The Importance of the Plant Circadian Clock to Confer Heat Tolerance

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ABSTRACT Most eukaryotic organisms display specialized cellular and behavioral oscillations with a period of approximately 24 hours, which are called circadian rhythms. The biological clock generates a rhythm that conveys temporal information over a day. Through this system, most eukaryotic organisms appropriately respond to daily or seasonal environmental changes by regulating their physiology and development in a time-dependent manner, conferring the organism with an adaptive advantage. In plants, the endogenous timing system also controls many important physiological processes including flower opening, hormone synthesis, metabolic pathways and gene expression so that these sessile species may survive efficiently in changing environments. Temperature compensation (TC) is one of the defining features of the clock mechanism. Under this mechanism, the pace of the clock, or period, remains stable over a broad range of physiologically relevant temperatures, which is unlikely to happen in other biochemical reactions. Thus, this mechanism allows organisms to sustain their ordinary life in various thermal environments by providing an accurate measure of the passage of time, regardless of the ambient temperature. Considering the current global climate changes our planet is undergoing, understanding the fundamental mechanism underlying TC cannot be overemphasized. In this review, we discuss the molecular organization of the plant circadian clock and the concept of TC, as well as the significance of plant TC in conferring fitness under the current increasing thermal environments.

Keywords Circadian clock, Temperature compensation, Global warming, Heat tolerance, Crop production

The plant circadian clock

The daily rotation of the earth on its axis and its annual revolution around the sun confer recurrent and rhythmic but predictable environmental changes (McClung, 2011). To face such challenges actively, most organisms have evolved the capability to measure time. The circadian clock is the time measuring system that establishes an endogenous rhythm with a 24 hr period, called a circadian rhythm (Jolma *et al.*, 2010; McClung, 2011). The rhythmic oscillation is persistent (self-sustaining), able to be synchronized to ambient environments (entrainable), and is stable in physiologically-ranged thermal environments (temperature compensated) (de Montaigu *et al.*, 2010; McClung, 2011; McWatters and Devlin, 2011).

In plants, about 10,000 transcripts are known to be regulated by the clock system (de Montaigu *et al.*, 2010).

Thus, many biological processes, including leaf movement, flower opening, hormone synthesis, metabolic pathways and gene expression, are rhythmic, displaying peaks and troughs in their activity during particular times of the day. As such, this clock system, present in plants and many other eukaryotes, confers fitness benefits, efficiently coordinating many important biological functions by integrating and anticipating the daily and seasonal bases of environmental changes (de Montaigu *et al.*, 2010; McWatters and Devlin, 2011).

The clock mechanism

The rhythmic oscillation by the circadian clock follows a common molecular signature in eukaryotes, including fungi, flies, mammals, and plants, wherein the mechanism is underpinned by transcription-translation feedback loops

Received December 11, 2014; Revised December 24, 2014; Accepted December 24, 2014; Published December 31, 2014

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(TTFLs)(Baker *et al.*, 2011; Jolma *et al.*, 2010; McClung, 2011; McWatters and Devlin, 2011). Arabidopsis circadian oscillators, like those of many other eukaryotes, are based on multiple-interlocked TTFLs consisting of three main ones (Figure 1) (Harmer, 2009; Locke *et al.*, 2006; McClung, 2011). These includes a central loop and two interlocked loops termed “morning” and “evening,” based on the times

of day at which the loop components are maximally expressed (Alabadi *et al.*, 2001; Locke *et al.*, 2006). To date, more than 20 clock or clock-associated components have been identified in the Arabidopsis oscillator.

The central loop consists of a pseudo-response regulator (PRR), TIMING OF CAB EXPRESSION 1 (TOC1), and two single Myb domain transcription factors (TF):

Fig. 1. Multiple-interlocked transcription-translation feedback loop model of Arabidopsis circadian clock.

In the “morning”, expressed CCA1 and LHY positively regulate PRR7 and PRR9; however, PRR7 and PRR9 proteins, along with the afternoon-expressed PRR5, bind to the CCA1 and LHY promoters to sequentially repress the CCA1/LHY transcriptional expression. In the evening, ZTL, an F-box-containing protein and part of a Skp/Cullin/F-box (SCF) E3 ubiquitin ligase complex, directly targets both TOC1 and PRR5 protein in the cytosol, leading to their degradation via the proteasome pathway. The evening-expressed gene GI, with no recognizable functional domain, physically interacts with ZTL in a blue light-stimulated manner, conferring ZTL with the post-transcriptional oscillation. This supports the amplitude of TOC1 protein to be time dependent, which is necessary for proper clock function. Phosphorylation of PRR5 promotes interaction with TOC1, enhancing its accumulation in the nucleus and preventing it from undergoing ZTL-dependent protein turn-over in the cytoplasm. In addition, a TOC1/PRR3 phosphorylation-dependent interaction may protect TOC1 from ZTL-mediated degradation. Meanwhile, evening phased genes, LUX, ELF3 and ELF4, interact to form the ‘evening complex’, which represses expression of the day-phased clock gene PRR9. TOC1 protein in the nucleus starts acting as a DNA binding transcriptional repressor of CCA1 and LHY; however, CCA1 and LHY expression is resumed just before dawn, which might be the result of a collaborative action with another CCA1 transcriptional repressor, CHE, in an undefined manner. The Myb transcription factor RVE8, a dawn-phased gene expression, provides an important signal to the plant early in the morning. REV8 protein, with the afternoon-phased peak, binds to the EE, which induces the expression of hundreds of evening genes, including PRR5, TOC1, GI, LUX and ELF4. PRR9, as well as PRR5, was also found to be activated by RVE8. Conversely, PRR9, 7 and 5 repress RVE8, suggesting a model in which PRRs and RVEs regulate each other to form a negative feedback loop. The two close homologs of REV8, RVE4 and RVE6, were reported to have partially redundant roles with RVE8, interconnecting the morning and evening loops. Red solid arrow: activation; red dashed arrow: indirect activation; black perpendicular bars: repression.

CCA1, CIRCADIAN CLOCK ASSOCIATED 1; LHY, LATE ELONGATED HYPOCOTYL; TOC1, TIMING OF CAB2 EXPRESSION 1; GI, GIGANTEA; ZTL, ZEITLUPE; PRR, PSEUDO-RESPONSE REGULATOR; LUX, LUX ARRHYTHMO; ELF, EARLY FLOWERING, CHE, CCA1 HIKING EXPEDITION REV, REVEILLE.

CIRCADIAN CLOCK ASSOCIATED1 (*CCA1*) and LATE ELONGATED HYPOCOTYL (*LHY*) (Alabadi *et al.*, 2002; Mizoguchi *et al.*, 2002). *CCA1* and *LHY* are negative regulators of *TOC1*, inhibiting its expression until the evening (Alabadi *et al.*, 2001; Alabadi *et al.*, 2002) (Figure 1). *CCA1* and *LHY* physically interact with each other and bind to a motif in the *TOC1* promoter, called the evening element (EE), to inhibit *TOC1* expression. It was recently reported that *TOC1* is a DNA-binding transcriptional repressor of *CCA1* and *LHY* (Gendron *et al.*, 2012; Huang *et al.*, 2012). *CCA1* HIKING EXPEDITION (*CHE*), a TCP transcription factor, might coordinate the link between *TOC1* and the regulation of *CCA1* in the central loop (Pruneda-Paz *et al.*, 2009) (Figure 1). *CHE*, as another transcriptional repressor of *CCA1*, recruits *TOC1* to a transcriptional complex at the *CCA1* promoter. However, the antagonistic interaction between those two components results in the indirect activation of *CCA1* (Pruneda-Paz, 2009).

In the “morning” loop, *CCA1* and *LHY* are positive regulators of two *TOC1* relatives, *PRR7* and *PRR9* (Harmer and Kay, 2005; Mizuno and Nakamichi, 2005). Conversely, *PRR5*, *PRR7* and *PRR9* bind to the *CCA1* and *LHY* promoters to repress their expression (Nakamichi *et al.*, 2010), which requires a co-repressor, encoded by members of the TOPLESS/TOPLESS-RELATED (*TPL*/*TPR*) gene family (Wang *et al.*, 2013). The peak binding of the three proteins occurs sequentially from early morning (*PRR9*) through midday (*PRR7*) to late afternoon/early night (*PRR5*), resulting in the repression of *CCA1* and *LHY* expression (Nakamichi *et al.*, 2010).

Although many clock genes of the evening phase, including *TOC1*, *PRR3*, *PRR5*, *ZEITLUPE* (*ZTL*), *GIGANTEA* (*GI*) and others are assigned in the evening loop, the negative feedback mechanism by which they are regulated is still elusive (Fujiwara *et al.*, 2008; Kim *et al.*, 2007; McClung, 2011). Instead, sophisticated post-translational mechanisms have been characterized in the evening loop (Fujiwara *et al.*, 2008; Kim *et al.*, 2007; McClung, 2011). *ZTL*, an F-box-containing protein which is part of a Skp/Cullin/F-box (*SCF*) E3 ubiquitin ligase complex, directly targets both *TOC1* and *PRR5*, leading to their degradation via the proteasome pathway (Fujiwara *et al.*, 2008; Kiba *et al.*, 2007; Mas, 2003). Due to the light-sensing

ability of *ZTL*, its involvement in the degradation of *TOC1* and *PRR5* is regulated by light (Fujiwara *et al.*, 2008; Somers *et al.*, 2000; Somers and Fujiwara, 2009). The light sensing function of the LOV domain was unveiled by the discovery that *GI* is essential for the stability of the *ZTL* protein (Kim *et al.*, 2007; Somers and Fujiwara, 2009). *GI*, with no recognizable functional domain, physically interacts with *ZTL* in a blue light-stimulated manner (Kim *et al.*, 2007; Somers and Fujiwara, 2009). *GI* transcription is clock-controlled, and *GI* protein levels closely follow the *GI* mRNA rhythm. Thus, it is the cycling of *GI* that confers a circadian rhythm to the abundance of *ZTL* rather than *ZTL* transcription, which is constitutive. As a result, the *GI*-mediated stabilization of *ZTL* affects the abundance of the *ZTL* substrates, *TOC1* and *PRR5*, in a time-dependent manner, which is necessary for proper clock function (Kim *et al.*, 2007; Somers and Fujiwara, 2009). Recently, the reciprocal stabilization of cytosolic *GI* by *ZTL* was reported, which further implicates the importance of the *ZTL*-*GI* relationship by demonstrating a role for *ZTL* in sequestering a portion of *GI* to the cytosol (Kim *et al.*, 2013).

Further control of the *TOC1* levels comes from *PRR5*, whose phosphorylation promotes interaction with *TOC1* and enhances the *TOC1* accumulation in the nucleus, preventing it from undergoing the *ZTL*-dependent protein turn-over in the cytoplasm (Wang, 2010). In addition, a *TOC1*/*PRR3* phosphorylation-dependent interaction may protect *TOC1* from *ZTL*-mediated degradation (Fujiwara *et al.*, 2008).

Other evening phased genes, including *LUX*, *ELF3* and *ELF4*, interact to form the ‘evening complex’, which represses the expression of the day-phased clock gene *PRR9*. Around late night, the *TOC1* protein in the nucleus starts acting as a DNA binding transcriptional repressor of *CCA1* and *LHY* (Gendron *et al.*, 2012; Huang *et al.*, 2012; Pokhilko *et al.*, 2010; Wang *et al.*, 2013). However, the expression of *CCA1* and *LHY* is resumed just before dawn, which might result from collaborative action with another *CCA1* transcriptional repressor, *CHE*, in an undefined manner (Pruneda-Paz, 2009).

Recently, the Myb transcription factor *REVEILLE8* (*RVE8*, also known as *LHY* and *CCA1-like 5*, *LCL5*) was assigned as an important clock component (Hsu, 2013; Hsu

and Harmer, 2014; Rawat, 2011). *RVE8* shows dawn-phased gene expression, providing an important signal to the plant early in the morning. Like CCA1 and LHY, REV8 protein, with an afternoon-phased peak, binds to the EE (Rawat, 2011). However, it induces hundreds of evening genes that contain EE in the promoter, including *PRR5*, *TOC1*, *GI*, *LUX* and *ELF4*, which is entirely opposite from the repressor role of CCA1 and LHY (Hsu, 2013). *PRR9*, as well as *PRR5*, is also activated by RVE8 (Hsu, 2013; Rawat, 2011). *PRR9*, 7, and 5 repress *RVE8*, suggesting a model whereby the PRRs and RVEs regulate each other to form a negative feedback loop (Hsu, 2013). Two close homologs of REV8, RVE4 and RVE6, were reported to have partially redundant roles with RVE8, interconnecting the morning and evening loops

Overall, the dedicated empirical and computational studies carried out in this field have developed the current models of the plant clock. However, the roles of significant portions of the identified clock genes in the clock network have yet to be identified. Furthermore, diverse post-transcriptional mechanisms, post-translational regulation and chromatin remodeling are emerging as important mechanisms in the clock network, adding a new layer of clock regulation (Cibois, 2010; Nagel and Kay, 2012). Thus, much remains to be understood to accommodate such mechanisms in the context of the current clock network.

The relevance of the Arabidopsis clock to other crop species

Although most of the knowledge of plant clocks has come from studies on Arabidopsis, homologs of these genes in other plant species have recently begun to be characterized. In addition, the agronomic importance of the circadian system in plants is becoming more apparent (Hsu and Harmer, 2014; McClung, 2013). In the major crop species including rice (Filichkin *et al.*, 2011; Mockler *et al.*, 2007; Nagano *et al.*, 2012), maize (Hayes *et al.*, 2010; Khan *et al.*, 2010), papaya (Zdepski *et al.*, 2008) and tomato (Facella *et al.*, 2008), clock control of the transcriptome levels has been characterized for many essential functions (e.g., photosynthesis, carbohydrate metabolism, light sensing and signaling).

In addition, key clock orthologues of CCA1, LHY and

the PRR family have been found in many crop species, including bean (*Phaseolus vulgaris*) (Kaldis *et al.*, 2003), chestnut (*Castanea sativa*) (Ramos *et al.*, 2005), pea (*Pisum sativum*) (Hecht *et al.*, 2005; Liew *et al.*, 2009; Ramos *et al.*, 2005), soybean (*Glycine max*) (Hudson, 2010), Brassica rapa (Kim *et al.*, 2012; Lou *et al.*, 2012), tomato (*Solanum lycopersicum*) (Facella *et al.*, 2008) and rice (*Oryza sativa*) (Murakami *et al.*, 2007a; Murakami *et al.*, 2007b). More recently, other clock genes such as GI and ELF3 were functionally characterized in rice (Izawa *et al.*, 2011; Yang *et al.*, 2013). In many cases, these clock genes have been shown to cycle with similar phases as their Arabidopsis counterparts. Thus, it can be speculated that there has been significant evolutionary conservation of clock function and organization in many cases (Song *et al.*, 2010). However, much remains to be understood about the clocks of non-model plant systems.

Temperature compensation (TC)

Along with the signal of light, temperature is one of the most important environmental cues in many important physiological and developmental responses, such as flowering and hormonal regulation (McClung and Davis, 2010). TC, as one of the defining features of circadian rhythms, refers to the relative insensitivity of the period length to ambient temperature over a range of physiologically relevant temperatures. The rate of a typical biochemical reaction doubles with an increase in temperature of 10°C (expressed as $Q_{10}=2$), but the rate of the circadian clock is relatively constant ($Q_{10} \sim 1$) (Jolma *et al.*, 2010; McClung and Davis, 2010). The reactions induced by change in the ambient temperature are presumably constrained by the TC mechanism. Otherwise, the period of the clock would fluctuate greatly, depending on the ambient temperature (Jolma *et al.*, 2010; McClung and Davis, 2010).

According to the research on one of most extensively studied organisms for TC, *Drosophila melanogaster*, the factors regulating the accumulation, dimerization, and nuclear transport of the core clock components PERIOD (PER) and TIMELESS (TIM) are important for the maintenance of TC (Hamblen *et al.*, 1998; Price, 1997). This suggests that TC acts directly from the intrinsic properties, wherein the dynamic interactions of core clock

proteins function across a wide temperature range (Hamblen *et al.*, 1998; Price, 1997). In contrast, *Neurospora* TC studies have suggested other mechanisms, such as the importance of altered levels or alternative isoforms of core clock proteins at certain temperatures (Baker *et al.*, 2011; Jolma *et al.*, 2010; Liu *et al.*, 1997; Price, 1997). At present, the mechanistic bases of TC have been incompletely defined, although it is likely that multiple pathways and mechanisms are involved (McClung and Davis, 2010).

In *Arabidopsis*, several studies have reported that both of the morning and evening loops play a role in TC. Within the evening loop, Hall and colleagues reported that loss of *GI* function reduces the robustness and period length at high (27°C) and low (12°C) temperatures, demonstrating that *GI* plays a critical role in TC (Gould *et al.*, 2006). They also found that *LHY* and *CCA1* contribute differentially to TC at high and low temperatures, suggesting that a dynamic balance between *LHY* and *GI* is key for TC at high temperatures, whereas *LHY* appears to be replaced by *CCA1* at low temperatures (Gould *et al.*, 2006).

In the morning loop, *PRR7* and *PRR9*, negative regulators of *CCA1* and *LHY*, were suggested to be important components of the TC mechanism by modulating the expression levels of those genes (Salome *et al.*, 2010; Salome and McClung, 2005). While simultaneous inactivation of both *PRR7* and *PRR9* has no effect on the periods at low temperature, it results in extreme period lengthening at high temperatures (overcompensation) (Salome *et al.*, 2010). Inactivation of *CCA1* and *LHY*, in turn, fully suppresses the overcompensation effects of *prp7prp9* double mutations, indicating that the temperature-dependent period lengthening of *prp7prp9* is due to the hyperactivation of *CCA1* and *LHY* (Salome *et al.*, 2010). Portolés and Más elaborated on the emphasized role of *CCA1* at low temperature by showing the antagonizing posttranslational modulation of *CCA1* activity by CASEIN KINASE2 (CK2)-mediated phosphorylation of *CCA1* (Portolés and Mas, 2010). At low temperatures, CK2-mediated phosphorylation is reduced, but a consequent enhancement in the *CCA1* binding activity occurs, indicating that these antagonizing actions may sustain a constant period at various ambient temperatures (Portolés and Mas, 2010).

Therefore, the TC mechanism in *Arabidopsis* may not be

an intrinsic property of the circadian oscillator, but rather may be derived from the recruitment of other genes which regulate the oscillator components (Edwards *et al.*, 2005; Portolés and Mas, 2010; Salome *et al.*, 2010). As with other areas, much remains to be characterized for this aspect of clock regulation in plants.

The significance of TC in fitness under extreme thermal environments

Plants, as sessile species, successfully grow and develop across a wide range of ambient temperatures. The species have adapted to persevere over a range of ~50°C, including extremes of growth near 0°C at the coastlines of Antarctica and at near 50°C in the deserts of the hottest places on Earth (McClung and Davis, 2010). To prevail in such diverse thermal environments, the plant populations in contrasting thermal environments may have accumulated relevant genetic modifications/natural variations as a result of differential selective pressures (Leinonen *et al.*, 2009).

Considering the dominant role of the clock in the development and physiology of plants, a TC mechanism that maintains the proper oscillator speed under physiologically relevant temperatures could be one of the most critical targets of the evolutionary forces/natural selection (Edwards *et al.*, 2005; Johnson, 2005). In an attempt to find genetic variations in TC, Millar and colleagues performed a QTL study on two natural accessions adapted in different thermal environments (Edwards *et al.*, 2005): one adapted to a hot climate, Cape Verde Island (Cvi), and the other originating from Northern Europe (Landsberg, *Ler*). In spite of the similar period phenotype between the parental lines, several temperature-specific QTLs for the clock period were identified, suggesting that natural genetic variations in TC mechanisms occur (Edwards *et al.*, 2005). Among the QTLs, the core clock components, *GI* and *ZTL*, were proposed as strong candidates, accounting for much of the variation (Edwards *et al.*, 2005). By sequence comparison, they postulated that the amino acid substitutions of *GI*^{L718F} and *ZTL*^{P35T} (*Ler* to Cvi) are the underlying causal factors for the period variation at the tested temperatures (22°C and 27°C respectively) (Edwards *et al.*, 2005). Since the effects of specific mutations in these genes on the period are in opposite directions at different

temperatures, the Cvi's clock system may have accumulated alleles with opposing effects epistatically acting at the different temperature regimes. This action would theoretically neutralize the effect on the period by balancing of the two across a range of relevant temperatures to attain TC. In reality, it was found that Cvi's period and the physiological response were much more stable at the high temperature (30°C) compared to *Ler* (Edwards *et al.*, 2005; Kusakina *et al.*, 2014). Thus, it is likely that an antagonistic balance among the alleles observed in Cvi's clock, including GI^{L718F} and ZTL^{P35T} , may be the result of an adaptation to different local thermal environments, presumably to the hot climate of Cape Verde Island (CVI) (Edwards *et al.*, 2005).

In the plant clock, as in other circadian systems, an oscillator whose period is consonant with the external environment significantly enhances the survival rates, which is the result of better physiological performances (Dodd *et al.*, 2005). Therefore, the recalibrated TC-related clock property through *GI/ZTL* natural variations that constrain the period to remain at a similar value even under the increasing thermal conditions, as in the CVI, may have significant fitness value.

Concluding remarks: the significance of TC study for future crop improvements

The process of crop domestication has led to the production of plants with many innovative features suitable for agriculture, but human selection has been trading off the natural diversity of gene/allelic pools, which may be critical for successful adaptation to various local environments (Vigouroux *et al.*, 2011). Thus, it is not just a coincidence that agriculture is affected by recent climate change, especially the global increase in temperature (Lobell *et al.*, 2011). For example, it is estimated that the mean temperature rise between 1981 and 2002 reduced the yields of major cereals by \$5 billion per year (Lobell *et al.*, 2011). Therefore, developing crops that are better adapted to the current temperature situation will be important for food production around the world (Varshney *et al.*, 2011).

Plant thermo tolerance is a multi-genic character; numerous biochemical and metabolic traits are orchestrated in the development and maintenance of heat tolerance, including the maintenance of membrane stability, scavenging

of reactive oxygen species (ROS), production of antioxidants, accumulation and adjustment of compatible solute, and induction of chaperone signaling and transcriptional activation (Bita and Gerats, 2013). Thus, breeding to provide greater stress tolerance is a great challenge due to the complexity. In this regard, implementing naturally modified diverse TC functions which exist in nature can be a reasonable approach in order to establish fundamental solutions for sustainable crop production under these changing thermal environments. Thus, it is important to understand and characterize the TC mechanisms as a parameter for temperature-related adaptive processes more precisely, so that such information can be applied more efficiently in related fields for various purposes.

ACKNOWLEDGMENTS

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Science and Technology (2014-0188).

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