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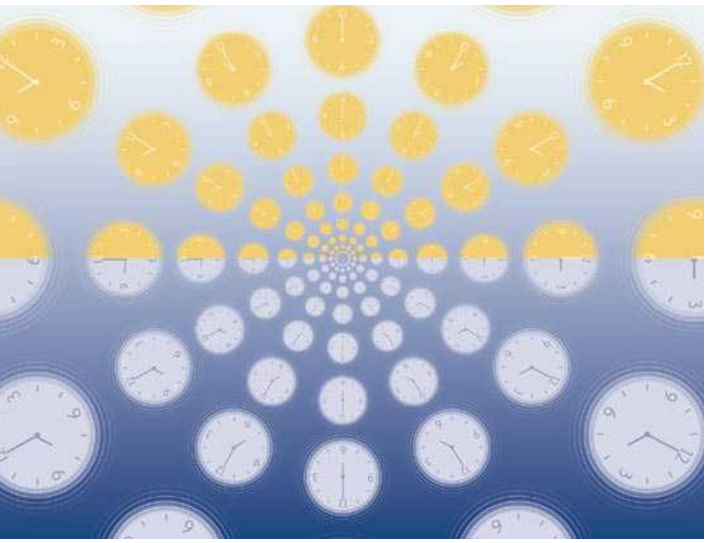
CIRCADIAN GENETICS

An enzymatic rheostat

> …SIRT1 transduces signals originating from cellular metabolites to the circadian clock.

The physiology and behaviour of mammals are subject to daily oscillations driven by an endogenous circadian clock. The circadian timing system is composed of a central pacemaker in the brain and subsidiary oscillators in most peripheral tissues. Although light–dark cycles are the predominant cue for the brain's pacemaker, cyclic feeding behaviour has a strong effect on clocks that operate in many other tissues. Reporting in *Cell*, two studies now suggest a strong molecular candidate for the long-sought link between metabolism and components of the internal clock that drive circadian rhythms.

The rhythm-generating mechanism is thought to rely on a feedback loop that involves the transcription factors BMAL1 and CLOCK, which activate the expression of *Period* (*Per*) and *Cryptochrome* (*Cry*) genes. When PER and CRY proteins accumulate to a critical level, they form complexes with BMAL1–CLOCK heterodimers and thereby repress transcription of their own genes.



Paolo Sassone-Corsi and colleagues have previously shown that CLOCK is an enzyme with histone acetyltransferase (HAT) activity. CLOCK also acetylates non-histone targets, such as its own dimerization partner BMAL1; this modification is essential for circadian function. If CLOCK is a HAT, the authors reasoned, then there must be a histone deacetylase (HDAC) that acts in the opposite manner. The sirtuin SIRT1 — best known for its potential anti-ageing properties — was the obvious candidate because of its dependence on NAD^+ (a factor that has been used as a read-out of metabolic state) and the fact that it preferentially deacetylates the same histone (histone H3) that CLOCK acetylates.

Sassone-Corsi and colleagues now show that the HDAC activity of SIRT1 is controlled in a circadian manner, correlating with the rhythmic acetylation of histone H3 and the clock component BMAL1 by CLOCK. Genetic ablation of the *Sirt1* gene or pharmacological inhibition of SIRT1 activity leads to disturbances in the circadian cycle and in the acetylation of histone H3 and BMAL1. Finally, using liver-specific SIRT1-mutant mice, Sassone-Corsi and colleagues showed that SIRT1 contributes to circadian control *in vivo* — increased BMAL1 acetylation and altered circadian expression of *Cry* and *Per2* genes was observed in the livers of the mutant mice. In a second paper, the group of Ueli Schibler report on another facet of the SIRT1-circadian clock connection. In agreement with Sassone-Corsi's team, these authors showed that SIRT1 associates with the CLOCK–BMAL1 complex but Schibler's group reported that SIRT1 promotes the deacetylation and degradation of PER2, an essential component for both core clock function and the synchronization of circadian oscillators.

It's been a dogma for years that the circadian clock is regulated by transcription feedback loops. These studies now highlight the importance of another loop — an enzymatic one — and indicate that SIRT1 transduces signals originating from cellular metabolites to the circadian clock.

Ekat Kritikou, Senior Editor,
Nature Reviews Molecular Cell Biology

ORIGINAL RESEARCH PAPERS Nakahata, Y. *et al.* The NAD^+-dependent deacetylase SIRT1 modulates CLOCK-mediated chromatin remodeling and circadian control. *Cell* **134**, 329–340 (2008) | Asher, G. *et al.* SIRT1 regulates circadian clock gene expression through PER2 deacetylation. *Cell* **134**, 317–328 (2008)
FURTHER READING Gallego, M. & Virshup, D.M. Post-translational modifications regulate the ticking of the circadian clock. *Nature Rev. Mol. Cell Biol.* **8**, 139–148 (2007)