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Review

Beyond *Arabidopsis*: The circadian clock in non-model plant species

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ABSTRACT

Circadian clocks allow plants to temporally coordinate many aspects of their biology with the diurnal cycle derived from the rotation of Earth on its axis. Although there is a rich history of the study of clocks in many plant species, in recent years much progress in elucidating the architecture and function of the plant clock has emerged from studies of the model plant, *Arabidopsis thaliana*. There is considerable interest in extending this knowledge of the circadian clock into diverse plant species in order to address its role in topics as varied as agricultural productivity and the responses of individual species and plant communities to global climate change and environmental degradation. The analysis of circadian clocks in the green lineage provides insight into evolutionary processes in plants and throughout the eukaryotes.

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1. Introduction: the plant circadian clock

The rotation of the earth on its axis confers dramatic daily changes in the environment with multiple consequences for organisms that must contend with the transitions from day to night and back again. Circadian clocks that temporally organize many aspects of biology are found in organisms across the three domains of life: Archaea, Bacteria, and Eucarya [1–3]. The first recorded observation of a diurnal rhythm was from Androsthenes, who described the sleep movements of plant (probably the tamarind tree) leaves during the expeditions of Alexander the Great in the fourth century BC [4]. Two millennia elapsed before the scientific study of clocks began with de Mairan, who showed that the sleep movements of *Mimosa* leaves persisted in constant darkness [5]. For nearly 200 years plant leaf movement remained the premier system for the scientific study of circadian rhythms, which expanded to encompass many plant species [e.g., 6]. However, plants are richly rhythmic [7–9] and the breadth of properties under circadian control has expanded dramatically to include many aspects of growth and metabolism [10–18], as well as interaction with the abiotic and biotic environment [9,19–23].

The molecular biological study of the plant circadian clock began with the seminal observation that the accumulation of three light-inducible transcripts, encoding a chlorophyll *a*/*b* binding protein, the small subunit of Rubisco, and an early light-induced protein (ELIP) oscillated in abundance in peas (*Pisum sativum*) grown in light dark (LD) cycles and that these oscillations persisted in plants transferred into continuous light (LL) [24]. Observations of circadian regulation of transcript abundance were soon made in multiple angiosperm species, including wheat [25], tomato [26], tobacco [27], maize [28] and *Arabidopsis* [29].

The initial molecular biological description of circadian rhythms in plants coincided with the emergence of *Arabidopsis* as the model plant for molecular genetic analyses [30–32]. The enabling attributes of *Arabidopsis* as a model system facilitated rapid progress on many aspects of plant biology, including the circadian clock, which now has been described in considerable architectural and mechanistic detail [22,33–36]. The value of a model plant such as *Arabidopsis* emerges from the generalization of knowledge acquired in the model. As early as 1988 Gerry Fink predicted [37] "The day is not far off when scientists will say, *Is it like Arabidopsis?*" Now, a quarter of a century later, it should be instructive to

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consider the extent to which the model of the circadian clock developed in *Arabidopsis* applies to other plant species, especially to those of agricultural significance.

2. Angiosperm clocks

Within the angiosperms, including both monocots and dicots, the evidence is quite strong that there has been considerable evolutionary conservation of clock components, architecture, and function [38]. Initial observations in a number of species focused on genes shown to play central roles in the feedback loops at the heart of the plant clock including those encoding the myb domain transcription factors (TFs) CIRCADIAN CLOCK ASSOCIATED1 (CCA1) and LATE ELONGATED HYPOCOTYL (LHY) and the PSEUDO RESPONSE REGULATOR (PRR) family, including TIMING OF CAB EXPRESSION1 (TOC1) [22,33–35]. Homologues to these clock genes were identified in many species as diverse as bean (*Phaseolus vulgaris*) [39], chestnut (*Castanea sativa*) [40,41], pea (*Pisum sativum*) [42,43], the ice plant (*Mesembrianthemum cristallinum*) [44], soybean (*Glycine max*) [45,46], *Brassica rapa* [47,48], tomato (*Solanum lycopersicum*) [49], and the cactus pear (*Opuntia ficus-indica*) [50]. *LHY*, *PRRs* including *TOC1*, as well as *GI* and *ELF3* have been identified in the monocots *Lemna gibba* and *L. paucicostata* [51]. In many cases, these clock genes have been shown to cycle in phase with their *Arabidopsis* counterparts, consistent with the conservation of clock architecture among plants.

More recently, the availability of multiple plant genomes has permitted a more systematic and comprehensive taxonomic survey of clock genes, and additional evidence has accumulated supporting conserved clock architecture. For example, *CCA1*/*LHY* and *PRR* homologues have been characterized in poplar (*Populus* spp.) [52,53], papaya (*Carica papaya*) [54], grape (*Vitis vinifera*) [55], and in *B. rapa* [48]. However, few of these studies provide functional assessment of the roles of these components in clock function, which remains an important experimental validation of clock conservation. One important exception is provided by rice, for which several *PRR* genes have been shown to functionally rescue *Arabidopsis* mutants deficient in the homologous *PRRs* [56–58]. A second notable exception is the monocot *L. gibba*, whose genetic advantages have permitted functional assessment (knockdown and overexpression) of *LHY*, *ELF3*, and *GI* indicating functional conservation of the *Lemna* circadian system with *Arabidopsis* and rice [59].

A second line of evidence involves conservation of clock-controlled transcriptional programs. It has become clear that a substantial portion of the transcriptome is under clock control. Initial estimates, based on microarray analyses in *Arabidopsis*, suggested that ~5–6% of the transcripts cycled in abundance in continuous light (LL) [60]. Such estimates were necessarily conservative, given the experimental challenges of assessing rhythmicity based on only two cycles of rather noisy data and the limitations of assessing rhythmicity based on curve fitting to smooth and symmetric sine waves. An enhancer trap study suggested that a larger portion, perhaps up to one-third, of the transcriptome was under circadian control [61]. Subsequent microarray studies yielded increased estimates of the scale of the cycling transcriptome [11,62–64] and meta-analysis of multiple datasets [62,63] are consistent with one-third of the transcriptome cycling in constant light and temperature [65].

More recent investigations suggested that the portion of the transcriptome that is rhythmically expressed is considerably larger than the already substantial one-third suggested by Covington et al. [65]. Broadening the assessment criteria to include waveforms other than the symmetric sine wave expanded the set of transcripts considered to cycle [64]. Biologically, of course, plants in the natural world never encounter continuous conditions of constant light and temperature. Thus, when the cycling transcriptome was assessed in plants exposed to multiple photo- and thermo-cycles, and combinations of those photo-and thermo-cycles [62–64,66,67], the surprising summative conclusion was that up to 89% of the *Arabidopsis* transcriptome cycled under one or more conditions of free run (continuous conditions) or imposed cycles [64].

These transcriptomic studies have revealed an intricate temporal coordination of multiple pathways of metabolism and growth in *Arabidopsis*, as detailed elsewhere [7–23,35]. To the point of this article, it is important to note that other studies that have considered the cycling transcriptomes of a number of other angiosperm species, including rice [64,68–70], maize [71,72], papaya [73], tomato [49], and poplar [64,68] come to the consistent conclusion that there is widespread clock control of the transcriptome, encompassing multiple pathways associated with metabolism (e.g., photosynthesis, carbohydrate metabolism, cell wall biogenesis), growth (often associated with phytohormone biosynthesis, transport, and signaling), and development. It is also becoming clear that the circadian clock also modulates the response to the biotic [74–76] and abiotic [77–81] environments. Moreover, there has been considerable conservation demonstrated among the cis-acting modules that mediate this time-of-day-specific regulation of gene expression among multiple species, including *Arabidopsis*, rice, poplar, and papaya [64,68,73].

A complementary approach to the assessment of clock function in non-model systems is the study of natural variation. Quantitative Trait Loci (QTL) for circadian clock function have been identified in *Arabidopsis* [62,82–85]. This approach has now been applied in crops, including *Brassica oleracea* [86] and *B. rapa* [87,88]. In *B. rapa*, there is an interesting colocalization of QTL for circadian clock function with QTL for water use efficiency (WUE) [88,89]. The circadian clock regulates a number of physiological traits that contribute to WUE, including photosynthetic carbon assimilation [10,90,91], stomatal aperture and conductance [90,92–94], and hydraulic conductivity [95–97]. In both *Arabidopsis* and poplar the circadian clock gates the transcriptomic response to drought [78,79]. Detailed elucidation of the mechanistic basis for clock contribution to WUE may offer strategies towards breeding for enhanced WUE.

3. Bryophyte clocks

The first experimental demonstration of circadian rhythms in bryophytes was of the transcription of a *PpLhcb2* (encoding a major light-harvesting chlorophyll *a*/*b*-binding protein)-luciferase gene fusion in the moss *Physcomitrella patens* [98]. *P. patens* has two *CCA1*/*LHY* and four *PRR* homologues, as well as *ELF3*, *LUX*, and possibly *ELF4* homologues [99,100]. Circadian oscillations in mRNA abundance and transcription have been demonstrated for *CCA1* and *PRR* homologues [99,100]. Mutants in which both *CCA1* homologues were disrupted exhibited a short period suggesting considerable functional similarity to the angiosperm clock [99]. Expression of *PpPRR2* in *Arabidopsis* shortened circadian period, consistent with this gene playing a conserved role in the *P. patens* clock [101]. However, neither *TOC1* nor *GI*, two members of the evening loop of the *Arabidopsis* clock, is represented in the *P. patens* genome [99,100]. Similarly absent from the *P. patens* genome are F-box proteins with blue light photosensing LOV domains and protein–protein interaction KELCH domains, which, in *Arabidopsis*, play important roles targeting clock components for ubiquitylation and proteasomal degradation [102–105]. These data suggest that the *P. patens* clock might have a considerably simpler architecture than the angiosperm clock [100].

4. Green algal clocks

Rhythms in phototaxis were described in the green algae *Euglena gracilis* [106] and *Chlamydomonas reinhardtii* and the rhythm in *C. reinhardtii* has been shown to persist in the microgravity environment of space flight [107]. Natural variants as well as induced mutants with altered period length of phototaxis have been identified in *C. reinhardtii* [108]. Subsequently, circadian rhythmicity has been established as widespread, controlling many properties including chemotaxis, nutrient uptake, starch metabolism, substrate adhesion, UV sensitivity, and cell division [109,110]. Consistent with this widespread rhythmicity, there is considerable (~2.6%) circadian control of transcript abundance [111], although this is less than in *Arabidopsis* (see above). Clock-controlled transcripts include, as in angiosperms, genes encoding the chlorophyll *a*/*b* binding protein [112] and the chloroplast gene *tufA* encoding elongation factor Tu [113].

The *C. reinhardtii tufA* promoter, when fused to the firefly luciferase gene (*tufA:lucCP*$^{+}$), recapitulated a robust rhythm in vivo that formed the basis of a systematic forward genetic analysis that identified ~30 loci, termed *RHYTHM OF CHLOROPLAST* (*ROC*), controlling clock function [114]. This screen represented a significant step towards understanding the construction of the *C. reinhardtii* clock. Moreover, the outcome of the screen was both surprising and intriguing. As described above, angiosperm clocks appear to be quite similar to one another, and the bryophyte *P. patens* clock also seems to be composed of homologous genes and proteins. In striking contrast, this conservation of gene and protein sequences does not seem to extend to *C. reinhardtii* [110,114]. Four of the *ROC* loci encode TFs with DNA-binding domains (DBDs) related to those of plant clock TFs. For example, the DBDs of ROC15 and ROC75 are similar to the GARP domain of *Arabidopsis* LUX ARRHYTHMO (LUX, also called PHYTOCLOCK1 [PCL1]) [115,116]. ROC40 has a single myb DBD similar to those of *Arabidopsis* CIRCADIAN CLOCK ASSOCIATED1 [117] and LATE ELONGATED HYPOCOTYL [118]. However, sequence similarity does not extend beyond the DBD and the *C. reinhardtii* sequences are much longer [110,114]. In functional terms, *Arabidopsis LUX* (*PCL1*) and *CCA1*/*LHY* are expressed in antiphase whereas *ROC15* and *ROC40* are in phase, with the admitted caveat that these phase measurements are based on transcript rather than protein abundance [114]. Nonetheless, these altered phase relationships suggest that regulatory relationships are unlikely to be conserved. Collectively, these observations raise doubts that *ROC15*/*ROC75*/*LUX* (*PCL1*) and *ROC40*/*CCA1*/*LHY* are true homologues [110]. Other *C. reinhardtii* clock loci, including *ROC55* and *ROC114*, lack sequence similarity to any known plant or animal clock genes [114]. RNA-binding proteins play important roles in plant and animal circadian systems [119–121]. In *C. reinhardtii*, CHLAMY1 was identified on the basis of its clock-regulated binding to the 3′ untranslated regions of a number of transcripts [109] and CHLAMY1 misexpression disrupts rhythmicity [122]. However, neither the C1 and C3 subunits of CHLAMY1 have sequence similarity to known clock proteins [123]. Instead, the C3 subunit resembles the rat CUG-binding protein in both sequence and immunological properties [109]. It seems that the *C. reinhardtii* clock differs considerably from the angiosperm clock.

A second alga, the marine picoeukaryote *Ostreococcus tauri*, has a minimal cellular organization including a single mitochondrion and chloroplast and has been described as the smallest living eukaryote [124]. *O. tauri* has a compact genome of 12.56 Mb, approximately one-tenth the size of the *Arabidopsis* or *C. reinhardtii* genomes. Consistent with this small genome, the circadian system of *O. tauri* seems to be considerably reduced, and includes homologues to *CCA1* and *TOC1*, but not to other higher plant clock genes such as *ELF3*, *ELF4*, *GI*, and *ZTL* [125]. *O. tauri CCA1* and *TOC1* both show circadian regulation of transcription and protein accumulation, and the two genes cycle out of phase with one another. As in *Arabidopsis*, in *O. tauri* CCA1 binding to an evening element (EE) in the *TOC1* promoter is necessary for circadian transcription of *TOC1*. Disruption of *CCA1* and *TOC1* expression via overexpression perturbs clock function and confers arrhythmia, indicating both genes are critical for rhythmicity [125]. The *O. tauri* clock has been modeled as a robust and flexible circadian clock consisting only of a simple feedback loop of *CCA1* and *TOC1* [126,127]. However, this may be an over-simplification. First, at least one additional clock component, a LOV-histidine kinase (LOV-HK) protein with an N-terminal blue-light photoreceptor LOV (light, oxygen, voltage) domain linked to a C-terminal histidine kinase domain, is important for clock function in *O. tauri*. *LOV-HK* gene expression is itself under clock control and altered *LOV-HK* expression (either overexpression or antisense knockdown) perturbs clock function [128]. This suggests an intriguing link to cyanobacterial clock function, where HKs function in both input and output pathways to the clock [129,130]. *O. tauri* also has a family of five cryptochrome/photolyase (*CPF*) genes. *CPF1* transcription is under circadian control and antisense knockdown of *CPF1* lengthens period, indicating a role in the circadian system [131]. In addition, there is an *O. tauri* gene with a GARP domain similar to that of *Arabidopsis LUX* [125]. Thus, as in *C. reinhardtii*, other genes either unrelated or only distantly related to higher plant clock genes may contribute to *O. tauri* clock function. Consistent with this hypothesis, although knockdown of *O. tauri TOC1* expression through antisense resulted in arrhythmia, knockdown of *CCA1* did not dramatically compromise clock function [125]. This suggests either inefficiency of the antisense knockdown or that *CCA1* functions redundantly with an as yet unidentified gene. As discussed with respect to the *C. reinhardtii* circadian system, the sequence similarity of *O. tauri* CCA1 to angiosperm CCA1 is limited to the myb domain and the similarity of TOC1 is limited to the PRR and CCT domains. Thus, whether they are true homologues is not unambiguously established. Clearly further study on clock architecture and function in *O. tauri* is needed.

5. Evolution of circadian clocks within the green lineage

Both the *O. tauri* and *P. patens* clocks have been suggested to have simplified clock architecture because they have apparent homologues to the genes forming the core CCA1/LHY/PRR loop but lack obvious homologues to numerous angiosperm clock genes that comprise the additional interlocked loops [100,125]. However, this analysis of the *P. patens* and *O. tauri* clocks to date has relied on sequence analysis and on reverse genetics to perturb expression of clock loci identified on the basis of sequence similarity with other angiosperm clock genes. In *C. reinhardtii*, forward genetic analysis has revealed multiple novel loci clearly involved in the clock but not obviously homologous to angiosperm clock genes [110]. Thus, the hypothesized simple architecture of the *P. patens* and *O. tauri* clocks may reflect an incomplete identification of clock components and a forward genetic analysis may be warranted.

The recruitment of novel loci to the *C. reinhardtii* circadian clock raises interesting evolutionary questions. It has been suggested that circadian rhythms evolved in response to the association of DNA damage from light, with clocks evolving to gate DNA replication to the dark, the so-called “flight from light” hypothesis [132]. Parsimony would suggest that clocks arose once in evolution, yet the dramatic difference between the post-translational rhythms arising from the Kai oscillator in cyanobacteria [133–135] and the transcription-based oscillators in plants, fungi, and animals argues in favour of at least two independent clock origins [136]. Should this argument be extended? Does the lack of homology among clock components in plants and animals argue in favour of multiple clock

origins within the eukaryotic lineage? And does the recruitment of novel loci to the *C. reinhardtii* circadian clock argue for independent origins of clocks within the green lineage?

Multiple independent clock origins within eukaryotes seems implausible, given the evidence (the existence of circadian clocks within Bacteria and Archaea) that natural selection has favoured circadian clocks since well before the origin of eukaryotes. Therefore, if clocks originated prior to divergence among eukaryote lineages, how might one reconcile the different consortia of components comprising *C. reinhardtii*, angiosperm, and animal clocks? The circadian system can be characterized as consisting of three units: input pathways by which environmental information is provided to the oscillator, a central oscillator that generates an oscillation with circadian period, and a set of output pathways that orchestrate overt metabolic, physiological, and behavioral rhythms. Natural selection will act on the output pathways that control rhythms, but not on the oscillator circuits that generate the oscillation. Thus, it is possible to evolve transcriptional circuits in which the components vary but the logic is retained.

For example, mating type is regulated transcriptionally in ascomycete fungi, but one group of mating genes is regulated by a transcriptional activator in ancestral yeast and in the modern *Candida albicans* but by a repressor in modern baker's yeast (*Saccharomyces cerevisiae*). Evidently, the regulatory controls on mating genes were reconfigured within the *S. cerevisiae* lineage [137,138]. A second example from the ascomycetes is the insertion of a novel TF into the circuit by which diploids repress expression of core haploid-specific genes (*hsgs*) [139]. In the ancestral *S. cerevisiae* and *C. albicans* lineages, the Mata1–Matα2 heterodimer is a direct repressor of the *hsgs* (Mata1–Matα2 –| *hsgs*), but in the derived *Kluyveromyces lactis* lineage, an intermediate regulator, Rme1 has been interpolated such that Mata1–Matα2 heterodimer represses the core haploid genes indirectly through Rme1 (Mata1–Matα2 –| Rme1 → *hsgs*). The logic of the circuit is retained (the Mata1–Matα2 heterodimer represses *hsgs*), but the insertion of this novel regulator introduces a new input to the circuit, because Rme1 is responsive to nutritional inputs [139].

Sequential rewiring events could replace one set of circuit components with another non-homologous set, which could explain how plant and animal clocks maintain the common logic of interlocked feedback loops yet utilize non-homologous components. Recruitment of novel TFs to the circadian oscillator circuit would likely require extensive gains and losses of cis-acting regulatory sequences, as the newly recruited TF would need to acquire a novel time-of-day-specific expression pattern. Similarly, genes targeted by the newly recruited TF, both within the circadian oscillator and among output pathways, would need to reconfigure their cis-acting TF binding elements to allow them to respond to the new TF and to lose responsiveness to their previous TF regulators. Gain or loss of cis-acting TF-binding elements can occur over quite short evolutionary time scales (<5–20 million years) [140,141]. An example of this type of network reconfiguration can be seen in the newly evolved network for biofilm formation in *C. albicans* [142]. Six master TFs have been characterized in this circuit, three of which (Tec1, Efg1, and Ndt80) have well characterized homologues in *S. cerevisiae*, where they play roles in pathways other than biofilm formation. Despite the strong conservation of DNA-binding specificity for each of these three TFs between *C. albicans* and *S. cerevisiae*, the sets of target genes controlled by each differ significantly between *C. albicans* and *S. cerevisiae* [142]. Regulatory neofunctionalization, the acquisition of a new expression pattern, is facilitated by the redundancy created by gene duplication [141]. The pattern of repeated whole genome duplication encountered in the evolution of the plant lineage [143] is consistent with considerable opportunity for redeployment of TFs into new networks, including the circadian clock.

To conclude, despite the common regulatory logic of interlocked feedback loops, plant and animal clocks have recruited largely distinct genes to generate their circadian clocks. The lack of homologous components suggests independent evolutionary origins, which is inconsistent with the "flight from light" hypothesis arguing for an early origin of circadian rhythmicity in eukaryotes [132]. The reconfiguration of a circadian clock in the common ancestor of plants and animals required the replacement of effectively all of the common ancestral components in one or both lineages. Nonetheless, the examples cited above suggest that this is indeed plausible. The apparent differences in the components of the clock in early plant lineages, the green algae and bryophytes, versus the angiosperms, argues that this evolutionary reconfiguration of the circadian clock has persisted throughout evolution of the green lineage. The existence of mechanisms to replace components in regulatory networks with non-homologous components places a significant constraint on the interpretation of the complexity of ancient plant clocks based solely on the conservation of angiosperm clock components. As forward genetic analysis of the *C. reinhardtii* circadian clock [110] exemplifies, functional analysis will be essential to ground such comparative analyses.

The speculation about the evolution of clocks within the eukaryotic lineage ignores another salient question about the evolution of clocks. The "flight from light" hypothesis posits an early evolutionary origin for clocks [132]. Consistent with this is the characterization of a cyanobacterial clock as well as the description of a circadian rhythm in the redox status of peroxiredoxin in bacteria and Archaea as well as in eukaryotes [3,144,145]. This latter rhythm is associated with the cellular response to reactive oxygen species and likely represents a response to the evolution of oxygenic photosynthesis and the accumulation of molecular oxygen, the Great Oxidation Event [3]. Strikingly, this peroxiredoxin rhythm persists in the absence of transcription in *O. tauri* and in human erythrocytes [144,145], as does the cyanobacterial rhythm in phosphorylation state of KaiC [133–135]. One hypothesis is that these post-transcriptional rhythms evolved very early and later the transcription-translation based rhythms found in eukaryotes were superimposed [3,136]. It seems reasonable that these underlying post-translational rhythms might have sustained circadian rhythmicity during the postulated reconfiguration of transcriptional circuitry in eukaryotic clocks discussed above.

This is an exciting time in the study of plant clocks. Genomic analyses enhance the ability to compare clocks among taxa, yet a purely comparative approach is limited. We need to identify "non-model" model species, such as *P. patens*, *C. reinhardtii*, *Brassica*, and certainly some monocots (possibly *Lemna* spp., or *Brachypodium distachyon* [146]) in which functional genomic approaches can transcend the limitations of purely sequence-based genomic analyses. Forward genetics remains an extraordinarily powerful approach in which the organism tells the investigator which genes are important to a process, and there is no question that forward, reverse, and quantitative genetics shall continue to guide us in the analysis of circadian clocks in the green lineage.

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