Nature Reviews Molecular Cell Biology | Published online 5 Jul 2017; doi:10.1038/nrm.2017.69

CIRCADIAN RHYTHMS

Replication keeps the clock ticking

> DNA replication feeds back into circadian oscillations and regulates the periodic expression of clock genes

Circadian rhythms encompass endogenous processes that oscillate with an approximately 24-hour periodicity. At the heart of circadian rhythms lies an evolutionarily conserved molecular clock, comprising positive elements that drive the expression of circadian genes and negative elements that provide an inhibitory feedback. Many biological processes are under circadian control, including oscillations associated with cell cycle progression. Liu *et al.* now show that DNA replication feeds back into circadian oscillations and regulates the periodic expression of clock genes.

To study the links between the cell cycle and the circadian clock, the authors used a filamentous fungus, *Neurospora crassa*, in which a heterodimer, the white collar complex (WCC; a positive element comprising the WC-1 and WC-2 proteins), binds to the promoter of the *frequency* (*frq*) gene and induces its expression, whereas the FRQ protein (a negative element) inhibits the WCC by preventing its interaction with DNA. Using luciferase-tagged histone H2B, which is incorporated into chromatin in a replication-dependent manner, the authors observed periodic bioluminescence, indicating that DNA content, and hence also DNA synthesis, follow a circadian rhythm. Interestingly, when DNA synthesis was blocked, the circadian rhythm was severely dampened or abolished, and the occupancy of the WCC at the *frq* promoter as well as *frq* expression were decreased. Thus, DNA replication, which is under circadian control, is also required for the periodic *frq* expression and for circadian oscillations.

The binding of transcription regulators is affected by changes in local nucleosome occupancy and composition. Accordingly, nucleosome occupancy at the *frq* promoter was rhythmic, and lower occupancy correlated with high *frq* expression. Changes in the ratio of histone H2A and its variant H2A.Z (which is commonly associated with gene silencing) were also periodic — a high ratio of H2A/H2A.Z correlated with high *frq* expression. Importantly, interfering with DNA replication increased nucleosome occupancy and decreased the H2A/H2A.Z ratio at the *frq* promoter.

The heterodimeric complex facilitates chromatin transcription (FACT) is a histone chaperone, which remodels nucleosomes during replication and prevents H2A.Z incorporation. FACT subunits showed rhythmic binding to the *frq* promoter in a replication-dependent manner, and their depletion increased H2A.Z levels at the *frq* promoter and interfered with *frq* expression. Furthermore, in cells that were unable to incorporate H2A.Z into nucleosomes, the coupling between DNA replication and circadian rhythms was abolished and circadian expression of *frq* persisted even when DNA replication was blocked. Thus, replication-coupled nucleosome dynamics — mostly the regulated incorporation of the H2A.Z variant — control periodic *frq* expression, thereby supporting the function of the circadian clock.

In conclusion, cell cycle progression and circadian rhythms are tightly coupled and impact each other. It would be interesting to study how other cell cycle-related processes regulate circadian clocks and to what extent these mechanisms are conserved in different cells and conditions and across evolution.

Paulina Strzyz

ORIGINAL ARTICLE Liu, X. *et al.* DNA replication is required for circadian clock function by regulating rhythmic nucleosome composition. *Mol. Cell* http://dx.doi.org/10.1016/j.molcel.2017.05.029 (2017)

FURTHER READING Lai W. K. M. & Pugh B. F. Understanding nucleosome dynamics and their links to gene expression and DNA replication. *Nat. Rev. Mol. Cell Biol.* http://dx.doi.org/10.1038/nrm.2017.47 (2017) | Talbert P. B. & Henikoff S. Histone variants on the move: substrates for chromatin dynamics. *Nat. Rev. Mol. Cell Biol.* **18**, 115–126 (2017)