CIRCADIAN RHYTHMS

Setting the clock

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URLs

CLOCK: http://ca.expasy.org/uniprot/O15516

BMAL1: http://ca.expasy.org/uniprot/O00327

Traditional clocks have always been associated with a winding mechanism. Sassone-Corsi and colleagues now show that nothing has changed — CLOCK, a key component in the machinery that controls our circadian rhythmicity, regulates the winding of chromatin and the circadian expression of proteins by functioning as a histone acetyltransferase (HAT).

Based on studies in mouse liver and hypothalamus, it has been suggested that the transcription of up to 10% of mammalian genes might be under circadian control. Circadian control is effected by a molecular machinery that consists of a network of transcription- and regulation-based feedback loops. The transcription factor CLOCK heterodimerizes with BMAL1 to modulate the expression of negative-feedback proteins and a number of circadian-cycle-associated (clock) genes. Recently it was shown that the activation of CLOCK–BMAL1-controlled clock genes is correlated with the circadian cyclic modulation of histone acetylation levels.

Histone acetylation, a type of chromatin remodelling, modulates transcriptional activation by controlling the accessibility of gene loci and the winding of DNA around histones. HATs, the molecules that are responsible for histone acetylation, can be divided into families on the basis of sequence similarity. But, until now, there have been no direct mechanistic links between any members of a HAT family and the circadian molecular machinery.

Doi *et al.* first found that CLOCK and the MYST family of HATs share homology within their acetyl-CoA-binding domains and that CLOCK has sequence similarity with a member of the Src family of HATs. Suspecting that CLOCK might be involved in histone acetylation, they carried out a HAT-activity assay on immunoprecipitated CLOCK and confirmed that it acetylates histones. Using mutated CLOCK, the researchers showed that the acetyl-CoA-binding motif is crucial for the HAT activity of CLOCK, but not for its capacity to associate with other transcriptional co-activators. Furthermore, the heterodimerization of CLOCK with BMAL1 significantly increases the *in vitro* HAT activity of CLOCK.

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Next, Doi *et al.* ectopically expressed wild-type and mutant forms of CLOCK in mouse embryonic fibroblasts that have no cyclic expression of clock genes. Following serum shock, which triggers circadian gene regulation, translation of the clock genes *Per1* and *Dbp* was monitored. The ectopic expression of CLOCK restored the circadian regulation of these genes, whereas the expression of the mutants did not.

By showing that CLOCK is a HAT, Sassone-Corsi and colleagues have linked the histone-acetylation-mediated transcriptional regulation of circadian genes with the known circadian molecular machinery. The authors suggest that CLOCK might be a good target for pharmaceutical agents that are aimed at regulating our circadian rhythms and sleeping patterns. But until such drugs are developed, we’ll need to count on our wind-up alarm clocks to get us up in the morning. Next time you wind your clock up, ask yourself — are you setting the clock, or is CLOCK acetylating you?

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ORIGINAL RESEARCH PAPER Doi, M. *et al.* Circadian regulator CLOCK is a histone acetyltransferase. *Cell* **125**, 497–508 (2006)