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Review

*Tansley insight*

# Retrograde signalling as an informant of circadian timing

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## Contents



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## Summary

The circadian system comprises interlocking transcriptional–translational feedback loops that regulate gene expression and consequently modulate plant development and physiology. In order to maximize utility, the circadian system is entrained by changes in temperature and light, allowing endogenous rhythms to be synchronized with both daily and seasonal environmental change. Although a great deal of environmental information is decoded by a suite of photoreceptors, it is also becoming apparent that changes in cellular metabolism also contribute to circadian timing, through either the stimulation of metabolic pathways or the accumulation of metabolic intermediates as a consequence of environmental stress. As the source of many of these metabolic byproducts, mitochondria and chloroplasts have begun to be viewed as environmental sensors, and rapid advancement of this field is revealing the complex web of signalling pathways initiated by organelle perturbation. This review highlights recent advances in our understanding of how this metabolic regulation influences circadian timing.

## I. The circadian system is responsive to environmental change

Circadian timing modulates many biological processes, ranging from gene expression to developmental decisions, such as the transition to flowering (Millar, 2016). Although the circadian system is able to oscillate in the absence of environmental cues, these endogenous rhythms are only useful if they are synchronized with and compensated against daily and seasonal changes in day length and temperature (Millar, 2016). Plants perceive changes in their environment through the actions of photoreceptors and indicators of temperature, although this distinction is somewhat muddled as temperature and light signalling pathways share common components (Casal & Qüesta, 2018). Changes in temperature and light intensity (or quality) are sufficient to alter the expression of clock components, with the sensitivity of the circadian system to such environmental changes varying over the course of the day (Millar, 2016). This circadian 'gating' of responses to environmental change prevents the continuous resetting of the circadian timer to environmental inputs, whilst also allowing for the entrainment of the circadian clock to seasonal variation in day length. Circadian gating also permits the modulation of the responses of plants to environmental change (for example, by enabling greater response to chilling stress during the evening).

The nuclear circadian system comprises interlocked transcriptional–translational feedback loops that combine to generate oscillations of *c.* 24 h (Millar, 2016). Successive waves of

transcriptional activators and repressors regulate gene expression, with the Myb-like transcription factors CIRCADIAN CLOCK ASSOCIATED1 (CCA1) and LATE ELONGATED HYPOCOTYL (LHY) repressing expression at dawn, whereas PSEUDORESPONSE REGULATOR9 (PRR9) and its orthologues PRR7/5/TOC1 limit expression during the day (Hsu & Harmer, 2014). Later in the evening, LUX ARRHYTHMO (LUX), EARLY FLOWERING3 (ELF3) and ELF4 associate to form an Evening Complex that similarly represses gene expression (Hsu & Harmer, 2014). Transcriptional activators, including REVEILLE8 (RVE8), NIGHT LIGHT-INDUCIBLE (LNK) and LIGHT-REGULATED WD (LWD) proteins, complement the activity of these transcriptional repressors (Hsu & Harmer, 2014). The combined activity of these feedback loops increases the amplitude of circadian rhythms and allows the clock to be compensated against seasonal changes in temperature, as well as improving the robustness of circadian rhythmicity (Shalit-Kaneh *et al.*, 2018).

Although the transcriptional components of the circadian system are comparatively well understood, how these interconnecting feedback loops are influenced by environmental change remains to be fully elucidated (Hsu & Harmer, 2014). The expression of dawn-phased clock components tends to be induced by light, whereas the Evening Complex has been identified as a likely hub for signal integration as it interacts directly with the photo- and thermo-sensor phytochromeB (phyB; Hsu & Harmer, 2014; H. Huang *et al.*, 2016; Ezer *et al.*, 2017). The role of phytochrome, cryptochrome and UVR8 photoreceptors in the circadian system has recently been discussed elsewhere (Oakenfull & Davis, 2017). Instead, this review focuses on our understanding of how metabolic changes induced by environmental fluctuations affect circadian timing.

## II. Photoassimilates regulate circadian timing

The photosynthetic nature of plants ensures that their metabolism is profoundly affected by the availability of light, with distinct changes in cellular energy levels and photoassimilates observed in the absence of this resource. Although the action of photoreceptors is sufficient to entrain and maintain circadian rhythms (Millar, 2016), the metabolic consequences of photosynthesis also contribute to circadian rhythms. Recent work has documented how the accumulation of sucrose (and other photoassimilates) is sufficient to reset the circadian system (Dalchau *et al.*, 2011; Haydon *et al.*, 2013, 2017). Products from photosynthesis are integrated with the circadian oscillator via at least two pathways, with one acting to alter phase in a PRR7- and CCA1-dependent manner (Haydon *et al.*, 2013), whereas GIGANTEA promotes circadian rhythmicity in constant darkness in the presence of sucrose (Dalchau *et al.*, 2011; Haydon *et al.*, 2017).

One possible mechanism linking photoassimilates with the circadian system revolves around the SnRK1 signalling hub (Fig. 1). SnRK1 regulates metabolism by phosphorylating metabolic enzymes, with its activity regulated in part through control of the AKIN10 catalytic subunit (Wurzinger *et al.*, 2018). SnRK1 activity is additionally repressed by the accumulation of trehalose-6-phosphate, which serves as a molecular indicator of intracellular sucrose (Figueroa & Lunn, 2016). Overexpression of AKIN10 extends the circadian period in the light (Shin *et al.*, 2017; Frank *et al.*, 2018), suggesting that the control of this subunit is sufficient to change circadian timing. Importantly, SnRK1 regulates the activity of bZIP63, a transcription factor that activates *PRR7* transcription (Mair *et al.*, 2015; Frank *et al.*, 2018). As a consequence, the regulation of SnRK1 activity by trehalose-6-phosphate provides a mechanism by which intracellular sugar levels can be interpreted by the circadian system (Frank *et al.*, 2018).

## III. Retrograde signals contribute to circadian timing

Cell function is ultimately a cooperation between distinct organelles, which is maintained by both anterograde and retrograde signalling pathways (recently comprehensively reviewed by Chan *et al.*, 2016b; de Souza *et al.*, 2017). Retrograde signals convey information provided by organelles, such as chloroplasts and mitochondria, to the nucleus, ultimately altering nuclear gene expression. For example, mature chloroplasts contribute to lipid, starch, sulfur and amino acid metabolism, as well as contributing to the production of several hormones, in addition to their primary role in photosynthesis (Chan *et al.*, 2016b; de Souza *et al.*, 2017). Similarly, mitochondria are essential for cellular respiration and contribute to the generation of reactive oxygen species such as $^1O_2$ and $H_2O_2$ (Wang *et al.*, 2018). Retrograde signals consequently relay the metabolic health of the cell to the nucleus, and so provide information useful for integration into the circadian oscillator, in addition to the signalling provided by photo- and thermo-sensors.

During chloroplast biogenesis, several pathways relay the general health and developmental status of the plastid to the nucleus, resulting in changes in nuclear gene expression as a consequence of biogenic control (Chan *et al.*, 2016b; de Souza *et al.*, 2017). Disruption of chloroplast function is sufficient to alter photosynthesis-associated nuclear genes (PhANGs) and nuclear circadian gene expression. For instance, loss of CHLOROPLAST RNA BINDING (CRB) delays phase and increases the amplitude of circadian gene expression (Hassidim *et al.*, 2007), whereas the application of norflurazon (an inhibitor of photosynthesis) and lincomycin (which inhibits plastid protein synthesis) extends the circadian period (Chen *et al.*, 2013). Similarly, iron deficiency extends the circadian period, probably as a result of gross disruption of chloroplast function (Chen *et al.*, 2013; Salomé *et al.*, 2013). It is therefore apparent that retrograde signals relaying the health of the chloroplast are sufficient to delay circadian timing.

In addition to signals relaying the developmental status of organelles, the operation of mature chloroplasts can be perturbed by environmental factors (Fig. 1). Increases in irradiance promote photosynthesis and induce nonphotochemical quenching, whereas changing temperatures govern the speed of enzymatic reactions. Such environmental stressors are often sufficient to induce metabolic imbalances, causing oxidative stress in mitochondria and chloroplasts and leading to changes to the energy status of the cell (Chan *et al.*, 2016b). Such disruption of metabolism additionally perturbs hormone biosynthesis and signalling, alters calcium signalling and induces the accumulation of metabolic

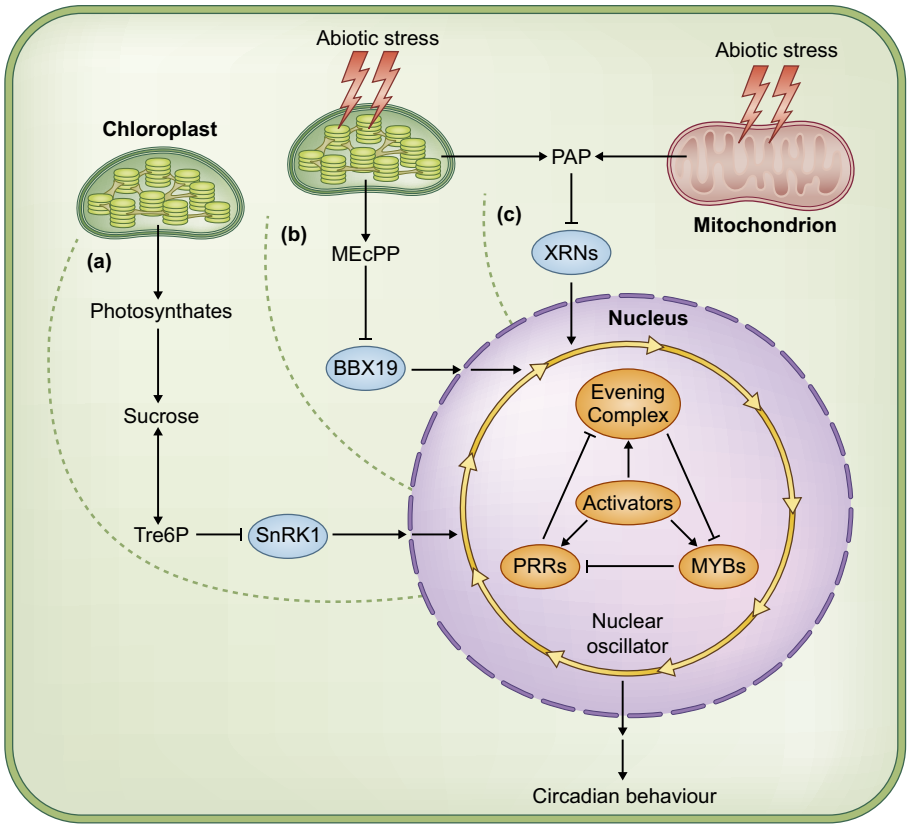


**Fig. 1** Operational retrograde signalling contributes to circadian timing in response to environmental factors. The nuclear circadian oscillator consists of multiple negative feedback loops (including Myb transcription factors (MYBs), PSEUDORESPONSE REGULATORs (PRRs) and the Evening Complex) in complex with activating proteins (summarized in Hsu & Harmer, 2014; Millar, 2016). These transcriptional–translational feedback loops are modified by metabolic intermediaries and products. (a) The sucrose/trehalose 6-phosphate (Tre6P) nexus regulates the activity of SnRK1 dependent on cytosolic sucrose accumulation. The SnRK1 complex phosphorylates bZIP63, allowing this transcription factor to dimerize and promote the expression of *PRR7*. (b, c) The infliction of abiotic stress induces the accumulation of reactive oxygen species (ROS) that alter the chloroplast redox state, such that methylerythritol cyclodiphosphate (MEcPP) and 5′-phosphoadenosine 3′-phosphate (PAP) accumulate. MEcPP represses the expression of *BBX19*, leading to the accumulation of EARLY FLOWERING3 (ELF3), which is a core constituent of the Evening Complex. PAP accumulation inhibits EXORIBONUCLEASE (XRN) activity, leading to defects in mRNA processing and an extension of the circadian period.

intermediaries that can subsequently be transported from the mitochondria or chloroplasts to the nucleus (Chan *et al.*, 2016b; Mullineaux *et al.*, 2018). With regard to circadian rhythmicity, high temperatures are sufficient to slow the circadian oscillator, and the circadian system is also delayed by osmotic stress (Gil *et al.*, 2017; Litthauer *et al.*, 2018). As with many stress responses, the question now facing the field is whether the clock is slowed under these environmental conditions as part of a generalized reaction to cellular damage, or whether specific retrograde signals delay circadian progression as part of an adaptive response.

## Reactive oxygen species

Reactive oxygen species (ROS) arise from the metabolic processes of mitochondria and chloroplasts (Murchie & Niyogi, 2011; S. Huang *et al.*, 2016). Both $H_2O_2$ accumulation and the oxidation state of peroxiredoxins (a ubiquitous family of enzymes that serve as antioxidants and regulatory proteins) vary with the circadian rhythm, suggesting that ROS generation is influenced by the circadian system (Edgar *et al.*, 2012; Lai *et al.*, 2012). Although ROS are produced as a consequence of the normal functioning of photosynthesis and respiration, their accumulation increases during suboptimal conditions, when environmental stresses, such as high light, induce an imbalance between photosynthetic and respiratory pathways (Mullineaux *et al.*, 2018). Under these stressful conditions, an increase in ROS production causes significant damage to the metabolic machinery, inducing photoinhibition and a generalized damage response (Mullineaux *et al.*, 2018). ROS, such as $H_2O_2$, can be transferred directly to the nucleus from the chloroplast (Exposito-Rodriguez *et al.*, 2017), where it is likely that the activity of redox-sensitive transcription factors is modulated. However, it remains unknown how these factors contribute to circadian timing. By contrast, shorter lived ROS, such as $^1O_2$, are likely to initiate signalling pathways by oxidizing carotenoids or polyunsaturated fatty acids (Mullineaux *et al.*, 2018). One such signalling trigger is β-cyclocitral, which is an oxidized derivative of β-carotene that accumulates as a consequence of $^1O_2$ production and induces gene expression in response to high light (Ramel *et al.*, 2012).

In addition to the direct role of ROS, or oxidized byproducts, plants also possess a suite of mechanisms, including nonphotochemical quenching, that allow for the sequestration of ROS below

critical thresholds (Ruban, 2016). Above these thresholds, ROS accumulation leads to the production of a range of metabolites that plants subsequently utilize as signalling molecules to report the metabolic status of the mitochondria and chloroplast. Such signals could be integrated into the nuclear circadian oscillator and include molecules such as methylerythritol cyclodiphosphate (MEcPP) and 5′-phosphoadenosine 3′-phosphate (PAP). Although these metabolites are now becoming accepted as authentic retrograde signals, it is not yet clear how these molecules integrate with circadian timing (Fig. 1).

### MEcPP

Methylerythritol cyclodiphosphate (MEcPP) accumulates in response to wounding or high light stress, inducing the expression of nuclear stress-responsive genes and repressing the accumulation of auxin (Xiao *et al.*, 2012; Jiang *et al.*, 2018). Our understanding of MEcPP is still developing, but one example of a signalling pathway repressed by MEcPP accumulation involves the transcription factor BBX19. *BBX19* transcription is repressed in *ceh1* mutants that constitutively accumulate MEcPP as a consequence of disruption of the methylerythritol phosphate pathway within the plastid (Xiao *et al.*, 2012; Wang *et al.*, 2014). BBX19 plays an important role in photomorphogenesis, repressing *PIF4* and *PIF5* expression by promoting the turnover of ELF3 (Wang *et al.*, 2015). As a consequence, MEcPP accumulation results in the accumulation of ELF3. As ELF3-overexpressing lines have been reported previously as having a long circadian period (Covington *et al.*, 2001), it is plausible that MEcPP accumulation could result in extended circadian rhythms, although this hypothesis is yet to be tested (Fig. 1).

### PAP

5′-Phosphoadenosine 3′-phosphate (PAP) is a byproduct of sulfur metabolism that is usually metabolized by SAL1, a redox-sensitive phosphatase that accumulates in both chloroplasts and mitochondria (Estavillo *et al.*, 2011; Chan *et al.*, 2016a). Following the application of high light or drought stress, SAL1 becomes oxidized, leading to its inactivation and the consequential accumulation of PAP (Estavillo *et al.*, 2011; Chan *et al.*, 2016a). PAP accumulation has several metabolic consequences, including the inactivation of EXORIBONUCLEASEs (XRNs; Dichtl *et al.*, 1997; Mechold *et al.*, 2006; Fig. 1). Loss of XRN function leads to the accumulation of uncapped RNAs, such as those generated from microRNA (miRNA) processing (Kurihara *et al.*, 2012). Interestingly, either the accumulation of PAP or the loss of XRN activity is sufficient to extend circadian period (Litthauer *et al.*, 2018). Although the mechanism underlying this phenotype remains unclear, such data are consistent with previous reports showing that gross defects in RNA processing slow circadian progression (Nolte & Staiger, 2015). It will therefore be important to examine how a loss of XRN activity alters the stability of circadian transcripts, and to understand how such post-transcriptional regulation acts in concert with previously reported variations in splicing to control functional gene expression.

## IV. Conclusions

Plants are highly sensitive to environmental change, and we have identified a complex suite of photo- and thermo-sensors that enable these responses, as well as the circadian system that anticipates and integrates these signals to regulate the development and responses of plants. However, it is also important to note the contribution of metabolism-induced signalling pathways to plant responses. We are beginning to appreciate how photosynthesis and metabolic perturbations within organelles lead to differential nuclear gene expression and, consequently, to circadian timing. An understanding of how mitochondrial and chloroplast signalling contribute to the circadian system (and how these pathways are reciprocally modulated by the circadian system) will allow the development of a holistic understanding of the responses of plants to environmental change.

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