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Keeping up with the times

As the season changes, daylight shifts and a new year looms, we consider cycles and the intrinsic clock that drives us.

One of the more uplifting events of 2010 was watching Chilean miners emerge after more than two months trapped underground, in a situation that seemed nothing short of a nightmare. It seems hard enough to deal with the lengthening dark of winter (except, of course, for our lucky tropical readers), let alone to spend significant time away from daylight. Yet, in 1938 Nathaniel Kleitman and Bruce H. Richardson chose to head underground into Mammoth Cave, Kentucky, for 32 days of dampness, dark and carefully timed temperature readings, all in the name of science. Subsequent experiments that refined this set up and isolated subjects in bunkers and even in spacecraft led to a demonstration that we humans have an endogenous cycle, of close to 24 hours, that persists even when a seemingly mercurial scientist attempts to alter it. The plant kingdom provided some of the first subjects for such experiments back in 1729, when Jean Jacques d'Ortous de Mairan confined "the sensitive plant" or *Mimosa pudica* to the dark to ascertain whether daily cycles of leaf movements were dependent on changes in light. Many organisms, before and since, have been exiled to carefully controlled conditions as a means to study this intrinsic cycle. From the daily drooping and rising of leaves to the daily cycles of rest and activity—fruit fly flight, rodent wheel-running, fungal growth—we know that we all share endogenous behavioral and physiological cycles that approximate the cycle of the earth's spin. In the 1950s, Franz Halberg coined the term 'circadian rhythm' to describe this cycle. With the power of fungal, fruit fly and rodent tools, a genetic basis for this intrinsic cycle was uncovered, and control centers—such as the suprachiasmatic nuclei in mammals—were defined that coordinate the rhythm across an organism and entrain circadian cycles with external cues. And just as remarkably, we now understand that in many organisms, a surprisingly simple molecular clock lies at the heart of this complex physiological response, a clock that can influence everything from mental health to cancer.

In the cyanobacteria, a 24-hour rhythm can be reconstituted *in vitro* through cycles of phosphorylation of three proteins. The cycles of transcriptional and translational regulation that underlie cycling in animals have been linked to a simple cast of transcription factors, key among them CLOCK and BMAL1, which are involved in a feedback loop with the PERIOD and CRYPTOCHROME factors. Nothing in life, however, is that straightforward, and because the clock must both be responsive to external cues and trigger an extraordinarily complex response in any given organism, while remaining robust to perturbations, this very simple cycle is actually the core set of cogs in a baroque machine (see discussion in *Nat. Struct. Mol. Biol.* **15**, 23–24, 2008).

It became clear some time ago that circadian rhythms involve a complex transcriptional output, and where there is a transcriptional output, there is often histone modification and chromatin remodeling. On page 1414 of this issue, Sassone-Corsi and colleagues now describe a layer of histone methylation regulation that ties the histone methyltransferase MLL1 into the heart of the mouse clock. The authors found that the levels of histone H3K4 trimethylation at clock-responsive promoters cycle. This cycling is underpinned by a direct recruitment of and interaction between MLL1 and the CLOCK–BMAL1 transcription factor complex. This histone methylation is also shown to be needed for circadian gene expression, as well as for the previously described periodic presence of histone acetylation at circadian promoters. Although the relevance of this histone methylation to the cycles of the animal itself remains unclear, this adds another layer to clock regulation—that is, the means through which clocks control life. In addition, it provides an explanation for the phenotype of the enigmatic CLOCKΔ19 allele, which turns out to be defective in MLL1 interaction and promoter recruitment. Thus, while new layers of complexity are added, light is also shed on an older mystery.

From worship of the ancient Greek god Chronos to our more contemporary fascination with CLOCK and BMAL1, we have been incessantly preoccupied with the mechanism of time. As we close 2010 and feel the pangs of the yearly cycle and the drive to circannual hibernation behavior in the Northern Hemisphere, it is perhaps worthwhile to think about rhythms at many different levels. Remembering Kleitman and Richardson's underground experiments in 1938 and de Marain's first recordings of daily rhythms in plants in the 1700s, it becomes clear our current molecular understanding is a testament to our ability to unravel dauntingly complex processes over time. Even as each puzzle gains a new piece, the molecules that drive us continue to fascinate and compel scientists to fight their own circadian rhythms, working late at the bench in an effort to understand them. We look forward to reading your findings in 2011 with just such fascination and wish you a happy and peaceful holiday season. ■