicase removes telomerase from telomeric DNA.

Boulé, J.-B. *et al. Nature* 24 August 2005 (doi:10.1038/nature04091)

The Pip1 DNA helicase is a negative regulator of telomerase, and consequently of telomere maintenance, in budding yeast. The authors now show the biochemical basis of this inhibition — Pip1 reduces the nucleotide addition processivity of telomerase *in vitro* and requires its helicase function to remove telomerase from DNA ends both *in vitro* and *in vivo*. The released telomerase is enzymatically active as it can lengthen an oligonucleotide.

RNA

Regulation by *let-7* and *lin-4* miRNAs results in target mRNA degradation.

Bagga, S. *et al. Cell* **122**, 553–563 (2005)

MicroRNAs (miRNAs) that form imperfect duplexes with their targets are thought to inhibit protein expression without affecting the mRNA levels. However, this model has become controversial recently. Bagga *et al.* now present evidence that the *Caenorhabditis elegans* miRNAs *let-7* and *lin-4*, which each form imperfect duplexes with their target mRNAs, cause their degradation. So, these results argue against the simple model that mRNA fate depends entirely on the degree of base-pairing with a miRNA.

TRAFFICKING

Sar1p N-terminal helix initiates membrane curvature and completes the fission of a COPII vesicle.

Lee, M. C. S. *et al. Cell* **122**, 605–617 (2005)

Vesicles form through the concerted effort of protein coats, which capture the cargo proteins and induce membrane curvature. Secretory proteins move from the endoplasmic reticulum to the Golgi through COPII vesicles, which are coated with COPII proteins including Sar1. Lee and colleagues now show that Sar1, when bound to GTP, deforms synthetic liposomes into narrow tubules by inserting its N-terminal amphipathic α-helix into the membrane. Sar1 mutants that are defective in membrane budding recruit coat and cargo proteins as normal, so vesicle biogenesis is independent of coat and cargo recruitment.

METABOLISM

Increased dosage of mammalian Sir2 in pancreatic β cells enhances glucose-stimulated insulin secretion in mice.

Moynihan, K. A. *et al. Cell Metab.* **2**, 105–117 (2005)

The Sir2 family of NAD-dependent deacetylases has been linked to the regulation of metabolic processes and ageing in a number of organisms. The metabolic link is strengthened by a new study, in which the authors found that transgenic mice overexpressing the mammalian Sir2 orthologue, Sirt1, in pancreatic β cells display enhanced glucose-stimulated insulin secretion. Sirt1 regulates a number of genes that are involved in β-cell function, including *Ucp2*, which encodes a protein that negatively regulates insulin secretion from β cells — indeed, Ucp2 is downregulated in the transgenic mice.