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Time for circadian rhythms: plants get synchronized

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Most organisms adjust their physiology and metabolism in synchronization with the diurnal and seasonal time by using an endogenous mechanism known as circadian clock. In plants, light and temperature signals interact with the circadian system to regulate the circadian rhythmicity of physiological and developmental processes including flowering time. Recent studies in *Arabidopsis thaliana* now reveal that the circadian clock orchestrates not only the expression of protein coding genes but also the rhythmic oscillation of introns, intergenic regions, and noncoding RNAs. Furthermore, recent evidence showing the existence of different oscillators at separate parts of the plant has placed the spotlight on the diverse mechanisms and communicating channels that regulate circadian synchronization in plants.

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Introduction

Circadian rhythms are oscillations in biological processes with a period of approximately 24 hours that are present in most living organisms. These rhythms persist under constant environmental conditions for several days or weeks indicating that are generated by a self-sustained endogenous oscillator known as the circadian clock [1]. In addition to the central oscillator, the circadian system involves input pathways that entrain or adjust the oscillator in response to daily and seasonal changes in light and temperature cycles. The so-called output pathways link the central oscillator with the multiple physiological and developmental processes that are rhythmically controlled by the clock [1]. In this review, we attempt to briefly summarize some basic notions on clock organization and function, highlighting a few of the many recent discoveries that have considerably improved our knowledge of circadian clock function in *Arabidopsis thaliana*. Many

excellent reviews cover with much more detail the advances on plant circadian clock research and readers are encouraged to consult them [2–4].

Circadian clock function and organization

The ultimate function of the circadian system is the generation of physiological and metabolic rhythms in close synchronization with the 24-hour period of the cyclic environment [1]. Underlying all these rhythmic biological activities are endogenous oscillations of gene expression. Indeed, recent genome-wide studies have shown that a high proportion of the *Arabidopsis* genes rhythmically oscillate under environmental cycles or under constant conditions [5^{*},6^{**},7^{*},8^{*}]. Analysis of *cis*-acting elements enriched in the promoters of these genes has allowed the identification of morning-specific and evening-specific motifs controlling the daily transcriptional program [5^{*},8^{*}]. By using tiling arrays, Hazen *et al.* also identified about 25% of the protein coding genes as circadianly regulated [6^{**}]. The use of this type of arrays has opened new horizons on clock function and regulation as many intergenic regions, introns, and natural antisense transcripts (NATs) were also found to be regulated by the circadian clock [6^{**}]. A majority of the cycling introns had a similar phase to that of the coding regions of the transcript, although in some instances, there was a difference of 4–12 hours between the peak phase of the intron compared to the exons. Unexpectedly, the authors also detected rhythmic introns and NATs in genes or sense strand transcripts lacking oscillations. It is possible that this represents a new mechanism for clock-controlled protein function at a very specific time window during the circadian cycle. Noncoding transcripts including microRNAs (e.g. miRNA160B, 167D, 158A, 157A), *trans*-acting siRNAs (e.g. TAS3), and small nucleolar RNA (e.g. snoRNA77) were also found to be rhythmically controlled, although the biological implications of this regulation are uncertain, as some known targets of the cycling miRNAs do not oscillate themselves. Overall, this study clearly extends the circadian function far beyond protein coding transcripts and opens exciting insights into new functional regulatory mechanisms within the clockwork. The circadian field waits for the biological relevance and impact on clock function of these newly discovered circadian regulations.

The biological rhythms rely on molecular oscillators whose expression and activities are in turn rhythmically controlled, mostly by interlocked transcriptional–translational feedback loops [1]. In *Arabidopsis*, a current model of these interlocked loops includes the morning-expressed MYB transcription factors CIRCADIAN

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CLOCK ASSOCIATED1 (CCA1) [9] and LATE ELONGATED HYPOCOTYL (LHY) [10] which negatively regulate the expression of the pseudo-response regulator *TIMING OF CAB EXPRESSION 1* (*TOC1*, also known as *PRR1*) [11,12]. *TOC1* in turn, positively drives *CCA1* and *LHY* transcription, closing the loop for the next cycle [13]. Evidence of a mechanism by which *CCA1* might repress *TOC1* expression during the day was provided in a recent study [14]. The mechanism includes the clock-controlled changes of histone acetylation at the *TOC1* promoter, which are antagonized by the direct binding of *CCA1* [15]. *LHY* might also participate in the repression of histone acetylation, as both transcription factors act synergistically in the control of circadian rhythms by the clock [16]. It would be interesting to examine whether the repression by *CCA1* and *LHY* of other evening-expressed genes also occurs by antagonizing histone acetylation at their promoters. The expression of *CCA1* and *LHY* is in turn tightly regulated by other clock components, including the members of the *TOC1* family, *PRR7* and *PRR9*, which altogether form the so-called morning loop [17–19]. Lastly, proper regulation of rhythmic expression in the evening was proposed to require the reciprocal regulation between the clock-associated protein GIGANTEA (*GI*) and *TOC1* [20] although the results of some genetic studies are now questioning the direct role of *GI* within the evening oscillator [21,22]. In any case, it is clear that these transcriptional feedback loops are not sufficient to explain all the rhythmicity in the plant [23] and thus, major research efforts have been devoted to the identification of new oscillator components. A recent study illustrates this point with the characterization of a TCP (TB1, CYC, PCFs) transcription factor denominated CHE (*CCA1* HIKING EXPEDITION) [24**]. CHE represses the expression of *CCA1* most likely through direct binding to the *CCA1* promoter. The elevated transcript abundance of *CHE* in a *cca1/lhy* double mutant background was indicative that *CCA1* and *LHY* in turn repress *CHE* expression, establishing a new transcriptional feedback loop between *CCA1/LHY* and CHE [24**]. CHE might also function as a molecular connector between *TOC1* and *CCA1/LHY* as the study reports the physical association of CHE with *TOC1*. Protein–protein interactions among clock components and regulation of protein stability are other regulatory mechanisms intimately linked with the circadian system and contribute to the stability and robustness of the clock [25,26].

New advances on clock synchronization with the environment

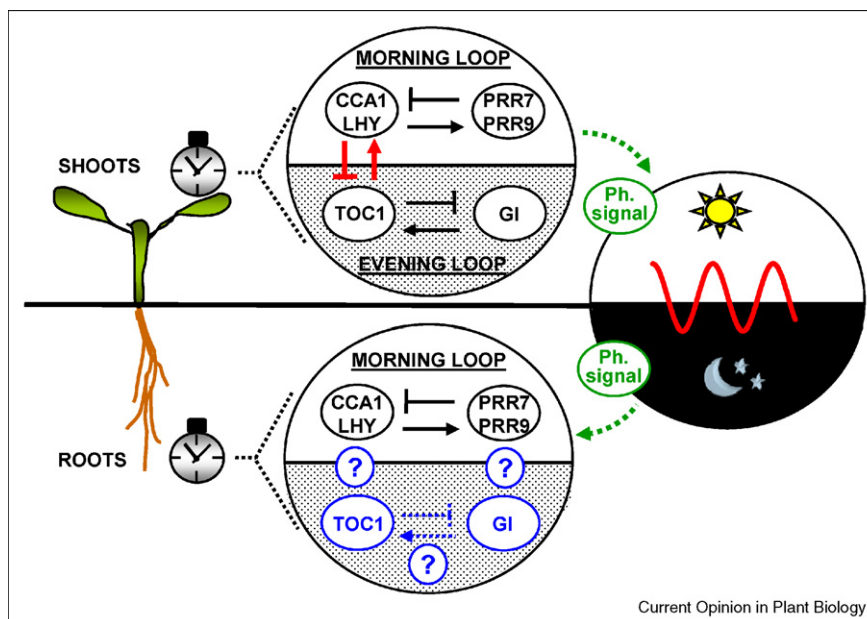
Light and temperature are the main environmental cues responsible for clock synchronization with the environment. The synchronizing signals help to adjust the endogenous period of the clock to exactly match the 24-hour environmental cycle [27]. The red/far-red and the blue light photoreceptors PHYTOCHROMES

(PHY) and CRYPTOCHROMES (CRY) have been known for a decade to play a central role in the synchronization of circadian oscillations to light/dark cycles [28] although the molecular mechanisms behind this regulation have remained obscure. These photoreceptors promote photomorphogenic development antagonizing the action of an E3 ubiquitin ligase, COP1 (CONSTITUTIVELY PHOTOMORPHOGENIC 1) that targets for degradation transcription factors involved in light signaling [29]. A role for COP1 in the regulation of circadian rhythms and flowering time had been reported, but how COP1 affects these processes was uncertain. A recent report has shed some light on how COP1 contributes to regulate flowering time and circadian rhythms [30**]. The study shows that the flowering phenotypes of *cop1* mutant plants can be largely rescued under short day cycles of 18 hours, which more closely resemble the circadian period of this mutant. Thus, an important part of the *cop1* flowering phenotype is owing to its circadian defect. In addition, *cop1* is epistatic to *cry2* in the regulation of flowering time while mutations in *GI* are epistatic to *cop1*. This establishes an order in which COP1 acts downstream of *CRY2* and upstream of *GI* in the regulation of flowering time. Furthermore, COP1 interacts *in vivo* with *GI* and this interaction contributes to regulate *GI* abundance specifically in the dark and in the presence of the clock-related and flowering-related gene *ELF3* (EARLY FLOWERING 3). Thus, light regulates circadian rhythms in part by antagonizing COP1 activity in the nucleus, which modulates *GI* protein stability through an interaction facilitated by *ELF3*.

In addition to the entrainment of the clock by light signals, the importance of other synchronizing cues has been highlighted in a number of interesting studies. These studies have shown the existence of a temperature sensitive oscillator that can be distinctly phased from the oscillator synchronized by light [31]. Furthermore, thermocycles synchronize the phase of the clock by a different mechanism than photocycles [8*] with the cyclic changes in temperature dominating over photocycles in the synchronization of processes such as cell cycle and protein synthesis [8*]. However, some connection between the light-sensing and temperature-sensing systems might exist as the photoreceptor signaling pathways are temperature sensitive [32,33]. Studies of rhythmic oscillations after entrainment to thermocycles and clock resetting in response to cold pulses suggested that the two pseudo-response regulators *PRR7* and *PRR9* might be essential components of an oscillator necessary for proper clock responses to temperature signals [19,34].

The studies of clock synchronization by environmental cues are usually performed with adult plants. Interestingly, a recent study has shown that in germinating seedlings, the rhythmic expression of clock genes can be detected as early as two days after imbibition, even

Figure 1



Schematic representation depicting a model for clock function in *Arabidopsis* shoots and roots. The circadian system in *Arabidopsis* shoots is composed of interconnected morning and evening oscillators. In the morning loop, CCA1 and LHY activate the expression of PRR7 and PRR9 that in turn repress CCA1 and LHY. In the evening oscillator, GI functions in the promotion of TOC1 that in turn represses GI expression. The morning and evening loops are connected by the reciprocal regulation between CCA1 and LHY with TOC1. In roots, there is only a morning loop; the interactions between TOC1 and GI in this organ are not clear. Under light:dark cycles, a photosynthesis-related signal (Ph-signal) from shoots synchronizes the morning loop in roots (discontinuous green arrow). For simplicity, some clock-associated components were not included in the scheme. Arrows denote transcriptional activation while lines ending in perpendicular dashes indicate repression. The white semicircles indicate light period during the day or subjective day; the dotted semicircles indicate the light conditions during the subjective night; the dark semicircles indicate the dark conditions during the night. In the root clock, the blue dashed lines and question marks in the subjective night indicate unknown components or regulatory mechanisms.

without a previous light or temperature entrainment [35]. It was concluded that seed hydration was sufficient not only for initiating rhythmicity but also for clock synchronization among individuals [35]. The presence of clock activity in etiolated seedlings is suggestive of an entrainment mechanism driven initially by temperature and followed by light–dark entrainment of the soil-emerged seedlings.

Internal coordination of circadian rhythms

An appropriate phasing of circadian rhythms generated in different organs is crucial for optimal fitness and adaptation. Indeed, jet lag symptoms arise when clocks present in different organs are not operating in synchrony because of a differential speed of adjustment to a new light/dark environment [36]. Plants, unlike animals, lack a central nervous system that keeps circadian oscillations synchronized within cells located in different organs. So what keeps the clocks from shoot and root cells in synch? A recent paper explored this question [37•]. The authors observed that the clock genes CCA1 and LHY oscillated in synchrony in roots and shoots under light:dark (LD) cycles but not under continuous light (LL), suggesting

that a shoot-derived signal was entraining the clocks in root cells under LD conditions [37•] (Figure 1). Indeed, addition of sucrose to the medium at dusk in plants grown under LD cycles mimicked the effect of LL conditions (i.e. there was a loss of synchrony between shoot and root clocks). In addition, blocking photosynthesis with an inhibitor of electron transport in chloroplasts, affected expression of clock genes in roots but not in shoots [37•]. Thus, all the above results suggest that an entraining signal, most likely carbohydrates produced by the photosynthetic process, is translocated from shoots to roots and contributes to synchronize circadian oscillations in root cells with those in the shoot (Figure 1).

How many oscillators?

A long-standing question closely related with the circadian synchronization of rhythms in separate parts of the plant is the possible existence of different oscillators with distinct properties. Studies showing various free-running periods of independent outputs were indeed suggesting the existence of more than one oscillator with a different molecular architecture [31,38,39]. However, it was not clear whether there was a cellular or tissular specificity in

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the organization of the multi-loop oscillators. The study by James *et al.* mentioned above, also provided new insights into variations of clock regulation and function among different *Arabidopsis* tissues [37**] (Figure 1). The study shows that *TOC1* mRNA clearly cycles under continuous light in shoots but not in roots. *TOC1* oscillations are normally driven by the direct binding of LHY and CCA1 to the evening element (EE) present in the *TOC1* promoter. In roots, however, LHY is unable to bind the EE, resulting in constant and elevated *TOC1* mRNA levels. Consistent with the lack of function of the evening loop in roots, *toc1* mutants shorten the period of *LHY* expression in shoots but not in roots. In animals, mice lacking the protein CLOCK are arrhythmic for locomotor activity, but show normal circadian rhythms of food anticipatory activity [40]. In contrast, *PER2* mutant mice have defects in both types of circadian rhythms. Interestingly, circadian rhythms in food anticipatory activity are driven by a food entrainable oscillator, which is distinct from the light entrainable oscillator present in the suprachiasmatic nucleus. The presence of different oscillators was also inferred in studies of the mechanism generating the methamphetamine-sensitive circadian oscillator which does not involve the extensively characterized and canonical molecular feedback loops [41]. Thus, the existence of circadian oscillators with different molecular architectures, different sensitivities to synchronizing signals, and localized in different organs appears to be a common theme in the plant and animal circadian systems.

Interaction with other signaling pathways

The proper timing of clock outputs with the external environment was suggested to confer an adaptive advantage to plants allowing both the anticipation of the environmental transitions and the proper phasing of physiology and metabolism. Indeed, various studies have shown that proper clock function enhances plant fitness and survival [42–44]. Furthermore, clock regulation of physiological and metabolic pathways provides gain advantages to hybrids and allopolyploids, leading to growth vigour and increased biomass [45*]. In this sense, it is not surprising that the critical interactions between the circadian clock and other pathways, including those of stress and hormone signaling [5*,46] exist. Consistent with this notion, microarray studies have revealed a significant overlap between transcripts controlled by the clock and auxin [47*], methyl jasmonate, and abscisic acid [48*]. Furthermore, the abundance of ABA, auxin, brassinosteroids, ethylene, and gibberellins was shown to be regulated by the clock [49–52]. The circadian clock also controls the sensitivity to auxin, affecting the plant responses to this hormone [47*]. In turn, circadian clock function can be also regulated by cytokinin, abscisic acid, and brassinosteroids which modulate a diverse range of circadian parameters [53,54]. A recent study has also shown that internal coincidence of phytohormone

signaling and external coincidence with darkness are both required to coordinate plant growth [7*]. Thus, the circadian clock was shown to indirectly control growth by gating light-mediated phytohormone transcript abundance [7*].

The circadian clock also interacts with signaling pathways involved in plant responses to cold temperatures [55,56]. Rhythmic expression of cold-induced transcription factors is gated by the clock which in this way modulates the plant tolerance to freezing conditions [57]. The complexity of interacting networks was exemplified by the finding that cold acclimation is also regulated by low red to far-red ratio (R/FR) light signals in a clock-dependent manner [58]. New studies are increasingly demonstrating a broader network of cross-talk between the clock with many other pathways including sugar signaling [59], nitrogen assimilation [60*], carbon status [61], metabolite abundance [62] as well as with other signaling molecules such as Ca²⁺ and cyclic adenosine diphosphate ribose [63*].

Concluding remarks

The plant circadian world has been shaken by a number of recent studies dealing with fundamental questions of circadian clock function. Plant organs with differential susceptibility to internal and external synchronization cues place the spotlight on the diverse mechanisms and communicating channels that regulate circadian synchronization in plants. Different oscillators in separate parts of the plant also open exciting research avenues on the molecular architecture of the oscillators that temporally and spatially regulate clock outputs. The recurring observation in plants and animals of transcriptional feedback loops that can be plugged or unplugged from the circadian network in specific organs opens a series of interesting questions: How are oscillations within morning loops regulated in the absence of the evening loop? Are there other connecting loops that aid in the generation of rhythmicity? What are the signals and mechanisms underlying synchronization in roots? Is the modular nature of the circadian system necessary for appropriate entrainment of the clocks from different organs, and/or for proper regulation of organ-specific outputs? Judging by the fast pace and the relevance of the recent findings, we are positive that these and other crucial questions will soon receive a conclusive answer.

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Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

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