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- PERSPECTIVE

CIRCADIAN RHYTHMS

A New Histone Code for Clocks?

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The DNA of eukaryotic cells is wrapped around proteins, mainly histones, in a complex called chromatin. According to the famous histone code hypothesis of Allis and colleagues, posttranslational modifications of these histone proteins serve not necessarily to change the stability of chromatin structure, but rather as combinatorial recognition sites for the binding of other proteins that either modify chromatin or directly modulate transcription (*1*). Several recent articles (*2*–*8*), including that by DiTacchio *et al.* on page 1881 of this issue (*9*), show that the circadian clock that governs diurnal rhythms of physiology and behavior uses this histone code extensively. But how?

The mammalian circadian oscillator is based on feedback loops of transcription, in which positive factors (such as the CLOCK-BMAL complex) drive transcription of negative factors (such as the PER-CRY complex) that interfere with the activity of the positive ones (see the figure). In synchrony with the resulting waves of transcription, histones are posttranslationally modified in rhythmic fashion at clock genes (*2*, *3*, *10*). Several of the proteins that perform these modifications—histone acetylases (*4*), deacetylases (*7*, *8*), methyltransferases (*5*), and adenosine 5′-diphosphate (ADP) ribosylases (*6*)—have been shown to play an important role in the circadian clockwork. DiTacchio *et al.* now show that the JARID1a histone demethylase is important for the activity of the circadian activator complex CLOCK-BMAL, and for circadian oscillations in general (*9*).

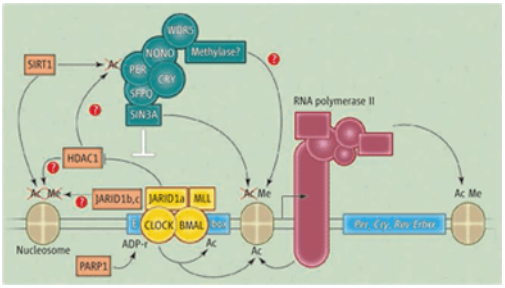
So far, it seems like a simple and elegant story. However, the "other half" of the story in Allis's histone code is that modified histones serve as platforms for giant adenosine 5′-triphosphate (ATP)—dependent motor complexes that reorganize chromatin (*11*). In other fields, the motor complexes have proven to be the essential effectors of sweeping reorganizations for which the histone modifications were the harbingers. Yet, in the circadian field, there is little evidence that these complexes play a role (*5*, *12*, *13*), and none that their nucleosome-remodeling activities are relevant. DiTacchio *et al.* show that the Jumonji histone demethylase domain of JARID1a is dispensable—a surprising finding if chromatin reorganization is the primary motor driving the transcriptional oscillations of the circadian clock. Instead, JARID1a perhaps acts as a platform and inhibits histone deacetylases, but their bona fide target is unknown.

Other studies also hint that histone modifier proteins might be more important than the histone modifications they are supposed to perform. Although the MLL histone methyltransferase is important for circadian oscillations (*5*), depletion of the WDR5 adaptor protein of this complex appears to eliminate circadian histone methylation at multiple clock genes without affecting clock function (*10*). Also, the proline/glutamine rich splicing factor (SFPQ) protein accounts for most PER-mediated histone deacetylation, but its absence does not disrupt the clock (*8*). In all these cases, histone modification occurs, but its importance is not proven.

So, what other targets are out there for histone modifier proteins? For the circadian clock, it has been established repeatedly that the histone-modifier proteins can also modify the clock proteins themselves. The CLOCK protein, also a histone modifier, acetylates BMAL (*14*), the histone deacetylase (HDAC) SIRT1 modifies BMAL and PER (*4*, *7*), and the ADP-ribosylase poly(ADP-ribose) polymerase 1 (PARP1) modifies CLOCK (*6*). Thus, much like the histones themselves, clock proteins are being phosphorylated, ubiquitinated, acetylated, and ADP-ribosylated by histone-modifier proteins.

Histone-modifying enzymes in the circadian clock.

The circadian clock consists of transcriptional feedback loops involving mutually antagonistic protein complexes that activate transcription (CLOCKBMAL complex, yellow) and repress it (PER-CRY, blue). Both complexes are targets of numerous other proteins that alter their function and/or abundance. The figure shows the proteins with known histone-modifying activities (rectangular; histones shown in brown) and the adaptors that recruit them (circles). In most cases, histone-modifying activity is accompanied by modification of the recruiting factors themselves (arrows). RNA polymerase–associated proteins (red) also contain numerous histone-modifying activities. Ac, acetylation; Me, methylation.



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Overall, the widespread importance of histone modifier proteins like JARID1a to the circadian clock suggests two questions. First, what is their regulatory significance? Post-translational modifications by these proteins might provide important nodes for the regulation of physiology by the circadian clock and vice versa (*15*) [such as the bidirectional interplay between metabolism and circadian function via histone deacetylases and poly-ADP ribosylases (*4*, *6*, *7*)]. Similar connections likely exist in the case of proteins like JARID1a. For example, this protein has been heavily implicated in hypoxia-induced regulation (*16*). Is there an unsuspected circadian component here?

Second, what is the real target and consequence of these modifications? Without evidence that chromatin modifier motors are important to clock function, it is not at all clear that histones are the primary target. RNA polymerase travels with a large array of histone modifiers. From the available evidence, the observed rhythmic modification of histones is as likely to be a consequence of transcription as a cause. Clearly, more experiments are needed.

If, however, not histones but clock proteins are the real targets of these modifiers, then what do they do? The initial histone code hypothesis of Allis and co-workers forced researchers to reevaluate the function of post-translational modification of histone proteins. Perhaps circadian clock researchers are on the verge of discovering their own "nonhistone code."

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