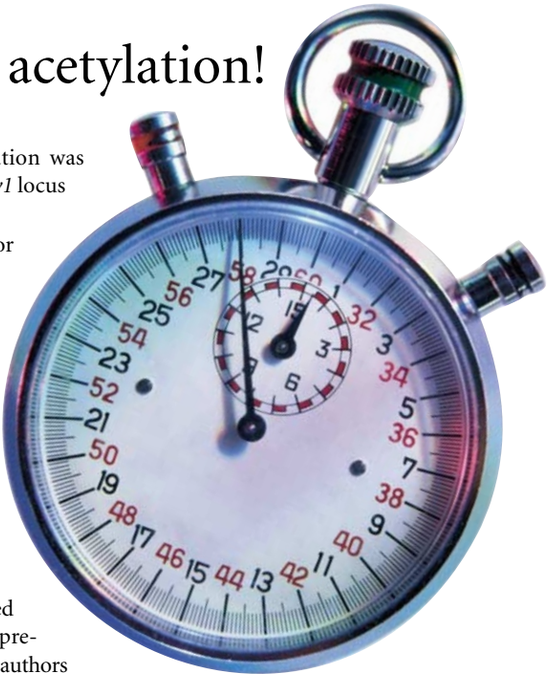
HIGHLIGHTS

EPIGENETICS

Clocking-on to histone acetylation!



The involvement of histone modification in the regulation of gene transcription has been widely demonstrated. Now, Jean-Pierre Etchegary, Steven Reppert and coworkers present data from mouse liver studies showing that histone modification, specifically histone acetylation, is important in the regulation of the mammalian circadian clock.

The key proteins that regulate the circadian clock (Clock and Bmal1) drive the transcription of three period genes (*Per1*, *2* and *3*) and two cryptochrome genes (*Cry1* and *Cry2*). The transcript levels of all five genes cycle over a 24-hour period. Paradoxically, the binding of Clock/Bmal1 to the *Per* promoters remains relatively constant, whereas the strongest binding to the *Cry1* promoter corresponds to the lowest levels of *Cry1* expression. In this paper, Etchegary *et al.* show that it is changes in chromatin modification that determine the level of *Per* and *Cry* gene transcription.

Using formaldehyde-crosslinked chromatin immunoprecipitation (X-ChIP) and semi-quantitative polymerase chain reaction on the *Per1* and *Per2* promoters, the authors showed that the level of histone 3 (H3) acetylation varies throughout the day, as does the recruitment of RNA polymerase II (polII) to these promoters. *Per* transcript levels are at their highest when H3 acetylation and polII binding are greatest, indicating that acetylation enhances transcription by increasing the recruitment of polII to the promoter. A similar correlation was seen when the *Cry1* locus was analysed.

In the search for what might regulate this dynamic H3 acetylation, the authors found that p300 — a protein with histone-acetylation activity — forms a complex with Clock in mouse liver cells. Based on their immunoprecipitation data, the authors propose that, during the day, p300/Bmal1/Clock binds to the promoter, leading to H3 acetylation, polII recruitment and transcription of the *Per* genes. At night, dissociation of p300 from Clock/Bmal1, together with deacetylase activity associated with the complex, results in promoter deacetylation and inhibition of transcription.

But what brings about the nighttime dissociation of p300? Transcription of circadian-clock genes is under the negative control of the Cry proteins. The authors used a luciferase reporter assay to show that Cry1 and Cry2 inhibit p300/Clock/Bmal1-driven transcription from the *Per1* promoter. They propose that Cry proteins achieve this inhibition by destabilizing the p300/Clock/Bmal1 complex.

Acetylation is only one of a number of types of covalent histone modification that regulate gene transcription. Further investigation of other chromatin-remodelling mechanisms, such as methylation and phosphorylation, will determine whether there is a general histone code for circadian-clock regulation.

Catherine Baxter

References and links

ORIGINAL RESEARCH PAPER Etchegary, J.-P. *et al.* Rhythmic histone acteylation underlies transcription in the mammalian circadian clock. *Nature* **421**, 177–182 (2003)

FURTHER READING Young, M. W. & Kay, S. A. Time zones: a comparative genetics of circadian clocks. *Nature Rev. Genet.* **2**, 702–715 (2001) | Reppert, S. M. & Weaver, D. R. Coordination of circadian timing in mammals. *Nature* **418**, 935–941 (2002)

WEB SITE

Steven Reppert's lab: http://www.umassmed.edu/neurobiology/faculty/reppert.cfm