and LeDoux, 2004), whereas the Rac dominant-negative transgene, which enhances memory in flies, is expected to produce a decrease in filamentous actin (Figure 1). It may be that an incomplete understanding of the signaling systems involved underlies the discordance in these results. Alternatively, the different stages of memory—acquisition, consolidation, and forgetting—may require distinct cytoskeletal arrangements.

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Circadian Cell-Cycle Progression: Cracking Open the Gate

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In cyanobacteria cell division is intimately linked with the circadian cycle. Dong et al. (2010) now identify components of the circadian clock that regulate the formation of the midcell ring for cytokinesis, revealing a critical link between the circadian cycle and the control of cell division.

Most light-sensitive organisms execute at least two fundamental processes that exhibit periodicity—cell-cycle progression and circadian physiology. Although the period length of endogenous circadian oscillators is approximately 24 hr, the length of the cell division cycle varies greatly among species. Although considerable progress has been made in uncovering the mechanisms and pathways controlling both of these cyclic processes, research aimed at understanding their interconnection is still in its infancy. In this issue, Dong et al. (2010) shed light on how circadian clock components impose restraints on the timing of cell division in the cyanobacterium *Synechococcus elongatus*.

We have recently witnessed groundbreaking progress in understanding the clockwork circuitry of cyanobacteria, including the reconstitution of a functional phosphorylation clock in vitro with only three proteins (KaiC, KaiA, KaiB) and adenosine triphosphate (Nakajima et al., 2005). KaiC is the only protein in the trio with known enzymatic activities, in that it can function as an autokinase, an autophosphatase, and an ATPase. The cyanobacteria "test tube-oscillator" still exhibits several key features of circadian clocks: it runs with a period length close to 24 hr, it is temperature compensated, and it can be synchronized (by the addition of ATP or KaiC subunit exchange).

The possibility of assembling a working clock from a small number of components has afforded detailed structure-function predictions and the examination of their validity by relatively straightforward biochemical experiments (Markson and O'Shea, 2009). Furthermore, in cyanobacteria the adaptive advantage of possessing an endogenous timing system has been clearly demonstrated. For example, in cocultures of cyanobacterial strains with or without functional circadian clocks, the strain with a functional clock outcompetes arrhythmic *kaiC* mutant strains when grown under light:dark cycles with a periodicity of 24 hr. However, this growth advantage disappears in cyanobacteria exposed to constant light (Woelfle et al., 2004). Moreover, if two mutant strains of cyanobacteria with circadian oscillators producing different period lengths are cocultured in light:dark cycles of different durations, the one with a resonating clock outgrows the one with the discordant oscillator after a few generations. These differences in fitness reflect interactions of endogenous clocks with external timing cues, rather than intrinsically different growth rates. In fact, when grown individually the examined wild-type and *kaiC* mutant stains proliferate at similar rates—approximately two doublings of the population per day in constant light and one doubling per day in circadian light:dark cycles (Woelfle et al., 2004).

In the current work, Dong et al. record the occurrence of cell division in single cells using timelapse microscopy. They find that wild-type cells grown on solid agar and in constant light display a bimodal distribution of doubling times, with peaks at around 10–12 hr and 24 hr. Interestingly, doubling times of *kaiC* null mutants follow a Gaussian distribution peaking at 10–12 hr. By plotting cell division events of single wild-type cells against circadian time (CT), the authors reveal the existence of a cell division gate centered at around 17 hr (CT 17), a time at which cells divide less frequently. This result confirms a previous report in which circadian gating had been measured at the population level (Mori et al., 1996). The interpretation of this finding is that behavior of wild-type cells situated around the doubling time of one day in the bimodal distribution represents a "queuing" until the gate opens again.

Based on the Gaussian distribution in doubling time, *kaiC* null mutants do not encounter any restriction in cell division. If cells grow at a constant rate and if cell division is inhibited during a given time window, they would be expected to elongate during the time of the closed gate. Dong et al. use cell length measurements as a readout to assess the impact of mutant clock proteins on cell division and cell size. They conclude that the ATPase activity rather than the kinase activity of KaiC correlates with cell elongation. After the ATPase activity of KaiC rises above a threshold value at approximately CT 12 in wild-type cells, the gate closes and cell division events become rare until the ATPase activity drops again (Figure 1). Characterization of the input pathway involving the bacteriophytochrome CikA, which conveys environmental cues to the core clock, suggests that CikA represses the ATPase activity of KaiC, and cells elongate in the absence of CikA. In cells lacking both CikA and KaiC elongation is bypassed, most likely as a consequence of the abrogation of the cell division gate in *kaiC* null cells. Similarly, in the absence of KaiB, cells have an elongated shape, and the concomitant disruption of *kaiC* eliminates this phenotype. Finally, the deletion of the candidate clock output genes *sasA* and *rpaA*, similar to that of the core clock gene *kaiC*, suppresses cellular elongation in cells lacking either CikA or KaiB. These findings suggest that information flows from environmental cues to cell division through players that control the input, core function, and output of the circadian clock. The authors furthermore identify the localization of FtsZ (the bacterial homolog of tubulin) at the midcell ring as a putative clock-controlled process in cell division. FtsZ localization, but not abundance, is reduced in *cikA* and *kaiB* mutant cells. The overexpression of FtsZ restores the frequency of ring structures with the correct localization and thereby rescues defects in cytokinesis in *cikA kaiB* double mutants.

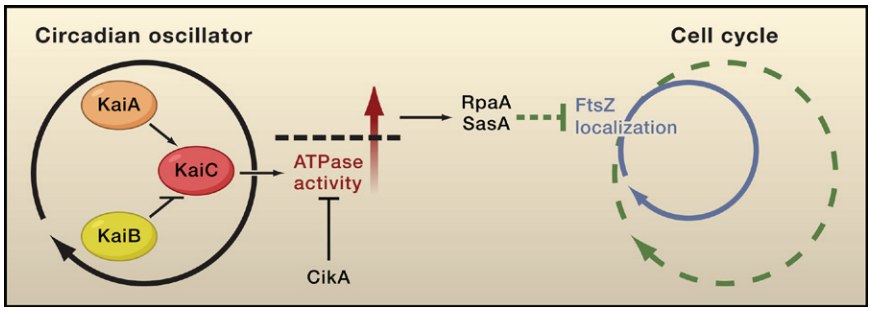

Figure 1. Regulation of KaiC ATPase Activity and Cell-Cycle Gating
The ATPase activity of circadian clock component KaiC is regulated as part of a signaling loop with KaiB and KaiC and receives input from CikA, a bacteriophytochrome that conveys environmental cues to the core clock. At 12 hr (circadian time [CT] 12), the ATPase activity of KaiC exceeds the threshold value (dotted line) and activates a signaling cascade including SasA-RpaA two component regulatory system. This cascade impedes proper localization of FtsZ at the midcell ring and results in the closing of a cell division gate at around CT 17. Cells encountering the gate increase their doubling time (depicted by the dashed green trajectory).

A circadian gating of cell-cycle progression has previously been observed in other organisms, including protozoans, algae, fungi, plants, flies, zebrafish, rodents, and humans, across a large evolutionary distance (Chen and McKnight, 2007). Nevertheless, the central question of why circadian clocks modulate cell division events remains to be elucidated. One hypothesis is that the role of cell division gating by circadian clocks is to limit the occurrence of particular processes to periods of time when they are less deleterious. For example, in transparent organisms it would make sense to replicate DNA during the dark phase, when genotoxic ultraviolet radiation is low or absent. However, in cyanobacteria the rate of DNA replication stays constant throughout the circadian cycle (Mori et al., 1996). Obviously, effective circadian gating of the cell cycle of all cells in a population could only be achieved if the cycle of cell division resonates with circadian oscillations. Therefore, a cell division gate in cyanobacteria with a population doubling time of less than 24 hr might not be an efficient mechanism for population-wide control, given that it would only impact a fraction of the cells. The authors thus speculate that the gate might ensure the symmetric distribution of clock complexes to daughter cells and thereby improve the accuracy of the circadian clock during cell division. Future experiments with cyanobacteria harboring mutations that affect the duration of their generation time will be required to address the validity of this conjecture.

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