DOI: 10.1002/cbic.200800385

Synchronization of the Fungal and the Plant Circadian Clock by Light

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Circadian clocks are endogenous time keeping devices that provide temporal control of physiology in accordance with predicted daily changes in the environment. Photoentrainment is the process that synchronizes circadian clocks-and thereby clock-controlled gene expression and physiology-to the environmental day/night cycles. Light is primarily detected by specialized photoreceptors that are coupled—directly or through other signaling components—to the rhythm-generating oscillator. As a consequence, the expression, the activity or the stability of oscillator components are altered, resulting in a change of phase and/or pace of the oscillator. In this review our present knowledge about light absorption/transduction and light-induced modifications of oscillator components in Neurospora crassa *and* Arabidopsis thaliana *is summarized. These systems provide a basis for understanding the molecular mechanisms of entrainment in the fungal and plant circadian systems.*

Introduction

Circadian clocks allow biological systems to anticipate daily changes in their surroundings and to prepare their physiology and behavior for these periodic events. Multiple lines of experimental evidence and epidemiological data suggest that circadian clocks improve the fitness of organisms. Recently, direct evidence for the selective advantage of the circadian clock was demonstrated in cyanobacteria and *Arabidopsis thaliana*.[1,2] All circadian rhythms share three basic properties: 1) they persist even under constant conditions, that is, in the absence of environmental signals, and display a period length of about 24 h; 2) the system is in continuous interaction with the environment, that is, the rhythm can be entrained or reset by environmental cues—light, temperature and nutrients are the most important ones; and 3) the system is temperature-compensated, that is, the period length is stable over a wide range of environmental temperatures.

Circadian rhythm is generated at the cellular level. Circadian oscillators in eukaryotes are based on networks of interconnected transcriptional/translational feedback loops.[3,4] These basic mechanisms are completed by other cellular events, such as post-transcriptional and post-translational modifications, subcellular distribution, assembly and turnover of clock components. A precise orchestration of these processes results in the complex organization of the oscillator. Many basic aspects of the generation of circadian rhythm are similar in eukaryotes. Therefore, model organisms are useful experimental tools for studying the general properties of these systems.

By mediating external signals, input pathways connected to the central oscillator can entrain the clock, and thereby, synchronize endogenous time to external time. This review will focus on and compare systems that mediate light signals to the circadian clock in plants and fungi, represented by *A. thaliana* and *Neurospora crassa*, respectively.

Molecular Organization of the Circadian Clock of *N. crassa*

The central clock proteins Frequency (FRQ) and white collar complex (WCC), which consists of the transcription factors white collar-1 and -2 (WC-1 and -2, respectively), are the classical elements of the interconnected transcriptional/translational feedback loops in *N. crassa*.[4,5] WCC is dominantly localized in the nucleus and promotes the transcription of *frq*. The activity of WCC correlates with its phosphorylation status; its hypophosphorylated form binds to the *frq* promoter with higher affinity than the hyperphosphorylated complex.[6] Phosphorylation of WCC is promoted by FRQ and oscillates in a circadian manner. The activity of WCC increases during the late night and reaches its maximum in the subjective morning. The active (hypophosphorylated) complex supports *frq* transcription, which is then followed, with a 4–6 h delay, by the accumulation of FRQ. FRQ interacts with FRH, which is an FRQ-interacting RNA helicase,[7] and in the nucleus the FRQ–FRH complex (FFC) inhibits WCC, and thus, its own expression.[8,9] In the course of a circadian period, FRQ undergoes various cycles of phosphorylation. Hyperphosphorylated forms of the protein are substrates for degradation pathways. At least a part of the hyperphosphorylated FRQ interacts with FWD-1, an F box/WD-40-repeat-containing protein, which is part of an SCF-type ubiquitin ligase complex. The ubiquitinated FRQ then becomes degraded by the proteasome system.[10] When FRQ levels are reduced below a certain threshold, active forms of WCC bind to the *frq* promoter, and *frq* transcription is initiated again.

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Since phosphorylation of both FRQ and the WCC is a crucial control mechanism, kinases and phosphatases are also important factors in the negative feedback loop. Casein kinase-1a (CK-1a) and -II (CKII) have been shown to contribute to the FRQ-dependent inactivation of WCC.[5] The kinases CK-1a, CKII and CAMK-1 and the protein phosphatases PP1 and PP2A are involved in the control of FRQ phosphorylation.[9,11–13]

The central negative feedback loop is interconnected with other feedback loops. By forming a positive loop, FRQ post-transcriptionally increases WC-1 levels and promotes *wc-2* expression at the level of transcription.[14–17] Additionally, WC-1 suppresses *wc-2* expression at the level of transcription,[15] and *wc-1* transcription is positively regulated by WCC.[18] In contrast to *frq*, *wc-1* and *wc-2* RNA levels do not display circadian rhythmicity. However, WC-1 levels show low-amplitude oscillation in a circadian manner.[19]

Blue-Light Receptors of *N. crassa*: Structure–Function Relationship

Two blue-light receptors have so far been characterized in *N. crassa*: WCC and Vivid (VVD). As the primary receptor, WCC is required for all blue-light responses, including clock reset and the control of light-inducible gene expression.[20–22] The WC-2 protein is expressed in excess relative to WC-1, which does not accumulate to detectable levels in the absence of WC-2.[23] The structural organizations of WC-1 and -2 display several similarities. Sequence analysis revealed that both proteins are PAS (Period-ARNT-Sim)-domain-containing transcription factors. WC-1 possesses three PAS domains. The N-terminal PASA domain shows striking similarity to known LOV (light, oxygen or voltage sensor)-domains and is required for all light responses examined so far, but is not necessary for the dark expression of FRQ.[24] The exact role of the second PAS domain (PASB) is not clear. Although the PASB-deleted form of WC-1 is stably expressed in *N. crassa*, both the light and dark functions of WC-1 are abolished in this mutant strain; this suggests an essential role for this domain.[15] The interaction of WC-1 with WC-2 is dependent on the C-terminal PAS domain of WC-1. Accordingly, both the light-induced and circadian functions of WC-1 are diminished when this domain is deleted.[15,25] Putative activation domains are located at both the N and C termini of WC-1. However, in mutants expressing WC-1 forms that lack these polyglutamine stretches, both the light and dark expression of FRQ was reported to be normal. A putative nuclear localization signal (NLS) and a zinc-finger DNA binding domain are located upstream of the C-terminal polyglutamine stretch. Surprisingly, deletion of the NLS structure does not alter nuclear localization of the protein, but is required, as is the zinc-finger domain, for the dark expression of FRQ. On the other hand, deletions of these domains do not influence the function of WCC as a blue-light receptor. In other words, light induction of early responding genes is normal in the mutant strains.[15]

Many aspects of the domain organization of WC-2 resemble the WC-1 structure. Based on sequence analysis five characteristic domains have been identified in WC-2: an activation domain at the N terminus, a PAS domain, a coiled-coil structure, an NLS and a zinc-finger domain.[22] Point mutations of conserved amino acids in the coiled-coil domain and an N-terminal deletion that includes the putative activation domain, lead to similar phenotypes.[25] The mutant WC-2 forms still interact with WC-1 and support FRQ expression, but conidiation rhythm dampens after two days in the mutants; this suggests that both regions are important for robust oscillation of the circadian clock. The WC-2 PAS domain, similarly to PASC in WC-1, is essential for the formation of WCC.[25] Surprisingly, also in case of WC-2, the putative NLS is not required for nuclear localization of the protein.[26] The GATA-type zinc finger motif of WC-2 is essential for both the light and dark functions of WCC.[22,27]

The VVD receptor is generally considered to be a repressor of light responses,[28–30] but its mode of action is still poorly understood. It is a small cytosolic protein consisting of a single LOV domain at the C terminus and an α-helix with a short extension at the N terminus.[31,32] Expression of VVD is dependent on light; neither *vvd* RNA nor VVD can be detected in constant darkness.[7,28–30] Following light-to-dark transfer, *vvd* transcript levels show circadian variations during the first day.[28] However, VVD levels decline rapidly in the dark, and after a 4–6 h incubation in the dark, VVD is undetectable. Both *vvd* transcript and protein levels depend on temperature; higher levels can be detected at lower temperatures.[33] Although VVD is not required for free-running rhythmicity, it does affect the circadian clock. In *vvd* mutants, a slightly longer free-running period and a significant (4 h) phase delay can be observed.[28] In addition, temperature compensation of phase setting on the first day in the dark also depends on VVD.[33]

Light Perception and Photoadaptation in *N. crassa*

The WC-1 conformation can be directly modified by light due to the photoreaction of its LOV domain. The LOV domains have been most thoroughly studied in plant phototropins. In the dark, LOV domains noncovalently bind flavin mononucleotide (FMN). Upon photoactivation, FMN becomes covalently coupled to a highly conserved cysteine by forming a reversible photoadduct.[34] In contrast to plant phototropins, the LOV domain of WC-1 is associated with FAD[24,35] and undergoes a photocycle with a relatively long period (>1 h).[36]

Light-induced genes can be divided into two main classes according to the kinetics of the light response. The induction of immediate light-inducible genes (e.g., *al-1*, *al-2*, *al-3*, *frq*, *wc-1*, *con-6*, *con-10* and *vvd*) begins after ≤ 5 min, and transcript levels reach their maximum within 15–20 min.[37] In contrast, late-responsive genes (e.g., *ccg-1* and *ccg-2*) show expression peaks 1–2 h after exposure to light.[38,39] Figure 1 summarizes the major effects of light on WCC. Light transiently induces binding of WCC to the light-responsive elements (LREs) in promoters of immediate light-induced genes.[36] All LREs characterized so far contain GATX repeats spaced by segments of 5–14 base pairs.[18,36,40,41] The initial burst of gene expression induced by light is transient, followed by a down-regulation of light-dependent transcription, a process called photoadaptation.

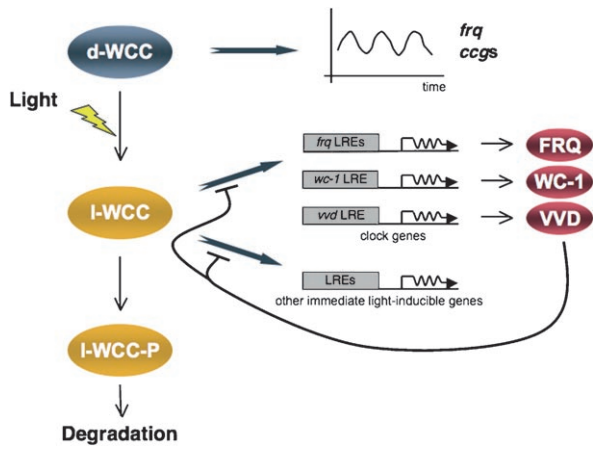

Figure 1. Our current molecular model of the light response of *N. crassa*. Light-activated white collar complex (WCC) induces gene expression, becomes phosphorylated and degraded. Both photoadaptation and gating are dependent on Vivid (VVD). For details, see the main text.

The mechanism by which light-activated WCC induces gene transcription is only partially understood. Recently, the light-inducible increase of acetylation of histone H3 has been reported in chromatin associated with the *al-3* promoter.[42] This acetylation is dependent on WC-1 and NGF-1, a *N. crassa* homologue of the yeast histone acetyltransferase GCN5. The kinetics of histone acetylation at the *al-3* promoter is tightly synchronized with both the binding of WCC to the LRE and changes in the transcript levels. These observations suggest a model in which NGF-1 is recruited by the light-activated WCC to the target gene. The corresponding histone then becomes acetylated and this "open" chromatin structure allows transcription of the light-induced gene.

A complex containing only recombinant WC-1 and -2 is sufficient to mediate light-dependent binding to the LREs.[36] Whether the light complex contains components other than WC-1 and -2 in vivo is still not known. The exposure of purified WCC to light reduces its electrophoretic mobility in electrophoretic mobility shift assays (EMSA); this suggests that light activation results in the formation of a larger complex.[40] Parallel to activation, light also triggers the phosphorylation and degradation of WCC.[16,43] The hyperphosphorylation of WC-1 coincides with the already reduced activity of the complex. In addition, the light-induced interaction of WCC with LRE in vitro does not require phosphorylation of WC-1 and can be enhanced by dephosphorylation of the protein. These data indicate that phosphorylation is coupled to the inactivation rather than to the activation of WCC.[36] However, it cannot be excluded that transcriptional induction by WCC is dependent on phosphorylation of the complex. Protein kinase C (PKC) was implicated as a negative regulator of light-activated WCC. PKC interacts with the dark complex, but this interaction is promptly destabilized by light. In a strain expressing a constitutively active form of PKC, light-induced gene expression has been found to be decreased, whereas in transformants expressing a dominant negative form of PKC, the opposite effect was observed. In addition, the light-induced degradation of WCC is also dependent on PKC.[44] Despite the data summarized above, the exact mechanism of how PKC affects the light response is still not clear. Photoactivated WC-1 again becomes dephosphorylated and is activatable within 2 h following a light-to-dark transfer.[36] However, the pathway of regeneration of photoactivatable WC-1 is still unclear.

Photoadaptation is dependent on VVD[19,28] (Figure 1). In strains expressing dysfunctional VVD, expression levels of immediate light-induced genes are elevated, photoadaptation is partially lost, and the light-induced hyperphosphorylation of WC-1 persists for several hours.[28,29] The LOV domain of VVD binds FAD and shows striking similarity to the WC-1 LOV domain. Analysis of the crystal structure of a functional fragment of VVD suggests that in the dark state the N-terminal helix tightly interacts with the LOV domain.[32] Upon illumination, the N terminus of VVD undergoes conformational changes and becomes partially released from the protein core. However, light-induced structural changes in VVD seem to be modest. In a recent study, light-dependent conformational changes were shown to lead to homodimerization of VVD in vitro. These results suggest a model in which a similar interaction between the LOV domains of VVD and WC-1 could lead to inhibition of light-activated WCC.[45] On the other hand, VVD was mainly detected in the cytosol,[31] and therefore, the exact mechanism by which it affects the activity of nuclear WCC is unclear.

Entrainment and Resetting of the *N. crassa* Clock by Light

The transcription of *frq* is immediately and strongly induced by light. This response is characteristically gated by the clock such that identical light signals result in a different extent of gene induction dependent on the circadian phase.[28] When a light pulse is administered around (subjective) dusk, the clock is reset towards the preceding afternoon, and the phase of clock-controlled processes is accordingly delayed. Light stimuli received in the subjective late night reset the clock to the next morning; this results in phase advance. However, throughout the middle of the day, the circadian clock is relatively unresponsive to light. The *wc-1* RNA is transiently induced by light and then adapts to levels similar to those detected in constant dark. When *wc-1* expression is controlled by a constitutive promoter, the phase of conidiation is delayed under light/dark conditions; this suggests that light-triggered elevation of *wc-1* expression is required to adjust the circadian phase of clock output.[18]

The VVD receptor is also an important modulator of the circadian clock under photoperiodic entrainment. On one hand, as a gating factor, VVD can shield the circadian oscillator from disturbing light effects, and thereby, contributes to the robustness of circadian oscillation. On the other hand, by muting the light induction of *frq* at dawn, VVD sustains a circadian clock running during the photoperiod, and thus, maintains the phase of spore formation during light/dark cycles.[46]

Molecular Organization of the Core Circadian Oscillator in *A. thaliana*

The first transcriptional/translational regulatory loop in a plant circadian clock was identified in 2001.[47] Late elongated hypocotyl (LHY) and circadian clock associated 1 (CCA1) are Myb-related transcription factors expressed in the morning.[48,49] LHY and CCA1 share a high degree of sequence homology, their expression pattern is almost identical, and they both repress the transcription of *timing of cab expression 1* (*TOC1*) during the day. When the expression levels of LHY and CCA1 are reduced and the proteins are degraded, the *TOC1* gene can be activated in the evening, and the accumulating TOC1 reinitiates *LHY/CCA1* transcription the next morning. The TOC1 protein belongs to the family of pseudo-response regulators (PRRs), which consists of five members (PRR1, 3, 5, 7 and 9);[50] TOC1 is also known as PRR1. All PRRs affect circadian rhythmicity, though the most severe phenotypes are caused by the misexpression of TOC1/PRR1. The PRRs are not DNA-binding proteins, so they probably do not regulate transcription directly, but through interaction with specific transcription factors and/or other signaling intermediates.

Both mathematical modeling and various experimental approaches have revealed two additional regulatory loops coupled to the *LHY/CCA1-TOC1* circuit. The "evening loop" is formed by TOC1 and a hypothetical factor Y, both of which are expressed in the evening. Factor Y positively regulates *TOC1*, whereas TOC1 represses *y* transcription, which is also inhibited by LHY/CCA1. TOC1 promotes *LHY/CCA1* transcription through another hypothetical component, X.[51] It has been demonstrated that Gigantea (GI), a nuclear protein with an unclear biochemical function, is an essential contributor to factor Y function.[52] The "morning loop" is formed by LHY/CCA1 and PRR7/9. LHY/CCA1 activates *PRR7/9* expression in the morning; conversely, PRR7/9 inhibits *LHY/CCA1* expression during the rest of the day.[53] The coordinated function of the three loops is required to generate the ~24 h basic oscillations in *A. thaliana* (Figure 2).

The genes and proteins described above can be considered oscillator components, since their participation in the transcriptional/translational feedback loops has been clearly demonstrated. However, a number of clock-associated components have also been identified, which are not elements of the regulatory circuits, but affect the transcription of clock genes or modulate the abundance or activity of certain clock proteins. Many of these components are implicated in the process of entrainment, and they are discussed in detail below.

The Origin of Light Signals: Photoreceptors Mediating Entrainment in *A. thaliana*

Plants are sessile and obligate photoautotrophs, and have therefore developed several photoreceptors to constantly monitor the changing light environment in order to adapt their physiology accordingly. These photoreceptors differ in spectral and fluence sensitivity and in the molecular/physiolog-

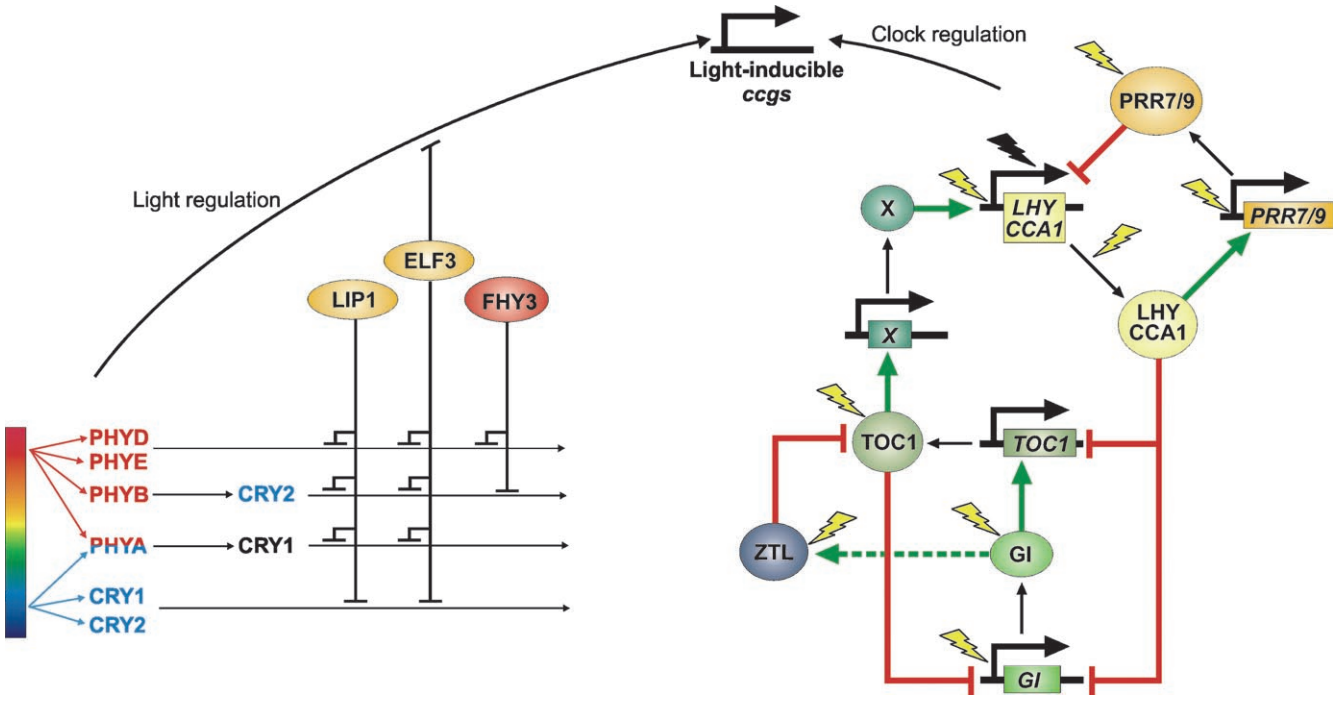

Figure 2. Light input routes to the plant circadian oscillator. Clock genes and proteins are symbolized by rectangles and ellipses, respectively; black arrows indicate translation. Components of the "morning" and "evening" loops are indicated by yellow and green, respectively. Green arrows and red blunt-ended lines represent activation and inhibition, respectively. Yellow bolts indicate the positive effect of light on transcription/translation rates or protein stability. The black bolt shows the negative effect of light on *circadian clock associated 1* (*CCA1*) and *late elongated hypocotyls* (*LHY*) mRNA stability. Zeitlupe (ZTL) promotes the degradation of timing of cab expression 1 (TOC1). Gigantea (GI) interacts with ZTL in a light-dependent manner; this results in the stabilization of both proteins.

ical responses they trigger. Here, we discuss members of two photoreceptor families that are involved in absorbing and transducing light signals to the plant circadian oscillator.

Phytochromes (PHYA–E) are red/far-red-light-absorbing photoreceptors and function as molecular light switches.[54] In the dark, PHYs are present in their inactive red-light-absorbing (Pr) form ($\lambda_{max} = 660$ nm). After capturing a photon with the covalently bound, linear, tetrapyrrol chromophore, they are converted to the active far-red-light-absorbing conformer (Pfr), which initiates downstream signaling events. The active Pfr form is converted to Pr by far-red light ($\lambda_{max} = 730$ nm). PHYA, the most sensitive and light-labile member of this family, has a slightly different absorption spectrum from that of the other PHYs; the Pr form of PHYA can absorb blue and far-red light in addition to red light. As a result, PHYA can be activated by almost any wavelength of visible light, but can be inactivated (converted to Pr) only by near infrared light ($\lambda_{max} = 775$ nm). The PHYs are synthesized in the cytosol in their Pr form, and after light activation, they are translocated to the nucleus, where they form characteristic nuclear bodies (NBs).[55] The exact composition and function of NBs is not yet known, but they might represent multiprotein complexes in which PHYs interact with transcription factors and other regulatory proteins to control the expression of light-induced genes. The first protein found to interact with PHYs was phytochrome interacting factor 3 (PIF3).[56] PIF3 is a member of a family of basic helix-loop-helix-type transcription factors implicated in phytochrome-dependent light signaling. PIFs appear to regulate the transcription of a subset of early light-induced genes, which are induced within an hour after exposure to light, and to negatively control PHYB levels during continuous red-light irradiation.[57] However, the misexpression of two members of the PIF family (PIF3[58] and PIF5[59]) does not affect entrainment of the plant circadian clock. Although the lack of such phenotypes could be explained by possible redundant coaction of several PIF3-like transcription factors,[60] PIFs are probably not the terminal components of PHY-mediated red-light input to the clock.

Another regulatory protein that interacts with PHYs in the nucleus is constitutively photomorphogenic 1 (COP1).[61] COP1 is an E3 ubiquitin ligase that promotes dark-dependent degradation of master transcription factors, and positively regulates light-responsive genes.[62] PHYs inhibit the activity of COP1 by excluding it from the nucleus during the light period.[63] This allows the accumulation of master transcription factors in the nucleus and the subsequent transcription of light-induced genes, which include at least two circadian clock genes, *LHY* and *CCA1*.[64]

In terms of circadian function, PHYA mediates far-red, low-intensity, blue and red light signals to the clock, whereas PHYB, D and E function redundantly as input receptors in the high-fluence range of red light (Figure 2).[65–67] The relatively low contribution of PHYD and E to the entrainment of the plant clock is indicated by the fact that the function of these receptors can be revealed in multiple mutant backgrounds that lack PHYA and B in addition to PHYD or E. The clocks of *phyd* and *phye* single mutants show a wild-type response to red light.[66]

A. thaliana cryptochromes (CRY1 and -2) are flavin-binding chromoproteins that absorb blue and ultraviolet-A (UV-A) light. The CRYs were first discovered in plants,[68] and it was soon demonstrated that they are present in most eukaryotes and are implicated in the circadian clocks of *A. thaliana*, *Drosophila* and mouse. In plants and insects, CRYs function as circadian photoreceptors that transduce blue light signals to the oscillator.[65,66,69] In *Drosophila*, CRY interacts with the oscillator component Timeless (TIM) in a light-dependent manner; this initiates the ubiquitination and subsequent degradation of TIM.[70] Although some data indicate a role for CRYs in circadian photoperception in mice,[71] mammalian CRYs have an essential light-independent function in the basic negative feedback loop by inhibiting the activity of transcription factors CLK and BMAL1.[72] In contrast, the molecular mechanism by which plant CRYs can affect the clock and blue-light-controlled gene expression is still not fully understood. Blue-light absorption causes the rapid reduction of the FAD chromophore followed by the phosphorylation of the apoprotein.[73,74] Phosphorylation probably occurs at multiple residues and is essential for the biological function of CRYs. Moreover, purified CRY proteins are phosphorylated in response to blue light in vitro; this indicates that the phosphotransfer function is an intrinsic property of photoactivated CRYs.[75] Phosphorylation might lead to a conformational change that results in the exposure of the C-terminal domain, which would then offer an interaction surface for downstream signaling partners.[76] This hypothesis is supported by the fact that expression of the C-terminal domain provokes constitutive light responses even in the dark.[77] CRYs interact with COP1 in the nucleus and inhibit its activity by an unknown mechanism.[78] This might explain the significant overlap of PHY- and CRY-induced genes.[79]

CRY1 and CRY2 show conditional redundancy when blue light is the input for the clock. Mutation of *cry1* affects the pace of the clock at low and high fluences of blue light, whereas the effect of *cry2* mutations is almost negligible. However, *cry1*/*cry2* double mutants show significant period lengthening over the entire range of fluence rates tested[66] (Figure 2).

Several results indicate functional and physical interactions between red and blue light receptors. CRY1 seems to be necessary for red-light signaling by PHYA, but this does not require light-activated CRY1.[66] On the other hand, photoactivated PHYB is required for the full function of CRY2[80] (Figure 2). Direct interactions between CRY1 and PHYA[81] and CRY2 and PHYB[80] have also been demonstrated, providing a physical basis for the functional crosstalk between the two light-signaling systems.

Figure 2 illustrates the functional organization of light-input pathways and the three-loop oscillator in *A. thaliana*. Red- and blue-light signals are detected and transduced by PHYA–B, D–E and CRY1 and -2 photoreceptors. PHYA is activated by low fluences of red and also blue light. CRY1 is required for PHYA signaling and CRY2 contributes to PHYB signaling to the clock. Light insensitive period 1 (LIP1) and early flowering 3 (ELF3) at-

tenuate light input of any quality during the early subjective night, whereas far-red elongated hypocotyl 3 (FHY3) specifically gates the effects of red light. Unlike LIP1 or FHY3, ELF3 inhibits the acute light induction of light-responsive and clock-controlled genes. The final molecular steps/events of light signaling to the clock remain to be elucidated.

Targets of Light Signals: Light-Induced Changes in Transcription, Translation or Protein Turnover of Clock Components

In general, light signals can entrain or reset the circadian clock by affecting the expression, activity, stability or subcellular localization of one or more oscillator components. In this section, we discuss the available data regarding the effect of light signals on the known components of the plant circadian clock (Figure 2).

The transcription of several clock genes shows an acute transient induction in response to light. These include *LHY*, *CCA1*, *PRR9* and *GI*.[50,51,82,83] These studies used monochromatic light with different wavelengths on different plant materials, but a set of comprehensive microarray data at AtGenExpress[84] demonstrates that the transcription of these clock genes can be induced by red, far-red and blue light; this indicates the contribution of both photoreceptor families. In order to link these transcriptional changes to the entrainment process, it will be necessary to 1) test how the light inducibility of these components is modulated over a circadian cycle and 2) test if significant protein accumulation follows the transient increase in mRNA levels.

Although the transcriptions of *LHY* and *CCA1* are induced by light, the corresponding mRNAs seem to be degraded by light.[85] It has been demonstrated that red and blue, but not far-red light, is effective in destabilizing *CCA1* mRNA. The simultaneous induction of transcription and mRNA degradation could narrow the expression peaks of LHY and CCA1 around dawn, which can contribute to a more precise timing of these expression events, and therefore, to proper entrainment.

Similar functional significance can be attributed to the light induction of *LHY* translation.[86] By using a transgenic line constitutively over-expressing LHY, it has been shown that the translation of *LHY* is induced by light. The induced level of LHY depends on the amount of the available *LHY* mRNA, which shows a peak at dawn in wild-type plants. Therefore, this mechanism is thought to increase the amplitude of LHY cycling and contribute to the robustness of the clock.

The cyclic removal of clock proteins is crucial for oscillator function. Not surprisingly, regulated proteolysis plays a crucial role in all eukaryotic circadian systems. In plants, the controlled degradation of TOC1, GI, PRR7 and PRR9 has been studied so far.[87–90] Interestingly, all proteins are preferentially degraded in the dark. TOC1 degradation is controlled by the F-box protein Zeitlupe (ZTL),[87,91] but the mechanism of GI degradation is still unclear. ZTL belongs to a small protein family consisting of two additional members: LOV kelch protein 2 (LKP2) and flavin binding, kelch repeat F-box 1 (FKF1).[92,93] These proteins share a unique combination of three protein domains: an N-terminal PAS-like LOV domain, a central F-box motif and a C-terminal domain of six kelch repeats. The F-box proteins direct substrates for Skp1–Cullin–F-box (SCF)-type E3 ubiquitin ligases.[94] The F-box motif mediates the interaction with the Skp1 protein of the complex, whereas the C-terminal part is responsible for binding the target protein. The LOV/PAS domain shows significant similarity to the chromophore-binding LOV domains found in the blue-light receptors WC-1 in *N. crassa*[40] and phototropin 1 in *A. thaliana*;[95] this suggests that ZTL, LKP2 and FKF1 could function as light-regulated F-box proteins. ZTL binds TOC1, an event that promotes TOC1 degradation.[87] Under these circumstances, TOC1 levels are high and show very low amplitude rhythms in *ztl* mutants. The interaction between the two proteins seems to be light-independent, but the degradation rate of TOC1 is increased in the dark.[87,96] The *ZTL* mRNA is expressed constitutively, but ZTL abundance shows rhythmic changes that are interestingly in-phase with TOC1. The rhythmicity in ZTL levels is due to an interaction between ZTL and GI. The interaction depends on blue light absorbed by ZTL and stabilizes both proteins. Since GI is expressed rhythmically at all levels, this rhythmic pattern is transferred to ZTL abundance as a result of the stabilizing ZTL–GI interaction.[96] The data discussed above show that light stabilizes ZTL, but this seems to be unrelated to its function, because light represses TOC1 degradation. It is possible that some aspects of ZTL function (e.g., those association with the SCF complex, but not binding to TOC1) are inhibited by light, or that another factor that co-acts with ZTL provides light control for the process. Nevertheless, this regulation ensures that ZTL and TOC1 levels can gradually build up during the day and reach their maxima soon after dusk. TOC1 degradation is then enabled in the dark and is facilitated by a large pool of accumulated ZTL. LKP2 could have a redundant function in this process,[93,96,97] whereas FKF1 is involved in the light-dependent degradation of repressors of flowering but has no function that targets the clock.[98]

Clock-Associated Factors Implicated in Entrainment

In addition to ZTL, there are several clock-associated components that are not part of the basic feedback loop but are important for the expression or modification of clock components. In this section, a brief overview that focuses on factors the functions of which are related to entrainment is provided. It should be noted, however, that the molecular mechanism by which these factors affect the light input pathways is not understood yet.

ELF3 is a rhythmically expressed nuclear protein required for the transcription of *LHY* and *CCA1*.[99,100] ELF3 has an essential function in gating the effect of red- and blue-light signals on the induction of clock-controlled and light-regulated genes and on the resetting of the oscillator itself.[101] In *elf3* null mutants, the clock stops after 10–12 h in constant light and restarts from this phase if the plants are transferred to the dark; this suggests that ELF3 is required to neutralize light signaling to the clock during the early night.[102]

FHY3 is a transcription factor originally identified as a component of PHYA-mediated signaling in photomorphogenesis.[103,104] The analysis of circadian properties in *fhy3* mutants revealed an important function of FHY3 in gating red-light signals to the clock during the morning.[105] The *fhy3* mutants become arrhythmic in constant red light after one day, and the oscillator appears to stop in a phase that corresponds to the subjective morning. The transfer of plants to darkness restarts the oscillator from this phase. Interestingly, the gating of induction of rhythmically expressed, light-regulated genes is unaffected by the mutation. Unlike ELF3, which has a general role in gating all light responses, FHY3 attenuates only red-light signaling to the oscillator. However, like ELF3, FHY3 also seems to be required for the transcription of the *LHY*/*CCA1* genes.

LIP1 is a small GTP-binding protein that affects entrainment in a specific way.[106] In wild-type plants, free-running periods are shortened with increasing fluences of constant light (Aschoff's rule). In contrast, only subtle changes in period length can be observed in *lip1* mutant plants; this suggests a role for LIP1 in the light-dependent period shortening of circadian rhythms. Moreover, LIP1 gates light signaling to the clock during the early subjective night. However, the elimination of this gating function (i.e., in the *lip1* mutant) does not lead to arrhythmicity under any conditions.

Outlook

In this review, we have introduced the light input pathways of two eukaryotic circadian clocks. In *N. crassa*, the same factors function as positive elements of the circadian oscillator and the blue-light receptor mediating environmental light signals to the clock. In *A. thaliana*, members of two photoreceptor families, PHYs and CRYs, are involved in the transduction of light signals to the circadian oscillator. Although light influences the expression of clock elements at almost all levels in *A. thaliana*, the molecular coupling between the photoreceptors and the circadian clock is still poorly understood. Two members of the phytochrome superfamily have also recently been characterized in *N. crassa*.[107] However, *phy* mutants synchronized by light-to-dark transfer fail to display a circadian phenotype; this suggests that PHYs are not involved in the light input to the *N. crassa* clock. In both systems, blue-light absorption is followed by phosphorylation of the corresponding photoreceptor. This modification in *A. thaliana* is supposed to be a prerequisite of photoreceptor interaction with downstream signaling partners, whereas the function and the direct consequence(s) of light-induced phosphorylation of *N. crassa* WC-1 is still unclear. Light-dependent change in the turnover of clock proteins seems to be a crucial mechanism both in *N. crassa* and *A. thaliana*. The light-triggered degradation of WC-1 is partially inhibited by VVD and compensated by the light induction of *wc-1* expression. The light-dependent repression of TOC1, GI, PRR7 and PRR9 degradation might be a mechanistic link between light signals and clock function in *A. thaliana*. ELF3 and VVD show parallel functions in entrainment of the circadian clock in *A. thaliana* and *N. crassa*, respectively. Both proteins are required to sustain the circadian clock running in extended photoperiods.

As a result of the temporal organization provided by circadian clocks, a wide range of molecular and physiological processes are scheduled to the most appropriate time of the day. It is generally accepted that this important function of circadian clocks has facilitated the evolution of these timing mechanisms. To fulfill this role, clocks must be precisely synchronized to day/night cycles. The synchronization process—also called entrainment or resetting—involves interactions between daily environmental signals and the core components of the oscillator and is absolutely required for the adaptive properties of the clock. Despite the substantial data reviewed in this paper, it is clear that further research is required to reveal the molecular details of entrainment in order to understand how the endogenous clock is ticking in the real world.

Acknowledgements

This work was supported by the European Molecular Biology Organization–Howard Hughes Medical Institute and the Hungarian National Scientific Research Fund (OTKA, K 68960) to K.K. and by the European Commission (Marie Curie European Reintegration Grant, No. MERG-CT-2006-044982) and the Hungarian Academy of Sciences (János Bólyai Research Scholarship) to L.K.-B. We thank Norbert Gyöngyösi for help in preparing the table of contents image and Erzsébet Fejes for critical reading of the manuscript.

Keywords: circadian rhythm · cryptochromes · frequency · phytochromes · white collar complex

[1] M. A. Woelfle, Y. Ouyang, K. Phanvijhitsiri, C. H. Johnson, *Curr. Biol.* **2004**, *14*, 1481–1486.
[2] A. N. Dodd, N. Salathia, A. Hall, E. Kévei, R. Tóth, F. Nagy, J. M. Hibberd, A. J. Millar, A. A. R. Webb, *Science* **2005**, *309*, 630–633.
[3] M. W. Young, S. A. Kay, *Nat. Rev. Genet.* **2001**, *2*, 702–715.
[4] J. C. Dunlap, J. J. Loros, *J. Biol. Rhythms* **2004**, *19*, 414–424.
[5] Q. He, J. Cha, Q. He, H. C. Lee, Y. Yang, Y. Liu, *Genes Dev.* **2006**, *20*, 2552–2565.
[6] T. Schafmeier, A. Haase, K. Kaldi, J. Scholz, M. Fuchs, M. Brunner, *Cell* **2005**, *122*, 235–246.
[7] Q. He, H. Shu, P. Cheng, S. Chen, L. Wang, Y. Liu, *J. Biol. Chem.* **2005**, *280*, 17526–17532.
[8] B. D. Aronson, K. A. Johnson, J. J. Loros, J. C. Dunlap, *Science* **1994**, *263*, 1578–1584.
[9] M. Gorl, M. Merrow, B. Huttner, J. Johnson, T. Roenneberg, M. Brunner, *EMBO J.* **2001**, *20*, 7074–7084.
[10] Q. He, P. Cheng, Y. Yang, Q. He, H. Yu, Y. Liu, *EMBO J.* **2003**, *22*, 4421–4430.
[11] Y. Yang, P. Cheng, G. Zhi, Y. Liu, *J. Biol. Chem.* **2001**, *276*, 41064–41072.
[12] Y. Yang, P. Cheng, Q. He, L. Wang, Y. Liu, *Mol. Cell. Biol.* **2003**, *23*, 6221–6228.
[13] Y. Yang, Q. He, P. Cheng, P. Wrage, O. Yarden, Y. Liu, *Genes Dev.* **2004**, *18*, 255–260.
[14] P. Cheng, Y. Yang, Y. Liu, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 7408–7413.
[15] P. Cheng, Y. Yang, L. Wang, Q. He, Y. Liu, *J. Biol. Chem.* **2003**, *278*, 3801–3808.
[16] K. Lee, J. J. Loros, J. C. Dunlap, *Science* **2000**, *289*, 107–110.
[17] T. Schafmeier, K. Kaldi, A. Diernfellner, C. Mohr, M. Brunner, *Genes Dev.* **2006**, *20*, 297–306.
[18] K. Káldi, B. H. González, M. Brunner, *EMBO Rep.* **2006**, *7*, 199–204.

[19] M. Merrow, L. Franchi, Z. Dragovic, M. Gorl, J. Johnson, M. Brunner, G. Macino, T. Roenneberg, *EMBO J.* **2001**, *20*, 307–315.
[20] P. Ballario, P. Vittorioso, A. Magrelli, C. Talora, A. Cabibbo, G. Macino, *EMBO J.* **1996**, *15*, 1650–1657.
[21] H. Linden, P. Ballario, G. Macino, *Fungal Genet. Biol.* **1997**, *22*, 141–150.
[22] H. Linden, G. Macino, *EMBO J.* **1997**, *16*, 98–109.
[23] D. L. Denault, J. J. Loros, J. C. Dunlap, *EMBO J.* **2001**, *20*, 109–117.
[24] Q. He, P. Cheng, Y. Yang, L. Wang, K. H. Gardner, Y. Liu, *Science* **2002**, *297*, 840–843.
[25] P. Cheng, Y. Yang, K. H. Gardner, Y. Liu, *Mol. Cell. Biol.* **2002**, *22*, 517–524.
[26] C. Schwerdtfeger, H. Linden, *Eur. J. Biochem.* **2000**, *267*, 414–422.
[27] S. K. Crosthwaite, J. C. Dunlap, J. J. Loros, *Science* **1997**, *276*, 763–769.
[28] C. Heintzen, J. J. Loros, J. C. Dunlap, *Cell* **2001**, *104*, 453–464.
[29] C. Schwerdtfeger, H. Linden, *Mol. Microbiol.* **2001**, *39*, 1080–1087.
[30] L. B. Shrode, Z. A. Lewis, L. D. White, D. Bell-Pedersen, D. J. Ebbole, *Fungal Genet. Biol.* **2001**, *32*, 169–181.
[31] C. Schwerdtfeger, H. Linden, *EMBO J.* **2003**, *22*, 4846–4855.
[32] B. D. Zoltowski, C. Schwerdtfeger, J. Widom, J. J. Loros, A. M. Bilwes, J. C. Dunlap, B. R. Crane, *Science* **2007**, *316*, 1054–1057.
[33] S. M. Hunt, M. Elvin, S. K. Crosthwaite, C. Heintzen, *Genes Dev.* **2007**, *21*, 1964–1974.
[34] S. Crosson, K. Moffat, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 2995–3000.
[35] P. Cheng, Q. He, Y. Yang, L. Wang, Y. Liu, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 5938–5943.
[36] Q. He, Y. Liu, *Genes Dev.* **2005**, *19*, 2888–2899.
[37] Z. A. Lewis, A. Correa, C. Schwerdtfeger, K. L. Link, X. Xie, R. H. Gomer, T. Thomas, D. J. Ebbole, D. Bell-Pedersen, *Mol. Microbiol.* **2002**, *45*, 917–931.
[38] G. Arpaia, J. J. Loros, J. C. Dunlap, G. Morelli, G. Macino, *Plant Physiol.* **1993**, *102*, 1299–1305.
[39] G. Arpaia, J. J. Loros, J. C. Dunlap, G. Morelli, G. Macino, *Mol. Gen. Genet.* **1995**, *247*, 157–163.
[40] A. C. Froehlich, Y. Liu, J. J. Loros, J. C. Dunlap, *Science* **2002**, *297*, 815–819.
[41] A. Carattoli, C. Cogoni, G. Morelli, G. Macino, *Mol. Microbiol.* **1994**, *13*, 787–795.
[42] B. Grimaldi, P. Coiro, P. Filetici, E. Berge, J. R. Dobosy, M. Freitag, E. U. Selker, P. Ballario, *Mol. Biol. Cell* **2006**, *17*, 4576–4583.
[43] C. Talora, L. Franchi, H. Linden, P. Ballario, G. Macino, *EMBO J.* **1999**, *18*, 4961–4968.
[44] L. Franchi, V. Fulci, G. Macino, *Mol. Microbiol.* **2005**, *56*, 334–345.
[45] B. D. Zoltowski, B. R. Crane, *Biochemistry* **2008**, *47*, 7012–7019.
[46] M. Elvin, J. J. Loros, J. C. Dunlap, C. Heintzen, *Genes Dev.* **2005**, *19*, 2593–2605.
[47] D. Alabadi, T. Oyama, M. J. Yanovsky, F. G. Harmon, P. Mas, S. A. Kay, *Science* **2001**, *293*, 880–883.
[48] R. Schaffer, N. Ramsay, A. Samach, S. Corden, J. Putterill, I. A. Carre, G. Coupland, *Cell* **1998**, *93*, 1219–1229.
[49] Z. Y. Wang, E. M. Tobin, *Cell* **1998**, *93*, 1207–1217.
[50] A. Matsushika, S. Makino, M. Kojima, T. Mizuno, *Plant Cell Physiol.* **2000**, *41*, 1002–1012.
[51] J. C. W. Locke, M. M. Southern, L. Kozma-Bognár, V. Hibberd, P. E. Brown, M. S. Turner, A. J. Millar, *Mol. Syst. Biol.* **2005**, *1*, 2005.0013.
[52] J. C. Locke, L. Kozma-Bognár, P. D. Gould, B. Fehér, E. Kevei, F. Nagy, M. S. Turner, A. Hall, A. J. Millar, *Mol. Syst. Biol.* **2006**, *2*, 59.
[53] E. M. Farre, S. L. Harmer, F. G. Harmon, M. J. Yanovsky, S. A. Kay, *Curr. Biol.* **2005**, *15*, 47–54.
[54] N. C. Rockwell, Y. S. Su, J. C. Lagarias, *Annu. Rev. Plant Biol.* **2006**, *57*, 837–858.
[55] S. Kircher, P. Gil, L. Kozma-Bognár, E. Fejes, V. Speth, T. Husselstein-Muller, D. Bauer, E. Ádám, E. Schäfer, F. Nagy, *Plant Cell* **2002**, *14*, 1541–1555.
[56] M. Ni, J. M. Tepperman, P. H. Quail, *Cell* **1998**, *95*, 657–667.
[57] B. Al-Sady, E. A. Kikis, E. Monte, P. H. Quail, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 2232–2237.
[58] A. Viczian, S. Kircher, E. Fejes, A. J. Millar, E. Schäfer, L. Kozma-Bognár, F. Nagy, *Plant Cell Physiol.* **2005**, *46*, 1591–1602.
[59] T. Fujimori, T. Yamashino, T. Kato, T. Mizuno, *Plant Cell Physiol.* **2004**, *45*, 1078–1086.
[60] A. Castillon, H. Shen, E. Huq, *Trends Plant Sci.* **2007**, *12*, 514–521.
[61] X. W. Deng, M. Matsui, N. Wei, D. Wagner, A. M. Chu, K. A. Feldmann, P. H. Quail, *Cell* **1992**, *71*, 791–801.
[62] C. Yi, X. W. Deng, *Trends Cell Biol.* **2005**, *15*, 618–625.
[63] M. T. Osterlund, X. W. Deng, *Plant J.* **1998**, *16*, 201–208.
[64] L. Ma, Y. Gao, L. Qu, Z. Chen, J. Li, H. Zhao, X. W. Deng, *Plant Cell* **2002**, *14*, 2383–2398.
[65] D. E. Somers, P. F. Devlin, S. A. Kay, *Science* **1998**, *282*, 1488–1490.
[66] P. F. Devlin, S. A. Kay, *Plant Cell* **2000**, *12*, 2499–2510.
[67] M. J. Yanovsky, M. A. Mazzella, G. C. Whitelam, J. J. Casal, *J. Biol. Rhythms* **2001**, *16*, 523–530.
[68] M. Ahmad, A. R. Cashmore, *Nature* **1993**, *366*, 162–166.
[69] P. Emery, W. V. So, M. Kaneko, J. C. Hall, M. Rosbash, *Cell* **1998**, *95*, 669–679.
[70] M. F. Ceriani, T. K. Darlington, D. Staknis, P. Mas, A. A. Petti, C. J. Weitz, S. A. Kay, *Science* **1999**, *285*, 553–556.
[71] C. P. Selby, C. Thompson, T. M. Schmitz, R. N. Van Gelder, A. Sancar, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 14697–14702.
[72] E. A. Griffin, Jr., D. Staknis, C. J. Weitz, *Science* **1999**, *286*, 768–771.
[73] R. Banerjee, E. Schleicher, S. Meier, R. M. Viana, R. Pokorny, M. Ahmad, R. Bittl, A. Batschauer, *J. Biol. Chem.* **2007**, *282*, 14916–14922.
[74] D. Shalitin, H. Yang, T. C. Mockler, M. Maymon, H. Guo, G. C. Whitelam, C. Lin, *Nature* **2002**, *417*, 763–767.
[75] D. Shalitin, X. Yu, M. Maymon, T. Mockler, C. Lin, *Plant Cell* **2003**, *15*, 2421–2429.
[76] C. Lin, T. Todo, *Adv. Genome Biol.* **2005**, *6*, 220.
[77] H. Q. Yang, Y. J. Wu, R. H. Tang, D. Liu, Y. Liu, A. R. Cashmore, *Cell* **2000**, *103*, 815–827.
[78] H. Wang, L. G. Ma, J. M. Li, H. Y. Zhao, X. W. Deng, *Science* **2001**, *294*, 154–158.
[79] S. Lorrain, T. Genoud, C. Fankhauser, *Curr. Opin. Plant Biol.* **2006**, *9*, 509–514.
[80] P. Más, P. F. Devlin, S. Panda, S. A. Kay, *Nature* **2000**, *408*, 207–211.
[81] M. Ahmad, J. A. Jarillo, O. Smirnova, A. R. Cashmore, *Mol. Cell* **1998**, *1*, 939–948.
[82] Z. Y. Wang, D. Kenigsbuch, L. Sun, E. Harel, M. S. Ong, E. M. Tobin, *Plant Cell* **1997**, *9*, 491–507.
[83] J. M. Tepperman, T. Zhu, H. S. Chang, X. Wang, P. H. Quail, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 9437–9442.
[84] T. Kretsch, http://www.weigelworld.org
[85] E. Yakir, D. Hilman, M. Hassidim, R. M. Green, *Plant Physiol.* **2007**, *145*, 925–932.
[86] J. Y. Kim, H. R. Song, B. L. Taylor, I. A. Carre, *EMBO J.* **2003**, *22*, 935–944.
[87] P. Más, W.-Y. Kim, D. E. Somers, S. A. Kay, *Nature* **2003**, *426*, 567–570.
[88] K. M. David, U. Armbruster, N. Tama, J. Putterill, *FEBS Lett.* **2006**, *580*, 1193–1197.
[89] E. M. Farré, S. A. Kay, *Plant J.* **2007**, *52*, 548–560.
[90] S. Ito, N. Nakamichi, T. Kiba, T. Yamashino, T. Mizuno, *Plant Cell Physiol.* **2007**, *48*, 1644–1651.
[91] D. E. Somers, T. F. Schultz, M. Milnamow, S. A. Kay, *Cell* **2000**, *101*, 319–329.
[92] D. C. Nelson, J. Lasswell, L. E. Rogg, M. A. Cohen, B. Bartel, *Cell* **2000**, *101*, 331–340.
[93] T. F. Schultz, T. Kiyosue, M. Yanovsky, M. Wada, S. A. Kay, *Plant Cell* **2001**, *13*, 2659–2670.
[94] R. D. Vierstra, *Trends Plant Sci.* **2003**, *8*, 135–142.
[95] S. B. Corchnoy, T. E. Swartz, J. W. Lewis, I. Szundi, W. R. Briggs, R. A. Bogomolni, *J. Biol. Chem.* **2003**, *278*, 724–731.
[96] W. Y. Kim, S. Fujiwara, S. S. Suh, J. Kim, Y. Kim, L. Han, K. David, J. Putterill, H. G. Nam, D. E. Somers, *Nature* **2007**, *449*, 356–360.
[97] M. Yasuhara, S. Mitsui, H. Hirano, R. Takanabe, Y. Tokioka, N. Ihara, A. Komatsu, M. Seki, K. Shinozaki, T. Kiyosue, *J. Exp. Bot.* **2004**, *55*, 2015–2027.
[98] T. Imaizumi, T. F. Schultz, F. G. Harmon, L. A. Ho, S. A. Kay, *Science* **2005**, *309*, 293–297.
[99] K. A. Hicks, T. M. Albertson, D. R. Wagner, *Plant Cell* **2001**, *13*, 1281–1292.
[100] X. L. Liu, M. F. Covington, C. Fankhauser, J. Chory, D. R. Wagner, *Plant Cell* **2001**, *13*, 1293–1304.
[101] M. F. Covington, S. Panda, X. L. Liu, C. A. Strayer, D. R. Wagner, S. A. Kay, *Plant Cell* **2001**, *13*, 1305–1315.

[102] H. G. McWatters, R. M. Bastow, A. Hall, A. J. Millar, *Nature* **2000**, *408*, 716–720.
[103] M. E. Hudson, D. R. Lisch, P. H. Quail, *Plant J.* **2003**, *34*, 453–471.
[104] R. Lin, L. Ding, C. Casola, D. R. Ripoll, C. Feschotte, H. Wang, *Science* **2007**, *318*, 1302–1305.
[105] T. Allen, A. Koustenis, G. Theodorou, D. E. Somers, S. A. Kay, G. C. Whitelam, P. F. Devlin, *Plant Cell* **2006**, *18*, 2506–2516.
[106] E. Kevei, P. Gyula, B. Fehér, R. Tóth, A. Viczián, S. Kircher, D. Rea, D. Dorjgotov, E. Schäfer, A. J. Millar, L. Kozma-Bognár, F. Nagy, *Curr. Biol.* **2007**, *17*, 1456–1464.
[107] A. C. Froehlich, B. Noh, R. D. Vierstra, J. Loros, J. C. Dunlap, *Eukaryotic Cell* **2005**, *4*, 2140–2152.

Received: June 9, 2008
Published online on October 10, 2008

