

REVIEW ARTICLE

The regulation of plant growth by the circadian clock

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ABSTRACT

Circadian regulated changes in growth rates have been observed in numerous plants as well as in unicellular and multicellular algae. The circadian clock regulates a multitude of factors that affect growth in plants, such as water and carbon availability and light and hormone signalling pathways. The combination of high-resolution growth rate analyses with mutant and biochemical analysis is helping us elucidate the time-dependent interactions between these factors and discover the molecular mechanisms involved. At the molecular level, growth in plants is modulated through a complex regulatory network, in which the circadian clock acts at multiple levels.

INTRODUCTION

The circadian clock is a biological oscillator that maintains rhythms of about 24 h under constant environmental conditions. In addition, the periodicity of biological oscillators does not change significantly with changes in temperature over the physiological range, an effect described as temperature compensation. In photosynthetic organisms numerous processes are regulated by the circadian clock, such as carbon fixation, transpiration and other ecophysiological traits, as well as the cell cycle, flowering time, stress responses and gene expression (Yakir *et al.* 2007; McClung 2008; Edwards *et al.* 2011; Matsuo & Ishiura 2011).

It is currently postulated that this endogenous rhythm allows the organisms to predict daily as well as seasonal environmental changes and coordinate their physiological process to optimise their growth. In support for this hypothesis, it has been observed that in several cases organisms grow more under light/dark diel cycles of overall length that match their endogenous circadian rhythms (Ouyang *et al.* 1998; Woelfle *et al.* 2004; Dodd *et al.* 2005; Graf *et al.* 2010; Yerushalmi *et al.* 2011). When their endogenous period differs from 24 h, such as under different temperatures or due to mutations in clock components, the optimal cycle length is often not 24 h (Ketellapper 1960; Dodd *et al.* 2005; Graf *et al.* 2010). Light/dark cycles of an overall length shorter or longer than 24 h are termed T-cycles. In *Arabidopsis thaliana*, *toc1* and *cca1/lhy*, both short period mutants with a period of about 20 h, grow better at T-cycles of 20 h than in 28 h cycles and the reverse is true for the long period *ztl* mutant that displays an endogenous period of about 28 h (Somers *et al.* 1998, 2000; Dodd *et al.* 2005; Graf *et al.* 2010). Interestingly, under the tested

conditions, the optimal cycle length for *toc1* and *ztl* mutants is still 24 h (Graf *et al.* 2010). Thus the role of the clock appears to be more complex than just matching internal with external rhythms. Furthermore, changes in expression of clock genes in *Arabidopsis* hybrids and allopolyploids have been correlated to the improved growth of these lines (Ni *et al.* 2009). However, the mechanisms leading to these changes in clock gene expression remain unknown.

Numerous endogenous and environmental factors regulate cell and organ growth in photosynthetic organisms and many of these factors are modulated through the circadian clock (Fig. 1). Recent advances are beginning to shed light on the role of the clock in these different processes and how these interactions specify the timing of growth under both light/dark and constant environmental conditions.

CIRCADIAN GROWTH RHYTHMS IN PLANTS

Numerous diel growth rhythms have been described in vascular plants (Walter *et al.* 2009), and in several cases these rhythms are maintained under constant conditions (Fig. 1). Growth in plants is regulated by environmental factors such as temperature, light and water availability, as well as by carbon availability, developmental stage and the circadian clock. The interaction between these factors determines the phase of maximal growth rate in different plant organs (Fig. 1).

In dicots such as *Nicotiana tabacum*, *Ricinus communis*, *Arabidopsis thaliana* and *Flaveria bidentis*, growth in older leaves predominantly occurs at the end of the night period and beginning of the light period when grown under light/dark cycles. This pattern does not change significantly when temperature cycles are supplemented to the light/dark cycles.

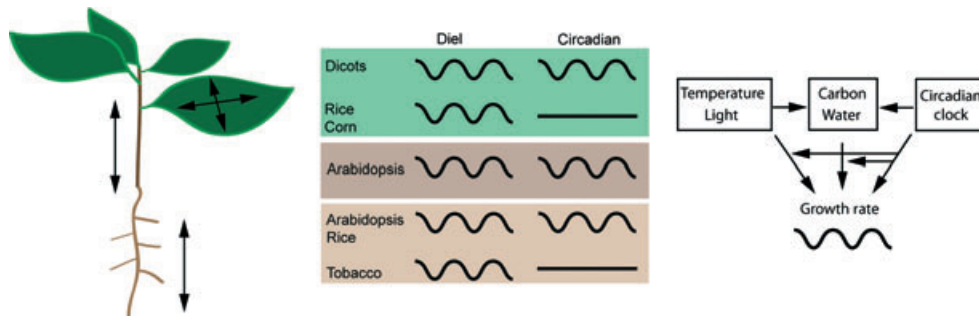


Fig. 1. Summary of current observations on growth dynamics and of factors affecting growth rates in plants. 'Diel' corresponds to growth under light/dark and/or warm/cold conditions. 'Circadian' describes growth under constant environmental conditions, either constant light or constant darkness. In the middle panel, green represents leaves, dark brown is stems and light brown is roots. References are provided in the text.

Under constant light and temperature conditions, the pattern continues, with a shift into the subjective day (Walter *et al.* 2002; Walter & Schurr 2005; Wiese *et al.* 2007; Poire *et al.* 2011). In contrast, under diel cycles *Zea mays* displays only a small increase in growth at the beginning of the dark and light periods whereas temperature cycles promote strong growth rate oscillations (Poire *et al.* 2011). With temperature cycles, the growth rate peaks a few hours after the maximum temperature is reached, in a similar pattern as observed for field-grown corn and sorghum (Johnson 1967; Acevedo *et al.* 1979). No growth rhythms were observed for either rice or corn under constant light conditions (Poire *et al.* 2011). These results suggest that monocot leaf growth is strongly influenced by temperature but not by the circadian clock.

Interestingly, the maximum rate of leaf growth in *Arabidopsis* varies depending on the leaf age (Pantin *et al.* 2011). Under well-watered conditions, very young leaves display maximum growth during the day and low growth at night. Depending on the ecotype, 2–5 days after emergence, maximal growth shifts to the night period, in agreement with other studies (Poire *et al.* 2011).

Aside from temperature and age of the leaf, plant growth is influenced by carbon availability in a clock-dependent manner (Fig. 1). In the presence of exogenous sucrose, in *Arabidopsis* the rate of hypocotyl growth oscillates for several days, with a maximum rate at the end of the night in light/dark cycles and during the subjective day under constant light conditions (Dowson-Day & Millar 1999; Nozue *et al.* 2007). In the absence of exogenous sucrose, hypocotyls grow for only 1 day, with peaks at both beginning of the day and beginning of the night, after which growth ceases (Stewart *et al.* 2011).

Root growth rates also display rhythms under diel growth conditions, which continue under both constant light and constant dark conditions in rice and *Arabidopsis* but not in tobacco (Nagel *et al.* 2006; Iijima & Matsushita 2011; Maizel *et al.* 2011; Yazdanbakhsh *et al.* 2011). In *Arabidopsis*, root growth rate starts increasing during the night, with a peak a couple of hours after dawn (Maizel *et al.* 2011; Yazdanbakhsh *et al.* 2011). In contrast, maximum growth rates occur during the day in rice (Iijima & Matsushita 2011). It is important to mention that roots were never illuminated in the rice experiments but were illuminated during the light periods in the *Arabidopsis* experiments. In order to study the shoot effect on root growth it might be important to carry out these

experiments with darkened roots in order to avoid direct light effects on these organs.

The clock also regulates phase-specific growth and cell division in unicellular and multicellular algae (Makarov *et al.* 1995; Mori *et al.* 1996; Luning *et al.* 1997; Nikaido & Johnson 2000; Serrano *et al.* 2009), with cell division occurring during the subjective night. The observation that growth rates oscillate under constant environmental conditions in different plant organs and different species with periods of ~24 h indicates that the circadian clock plays a nearly universal role in the regulation of growth in photosynthetic organisms.

THE CIRCADIAN CLOCK IN *ARABIDOPSIS THALIANA*

The circadian clock in photosynthetic eukaryotes is regulated by multiple interlocked transcriptional/translational feedback loops. The clock of *A. thaliana* is the best described so far and therefore a more detailed summary will be restricted to this model plant.

The *Arabidopsis* circadian clock has a complex interconnected structure formed by positive and negative feedback loops. The dawn-expressed MYB transcription factors CCA1 and LHY repress the expression of evening genes *TOC1*, *LUX*, *ELF3* and *ELF4* (Alabadi *et al.* 2001; Hazen *et al.* 2005; Kikis *et al.* 2005; Li *et al.* 2011). In turn, the expression of these evening genes is necessary for CCA1 and LHY transcription (Alabadi *et al.* 2001; Hazen *et al.* 2005; Kikis *et al.* 2005; Pruneda-Paz *et al.* 2009; Li *et al.* 2011). Furthermore, CCA1 and LHY act positively on the expression of *PRR9* and *PRR7* that are expressed during the day (Farre *et al.* 2005). *PRR9* and *PRR7* as well as *PRR5* directly repress CCA1 and LHY expression (Nakamichi *et al.* 2010).

Recent results indicate that the activation of CCA1 and LHY by evening-expressed clock genes is indirect (Fig. 2). It has been shown that *TOC1*, at least partly, activates CCA1 expression by counteracting the negative effect of the CCA1 repressor CHE1 (Pruneda-Paz *et al.* 2009). *ELF3*, *ELF4* and *LUX* have been shown to directly repress the expression of *PRR9* (Dixon *et al.* 2011; Helfer *et al.* 2011). Since the levels of *PRR7* are also elevated in *elf3* mutants (Dixon *et al.* 2011), the positive effect on CCA1 and LHY expression might be *via* the regulation of these repressors, *PRR9* and *PRR7*, by *ELF3*, *ELF4* and *LUX*. Based on mathematical modelling and gene expression analyses, a third negative transcriptional feedback loop between *TOC1* and *GI* has been proposed (Locke *et al.* 2005, 2006).

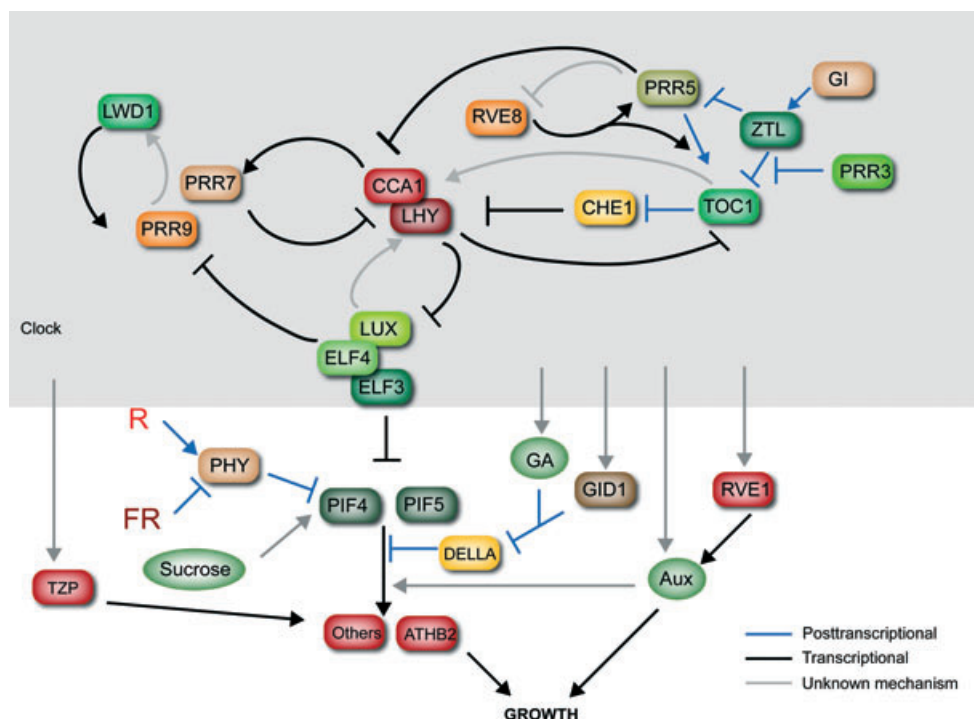


Fig. 2. Graphic representation of the circadian clock and of signalling processes regulating hypocotyl growth in *Arabidopsis thaliana*. Black lines indicate transcriptional regulation by a known mechanism. Blue lines, indicate post-translational regulation processes and grey lines, represent processes in which the molecular mechanisms remains unknown. Aux, auxin; GA, gibberellin; R, red light; FR, far-red light.

Two additional transcriptional regulatory loops have been recently described. RVE8, a MYB transcription factor closely related to CCA1, is involved in a feedback loop with PRR5 (Rawat *et al.* 2011). In addition, RVE8 positively regulates the expression of *TOC1* (Farinas & Mas 2011). This indicates that RVE8 could be the long-missing activator of several evening-expressed genes. Furthermore, LWD1 and LWD2 are two WD domain-containing proteins expressed in the evening that play a role in regulation of the circadian period in *A. thaliana* (Wu *et al.* 2008). LWD1 forms a positive regulatory loop with PRR9 (Fig. 2) and also directly regulates the expression of *TOC1* and *PRR5* (Wang *et al.* 2011).

Clock gene expression in several organisms is regulated *via* post-transcriptional processes (recently reviewed in Staiger & Green 2011). In *Arabidopsis*, alternative splicing plays an important role in maintaining rhythms (Hong *et al.* 2010; Sanchez *et al.* 2010). *PRMT5* is a protein involved in regulation of the spliceosome, and *prmt5* mutants are affected in the splicing of *PRR9* leading to a long-period phenotype (Deng *et al.* 2010; Hong *et al.* 2010; Sanchez *et al.* 2010).

The activity and levels of many of these clock components are also post-translationally regulated. The F-box protein ZTL is a novel photoreceptor that mediates the degradation of both PRR5 and TOC1 (Mas *et al.* 2003; Kiba *et al.* 2007; Baudry *et al.* 2010). In addition, PRR3 stabilises TOC1 most likely by inhibiting the TOC1–ZTL interaction (Para *et al.* 2007). GI regulates stability of ZTL (Kim *et al.* 2007) and PRR5 regulates the nuclear import and phosphorylation of TOC1 (Wang *et al.* 2010) (Fig. 2). PRR7 protein levels are regulated by both light and the circadian clock *via* a still unknown mechanism (Farre & Kay 2007). Furthermore,

PRR9 protein levels are also regulated by light (Ito *et al.* 2007) and the content of ELF3 and GI is modulated by COP1 (Yu *et al.* 2008). CCA1 is also phosphorylated by CK2, which is important for its DNA binding activity and affects temperature compensation in *Arabidopsis* (Sugano *et al.* 1998, 1999; Daniel *et al.* 2004; Portoles & Mas 2010).

Mutant analysis has led to the discovery of several other genes with important roles in maintaining rhythmicity in *Arabidopsis*. Currently, data are lacking to directly relate these genes into the above-mentioned feedback loops (Ding *et al.* 2007; Kim *et al.* 2008; Jones *et al.* 2010; Lu *et al.* 2010; Johansson *et al.* 2011; Jones & Harmer 2011). Finally, numerous light signalling components also play important roles in maintaining rhythms under constant conditions (Millar *et al.* 1995; Millar & Kay 1996; Devlin & Kay 2000; Staiger *et al.* 2003; Allen *et al.* 2006; Yu *et al.* 2008; Strasser *et al.* 2010; Li *et al.* 2011). Recent results are beginning to shed light on how light and circadian signalling networks interact. For example, the expression of *ELF4* is regulated by light *via* the constitutive activators FHY3, FAR1 and HY5, and is repressed in a time-specific manner by the clock components CCA1 and LHY (Li *et al.* 2011). In addition, it has been recently shown that DET1 mediates the transcriptional repression activity of CCA1 and LHY (Lau *et al.* 2011).

CONSERVATION OF CLOCKS AMONG PHOTOSYNTHETIC EUKARYOTES

Although little is known about the mechanisms regulating the circadian clock in other plants, orthologues of *Arabidopsis* genes have been identified in a number of vascular plants

and functional conservation has been described in several cases (for a recent review see Song *et al.* 2011). Furthermore, recent genomic efforts have identified orthologues of *Arabidopsis* clock genes in *Selaginella* (Banks *et al.* 2011) and *Physcomitrella* (Okada *et al.* 2009a,b; Holm *et al.* 2011; Satbhai *et al.* 2011b). Functional characterisation of putative clock genes in *Physcomitrella* suggests a functional conservation with vascular plants (Okada *et al.* 2009b; Satbhai *et al.* 2011a). Green algae have also been shown to have at least a subset of similar clock genes (Corellou *et al.* 2009; Matsuo & Ishiura 2011). Interestingly, post-transcriptional regulation is sufficient for rhythmicity in the green alga *Ostreococcus*, as is the case in cyanobacteria (Nakajima *et al.* 2005; O'Neill *et al.* 2011). Little is known about the mechanisms underlying the circadian clock in red algae and secondary endosymbionts. However, circadian rhythms have been detected in all algae analysed and have been extensively studied in some systems such as the dinoflagellate *Gonyaulax polyedra* (now *Lingulodinium polyedra*) (Suzuki & Johnson 2001; Hastings 2007).

ROLE OF CELL EXPANSION AND CELL DIVISION ON CIRCADIAN GROWTH RHYTHMS

The coordination of cell expansion, DNA replication and cell division is necessary for optimal growth in plants. The circadian clock controls reversible cell expansion processes such as stomatal opening (Gorton *et al.* 1989; Meidner & Willmer 1993; Salome *et al.* 2002) and pulvini motor cell volume changes (Satter *et al.* 1974; Mayer & Fischer 1994). Circadian regulated growth has also been observed in tissues where growth is due to cell expansion. In the *Arabidopsis* hypocotyl the majority of cells are formed in the embryo and, therefore, growth is due to cell volume change (Gendreau *et al.* 1997; Saibo *et al.* 2003). The same occurs at the later stages of leaf expansion, since cell division rates decrease rapidly during the first 6–8 days after leaf emergence (Donnelly *et al.* 1999; De Veylder *et al.* 2001; Autran *et al.* 2002; Asl *et al.* 2011). This shows that the circadian clock regulates cell expansion processes that lead to organ growth.

It remains an open question whether the circadian clock regulates DNA replication and/or cell division in plants. In *Arabidopsis*, cell division rates in different organs do not always match a 24-h cycle, although maximal cell division rates in leaves are about 1.0–1.6 divisions per day (De Veylder *et al.* 2001; Autran *et al.* 2002). In plants, DNA replication does not necessarily correlate with cell division and cells undergo several cycles of endoduplication during cell differentiation. Furthermore, nuclear ploidy level correlates strongly with cell size (Sugimoto-Shirasu & Roberts 2003). It will be interesting to study whether DNA replication and/or cell division events occur continuously or are regulated in a diel and/or circadian fashion. The expression of several cell cycle genes oscillates in constant conditions (Blasing *et al.* 2005). For example, the expression of the mitotic marker *CYCB1;1* cycles under light/dark, with a peak in the middle of the night (<http://diurnal.cgrb.oregonstate.edu/>). In addition, the expression of *CYCD3;3*, which is involved in regulating the duration of the mitotic phase and the transition to endocycles (Dewitte *et al.* 2007), cycles in both light/dark and constant light conditions, peaking during the second part of the night and at dawn, respectively. *CYCD3;1* and *CYCD3;2* both cycle strongly

in light/dark but only weakly under constant light. Moreover, leaf growth rhythms oscillate under light/dark cycles at early stages of leaf development where there is a high mitotic index (Pantin *et al.* 2011). Taken together, these results indicate that circadian-regulated growth may be partly attributed to clock-regulated cell division.

In unicellular and multicellular algae, cell division occurs during the night (Sweeney & Hastings 1958; Edmunds & Laval-Martin 1984; Carre & Edmunds 1993; Goto & Johnson 1995; Makarov *et al.* 1995; Titlyanov *et al.* 1996; Luning *et al.* 1997) as observed in cyanobacteria (Mori *et al.* 1996). This process is regulated/gated by the circadian clock and has been proposed to protect DNA from damaging UV radiation during the DNA replication process (Nikaido & Johnson 2000). Interestingly, it has recently been shown in *Arabidopsis* that UVB-induced gene expression is gated *via* the circadian clock, but no time-specific changes in UV sensitivity have been detected so far (Feher *et al.* 2011). New technologies such as sheet fluorescence microscopy, which allows imaging of whole organs at a single-cell resolution, will allow us to differentiate growth due to cell division and cell expansion, and analyse rates of cell division over longer time scales at the whole organ level (Maizel *et al.* 2011; Sena *et al.* 2011).

WATER AND CARBON AVAILABILITY AFFECT GROWTH RHYTHMS

Negative water potential is necessary for growth. If the growth-induced water potential is smaller than the gradient due to transpiration, cell expansion will be limited (Tang & Boyer 2002; Boyer & Silk 2004). Circadian changes in water potential regulate leaf movement in *Phaseolus vulgaris*, which is caused by reversible changes in cell volume (Kiyosawa 1979). The circadian clock also regulates stomatal conductance and transpiration (Sothorn *et al.* 2002; Dodd *et al.* 2004, 2005). Therefore, circadian growth rhythms might be partly regulated by circadian changes in water availability in different parts of the plant.

It has been proposed that diurnal changes in transpiration are due to changes in ABA levels (Tallman 2004). Since ABA levels are modulated by clock components, they could also explain oscillations in transpiration rates under constant conditions (Fukushima *et al.* 2009). In addition, the expression of many ABA-modulated genes is regulated by the circadian clock (Mizuno & Yamashino 2008). For example, it has been shown that TOC1 represses the expression of *GUN5*, which is induced by ABA (Legnaioli *et al.* 2009). However, changes in night transpiration rates in *Arabidopsis* do not affect overall plant growth in well-watered plants (Christman *et al.* 2009), and therefore the role of ABA and transpiration rate on plant growth under non-stress conditions remains to be investigated.

In *Arabidopsis* roots, water content oscillates, with a peak at dusk (Takase *et al.* 2011). These oscillations are maintained under both constant light and darkness, with the peak shifted to the subjective night. These circadian oscillations are absent in the arrhythmic *elf3-1* mutant. As mentioned, *Arabidopsis* roots start growing at dusk, and their growth peaks at the end of the subjective night under constant conditions (Yazdanbakhsh *et al.* 2011), indicating that high water content precedes maximal growth rates. At the whole seedling level, the expression of the cell membrane aquaporins *PIP1;2*

and *PIP2;1* is clock-regulated (Takase *et al.* 2011). The authors hypothesise that increased aquaporin levels at dawn increase water transport from the root to the shoot. This increased influx could correspond with the acceleration in growth rate at dawn in *Arabidopsis* leaves and hypocotyls under both light/dark and constant light conditions (Nozue *et al.* 2007; Poire *et al.* 2011; Stewart *et al.* 2011).

Aquaporins could also be involved in both reversible as well as irreversible circadian-regulated changes in cell volume in leaves. Leaf movements can be caused by differential growth in the adaxial and abaxial sides of leaf blades and petioles or by the reversible changes in turgor in legumes (Uehlein & Kaldenhoff 2008). Oscillations in the expression of plasma membrane aquaporins in both pulvinus cells of *Samanea saman* and *Nicotiana tabacum* petioles correlate with changes in water permeability under constant light conditions (Moshelion *et al.* 2002; Siefritz *et al.* 2004).

Overall plant growth is also limited by the rate of degradation of transient leaf starch at night, a process regulated by the circadian clock. Short period clock mutants (*cca1/lhy*) that degrade transient starch faster and therefore 'run out' of starch by the end of the night display low biomass accumulation (Graf *et al.* 2010). This phenomenon is not observed when these mutant plants are grown in shorter T-cycles that match their endogenous short period. In a similar way, leaves of starchless *Arabidopsis* mutants display reduced nocturnal growth (Wiese *et al.* 2007).

As described above, the presence of exogenous sucrose leads to elevated growth rates of *Arabidopsis* hypocotyls at the end of the night (Nozue *et al.* 2007; Stewart *et al.* 2011). In the absence of exogenous sucrose, *Arabidopsis* hypocotyls grow in the morning and at the beginning of the night until the cotyledons have expanded. Sucrose addition leads to the majority of hypocotyl growth occurring at the end of the night, and continued extension of the hypocotyl growth phase after the expansion of the cotyledons (Stewart *et al.* 2011). This indicates that hypocotyl growth is carbon-limited, particularly during the night.

Sink organ growth is dependent on an imported carbon source and, therefore, carbon availability is necessary for growth and growth oscillations in roots. For example, root growth stops after removal of the shoot in *N. tabacum* (Nagel *et al.* 2006). In 11- to 15-day-old *Arabidopsis* roots, the transfer of the plant to constant darkness stops root growth, but one additional weak growth cycle is achieved when the seedlings are placed on media containing sucrose. This exogenous sucrose, however, is not able to maintain either the overall root growth rate or the strong growth rate oscillations of light-grown *Arabidopsis* seedlings (Yazdanbakhsh *et al.* 2011). It has been shown that the circadian clock in *Arabidopsis* roots, in contrast to leaves, is influenced by sucrose and leaf photosynthesis (James *et al.* 2008). Therefore, the small effect of exogenous sucrose on root growth could indicate that this sucrose is not metabolised as efficiently as endogenous sugars, and/or that fluctuations in sucrose availability from the leaves is necessary for entraining the circadian clock and maintaining optimal growth oscillations in the roots.

The circadian-controlled supply of carbon from the shoot during the night is necessary for optimal root growth. The roots of *Arabidopsis* *pgm* mutants, which are starchless, as well as roots of the *cca1/lhy* double mutant that have reduced

leaf starch levels early during the night, display very low growth rates at the end of the night (Yazdanbakhsh *et al.* 2011). These results contrast with cyclic growth in constant darkness in very young rice seedlings (Iijima & Matsushita 2011). This observation might be due to carbon coming from the endosperm and not only from photosynthesis at early stages of root development. Therefore, root developmental stage is likely to have a strong influence on root growth.

It remains an open question whether the oscillations in root growth rates under constant light conditions are caused by changes in photosynthate availability from the shoots. Although leaf starch accumulation in constant light follows a circadian rhythm, there is no depletion of starch during the subjective night in higher plants (Lu *et al.* 2005, 2006; Weise *et al.* 2006). However, the levels of maltose, a product of starch degradation, display strong circadian oscillations in *Arabidopsis* (Lu *et al.* 2005). Furthermore, starchless mutants still displayed circadian root growth rate oscillations under constant light conditions (Yazdanbakhsh *et al.* 2011). Thus it is still possible that export of photosynthate from the leaves is controlled by the clock and might influence the root circadian clock and its growth (James *et al.* 2008; Haydon *et al.* 2011).

Interaction between high carbon availability during the day but high water availability during the night could explain the changes in the time of maximal growth rates in *Arabidopsis* leaves grown under light/dark cycles. As mentioned, young *Arabidopsis* leaves grow predominantly during the day, although under water stress growth occurs at night even during the very early stages of development (Pantin *et al.* 2011). In contrast, starchless mutants maintain the 'growth in the light' pattern until later in development. Leaf turgor in 1-day-old leaves is higher at the end of the day than at the end of the night, which is opposite to what is observed in older leaves. In addition, young leaves accumulate less starch at the end of the day and, therefore, might not be able to maintain high growth rates during the night (Pantin *et al.* 2011). Detailed analysis of water and carbon availability and growth rates in constant light will help us determine how these factors affect circadian-regulated growth.

MOLECULAR MECHANISMS REGULATING GROWTH

The elongation of the *Arabidopsis* hypocotyl is the best-studied model at the molecular level. Recent discoveries show the circadian clock modulates light, sugar and hormone signals to regulate rhythmic growth of this organ under different environmental conditions. In *Arabidopsis*, the increased growth of the hypocotyl under short photoperiods and shading (low R/FR ratios) can be explained by the interaction of the clock and light signals with the bHLH transcription factors PIF4 and PIF5. *PIF4* and *PIF5* RNA levels are regulated by the circadian clock and peak in the first half of the day under long days. Under shorter photoperiods, a larger proportion of their expression occurs in the night period (Niwa *et al.* 2009; Kunihiro *et al.* 2011; Nusinow *et al.* 2011). This pattern of expression is regulated by the repression of *PIF4* and *PIF5* transcription through a complex formed by clock components LUX, ELF3 and ELF4 (Fig. 2) (Nusinow *et al.* 2011). *PIF4* and *PIF5* protein levels are additionally regulated by light in a phyB-dependent manner (Fig. 2). *PIF4* and *PIF5*

interact *via* their N-terminus PHYB-interacting domain with PHYB (Khanna *et al.* 2004; Lorrain *et al.* 2008). They become phosphorylated upon light exposure and are degraded by activated phytochrome, thus their levels are elevated in the shade and under low R/FR ratios if these conditions coincide with high RNA levels (Nozue *et al.* 2007; Shen *et al.* 2007; Lorrain *et al.* 2008; Hornitschek *et al.* 2009; Nusinow *et al.* 2011).

This is a novel external coincidence model that explains the clock and photoperiod dependence of hypocotyl growth as well as its shade avoidance response in *Arabidopsis* (Weinig 2000; Salter *et al.* 2003; Nozue *et al.* 2007; Niwa *et al.* 2009; Coluccio *et al.* 2011; Kerwin *et al.* 2011; Kunihiro *et al.* 2011). High levels of PIF4 and PIF5 during the night period explain the long hypocotyl phenotype of several circadian clock mutants and their different responses to different photoperiods (Niwa *et al.* 2009). *ATHB-2* is a far-red light-induced gene that regulates cell expansion and the shade avoidance response (Fig. 2) (Steindler *et al.* 1999). It is directly regulated by PIF4 and PIF5 in a photoperiod-dependent manner (Kunihiro *et al.* 2011). *ATHB-2* is further regulated by a putative circadian transcription factor, TZP, which is expressed in the morning and is involved in the control of hypocotyl growth (Fig. 2) (Loudet *et al.* 2008). These observations show that growth is regulated through a complex regulatory network in which the clock modulates several components. A similar mechanism could regulate growth in other plants. The photoperiod-dependent growth of *Physcomitrella* protonemal colonies is dependent on the circadian clock. Specifically, the disruption of *PpCCA1a* and *PpCCA1b*, which leads to a short period phenotype, also causes faster growth under long days but not short days (Okada *et al.* 2009a,b). This finding suggests that a clock-dependent photoperiod regulation of growth might be conserved in non-vascular plants.

It has recently been shown that sucrose increases hypocotyl growth rate and leads to elevated PIF5 protein levels in both light and darkness in transgenic *Arabidopsis* plants constitutively expressing *PIF5* (Stewart *et al.* 2011). Furthermore, the growth response to sucrose is significantly reduced in the *pif* quadruple mutant (Leivar *et al.* 2009; Stewart *et al.* 2011). In the wild type, *PIF5* RNA levels are regulated by the circadian clock and, therefore, it is likely that this sucrose-mediated induction of PIF5 protein levels is dependent on the time of day. This result would indicate that carbon induction of hypocotyl growth is gated by the circadian clock and place PIFs as central hubs integrating circadian, environmental and metabolic signals.

The circadian clock gates the transcriptional regulation of auxin-responsive genes as well as auxin-promoted hypocotyl growth in *Arabidopsis* seedlings. Both maximal auxin-induced gene expression and growth occur at the end of the night (Covington & Harmer 2007). Since *pif4pif5* double mutants are less responsive to auxin-induced growth, this effect might also be partly mediated by PIF4 and PIF5 (Nozue *et al.* 2011). It has recently been shown that PIF4 and PIF5 regulate the expression of several auxin-inducible genes in a photoperiod-dependent manner (Kunihiro *et al.* 2011), indicating that they might be involved in the circadian gating of auxin signals. In addition, the clock-regulated transcription factor RVE1 mediates auxin-dependent hypocotyl growth, probably by regulating auxin biosynthesis genes (Fig. 2) (Rawat *et al.*

2009) in a manner independent of *PIF4* and *PIF5*. Auxin also strongly influences the rhythmic growth of the *Arabidopsis* floral stem (Jouve *et al.* 1998, 1999). The inhibition of stem growth caused by decapitation can be reversed by auxin treatment. This treatment also restores growth rate oscillations. These results suggest that although auxin levels cycle in the stem and rosette leaves of *Arabidopsis* under both diel and constant light conditions, peaking at dusk (Jouve *et al.* 1999; Rawat *et al.* 2009), auxin synthesis is not the only cause of the growth rate oscillations. It will be interesting to study whether PIF4 and PIF5 are involved in the floral stem auxin-dependent rhythmic growth.

In a similar manner as auxin, it has recently been shown that gibberellin (GA)-induced gene expression is also gated by the circadian clock in *Arabidopsis* (Arana *et al.* 2011). In addition, GA induces hypocotyl growth during the night but not during the day. During the GA signalling process, the binding of GA to the GID1 receptor leads to the degradation of DELLA proteins (Gao *et al.* 2011). In turn, DELLA proteins repress growth at least partly by inhibiting the activity of PIF4 (Gao *et al.* 2011). Arana *et al.* (2011) showed that the activation of *DELLA* expression only restricts hypocotyl growth when it occurs during the night, but not during the day. The RNA levels of the GA receptors *GID1a/b/c* cycle, and cyclic growth occurs even when these receptors are expressed constitutively, indicating that it is likely that GA levels also oscillate. In contrast, a *DELLA* quintuple mutant does not display growth oscillations, even though it does not have clock defects. Thus cyclic repression of growth by DELLAs is necessary for rhythmic hypocotyl growth. Although it has been shown that DELLA proteins inhibit the activity of PIF4 and that *pif4* mutants display a reduced sensitivity to GA (de Lucas *et al.* 2008), there is little overlap in gene expression changes between a *DELLA* quintuple mutant grown under light/dark cycles and *pif* quadruple mutants grown under constant dark or light conditions (Arana *et al.* 2011). This discrepancy might be due to the different roles of PIF transcription factors during early stages of photomorphogenesis and diurnal growth conditions.

CONCLUDING REMARKS

The circadian clock modulates numerous signalling and physiological processes that regulate plant growth. In spite of recent advances on this topic, several open questions remain. For example, it is still unclear which are the mechanisms regulating growth oscillations under constant light conditions. In the case of the *Arabidopsis* hypocotyl, PIF4 and PIF5 appear to play a role under constant conditions since *pif* mutants display a short hypocotyl phenotype under constant light (Leivar *et al.* 2008; Shin *et al.* 2009). However, since PIF4 and PIF5 are degraded in the light, their function in extended constant light conditions remains to be investigated. There is also little known about the mechanisms regulating time-dependent growth in tissues other than the *Arabidopsis* hypocotyl. Environmental conditions differentially regulate growth of different organs. For example, PIF4 and PIF5 mediate hypocotyl/stem elongation under low R/FR. However, under these conditions leaf blade growth is inhibited (Tsukaya 2005), suggesting that the mechanisms of leaf and hypocotyl growth might be different.

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