1 **Temporal control of plant-environment interactions by the circadian clock.**

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19 **Keywords**

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21 Arabidopsis

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23 **Abstract**

24

25 The rotation of the earth generates dramatic daily and seasonal variation in the terrestrial

26 environment. Plants, like other organisms, have evolved an endogenous biological oscillator to

27 predict these daily changes in light and temperature and adjust to shifting seasonal conditions.

28 This system must be robust to unexpected environmental challenges but can also assist plants to

29 adjust physiology accordingly. Key features of the circadian system which contribute to achieve

30 these are the process of entrainment, by which external cues adjust the state of the oscillator, and

31 gating, by which the sensitivity to a stimulus is modified according to the time of day. In this way,

32 the circadian clock is a dynamic hub which integrates physiology, metabolism and growth in the

33 context of a plant's current environment. We provide a comprehensive summary of the molecular

34 composition of the core oscillator in Arabidopsis and the mechanisms of entrainment and gating. In

35 particular, we focus on phytohormone signalling, photosynthetic metabolism and defense

36 responses as examples of core plant responses to environment that are integrated within the

37 circadian system.

38

1.1 Introduction

Life has evolved on a rotating planet, which orbits the sun on a tilted axis. The orbit and rotation of the Earth gives rise to dramatic daily and seasonal variation in the environment at any given fixed position on its surface. For terrestrial organisms, these environmental variations are particularly extreme. Plants, which are normally rooted in place for their life cycle, face heightened challenges. To adapt to these conditions, organisms from all three domains of life have evolved a timing mechanism to align their biology according to these predictable daily and seasonal rhythms (Edgar et al., 2012). This biological timer is a circadian clock (*circa*, about; *diem*, day), which generates rhythms of approximately 24 h to control metabolism, physiology and behaviour. A defining feature of circadian rhythms is that they are sustained in continuous conditions, illustrative of their endogenous nature, and crucial to allow an organism to predict the external environment. Circadian clocks also adjust to changes in photoperiod, which allows plants to sense and adapt to seasonal variation.

There is circadian control of vegetative and reproductive growth, transpiration, metabolism, nutrient transport and responses to the biotic and abiotic environment. There is probably not any aspect of plant physiology that is not affected by the circadian system. This is driven by an extensive regulatory network. Circadian clocks control at least 30% of the transcriptome in plants (Michael et al., 2008b), with additional layers of post-transcriptional, translational and post-translational control. Circadian clocks confer a fitness advantage. Plants grow better when their endogenous rhythms are matched to the external light-dark cycle (Dodd et al., 2005).

Although the circadian system is broadly conserved among land plants, there is genetic variation both within and between species. This variation contributes to geographic adaptation in natural populations and has been selected for in numerous crops to adjust life cycle and improve yield (Bendix et al., 2015). For example, mutants in circadian clock genes in rice, wheat and barley with phenotypes affecting photoperiodic flowering have been introduced into breeding programs (Turner et al., 2005; Beales et al., 2007; Faure et al., 2012; Campoli et al., 2013; Koo et al., 2013). Similarly, in elite cultivars of soybean (*Glycine max*) which have been artificially selected for specific growing regions, variation in circadian period correlates with latitude (Greenham et al., 2017). In *B. napus*, circadian period varies between different crop morphotypes. Root and leaf crops have longer period than oilseed crops, which is likely associated with vegetative versus reproductive productivity (Yarkhunova et al., 2016). The potential impact of selecting for circadian-regulated traits in agriculture and horticulture is only beginning to be realised because the circadian system integrates a wide range of important environmental cues and responses including drought and defense.

Circadian rhythms arise from a system comprised of three components: a core oscillator, which generates a self-sustaining rhythm; inputs, which provide reference information to adjust the state of the oscillator; and outputs, which are the processes controlled by the oscillator. The genetic architecture of the circadian oscillator in plants is distinctly different from animals, fungi and even green algae and photosynthetic bacteria (Hurley et al., 2016). Nevertheless, there is deep conservation of the architecture of the circadian clock among land plants (Lou et al., 2012; Calixto et al., 2015; Linde et al., 2017). The core oscillator is comprised of three classes of transcriptional regulators: the REVEILLE (RVE) class of myb-like transcription factors expressed from the morning; PSEUDO RESPONSE REGULATORS (PRRs) which generate a wave of transcriptional repression throughout the day; and the evening complex (EC), a night-active trimeric transcriptional repressor. An intricate understanding of the plant circadian system has been developed over the last two decades using the model genetic organism, *Arabidopsis thaliana*. Our knowledge of the circadian system in other plants is slowly expanding but we focus here on the state of knowledge with respect to each of the three components of the circadian system in *Arabidopsis*.

1.2 Environmental inputs to the circadian system

The core oscillator is a gene regulatory network which has evolved to generate a cycle with a near-24 h period. The oscillator is temperature-compensated to maintain this period over a wide range of ambient temperatures, but this timing is plastic. For example, Aschoff's Rule is a well-described phenomenon in chronobiology, whereby the pace of the oscillator increases with light quantity (Pittendrigh, 1960). Similarly, despite temperature compensation, the *Arabidopsis* clock does modestly accelerate with elevated temperatures (Salomé et al., 2010). A wide range of other internal stimuli, including metabolites and nutrient status, can also adjust the pace of the oscillator (Haydon et al., 2015).

The plasticity of the oscillator is crucial for entrainment, the process by which the phase and period of the oscillator is adjusted according to environmental stimuli. Entrainment ensures that endogenous rhythms of an organism can adjust to the continuously shifting photoperiod in the natural environment. Entrainment can also modify the timing of rhythmic processes controlled by the oscillator by less predictable events such as fluctuations in daylight, rainfall or nutrient availability. These phase adjustments enable fine-tuning of rhythmic physiology and metabolism. Entrainment cues are called *zeitgebers* (timers), which include light, temperature and sugar. The nature of a *zeitgeber* in circadian entrainment can be determined experimentally by generating a Phase Response Curve (PRC), which quantifies the change in phase of circadian rhythms in response to a pulse of stimulus during free-running conditions. PRCs to pulses of either red or blue light induce dramatic phase delays early in the night and phase advances late in the night

115 (Covington et al., 2001). In this way, the oscillator is adjusted to match the light-dark cycles
116 according to shifting photoperiod. By comparison, the shape of a temperature PRC is different with
117 phase delays around dawn and phase advances around dusk (Michael et al., 2003). A PRC to
118 sucrose has a similar shape to light PRCs, but with less dramatic phase shifts, advanced around
119 dawn and delayed around dusk, which is consistent with a role for photosynthetic output adjusting
120 rhythmic metabolism and physiology during the morning (Haydon et al., 2013).

121 Despite the well-defined importance of light for circadian entrainment, the precise mechanisms by
122 which light signalling affects phase adjustment are not known. Functional red- and blue-light
123 photoreceptors are required for sensitivity of the oscillator to light quantity. For example, under
124 continuous red light, *phytochrome A* (*phyA*) and *phyB* mutants have lengthened circadian period
125 under low and high light quantity, respectively, and *cryptochrome1* (*cry1*) and *cry2* mutants have
126 lengthened circadian period under blue light (Somers et al., 1998). The oscillator in a *phyABCDE*
127 quintuple mutant is severely impaired in period adjustment to red light, with a nearly insensitive
128 response to change in red light quantity (Hu et al., 2013). Thus, the importance of phytochromes
129 and cryptochromes for light entrainment are clear, but precisely how they adjust the oscillator is
130 not. Several genes in the circadian oscillator are strongly induced by light. NIGHT-LIGHT
131 INDUCIBLE AND CLOCK REGULATED 1 (*LNK1*) and *LNK2* are transcriptional coactivators of
132 clock genes and *lnk1* and *lnk2* mutants have reduced sensitivity to period shortening by red or blue
133 light, similar to photoreceptor mutants (Xie et al., 2014). Therefore, LNKs may represent a key
134 component of light entrainment of the oscillator. Alternatively, since the inactive Pr form of PhyB
135 has been proposed as a transcriptional repressor (Jung et al., 2016) and CRY2 binds to DNA and
136 has been reported as a transcriptional activator (Pedmale et al., 2016; Yang et al., 2018),
137 photoreceptors might regulate clock genes directly. Indeed, PhyB associates with promoters of
138 light-responsive clock genes *LNK1*, *PRR9*, *PRR7*, *LUX ARRHYTHMO* (*LUX*) and *GIGANTEA* (*GI*)
139 (Jung et al., 2016).

140
141 Two components of the circadian oscillator, *PRR9* and *PRR7*, are necessary for temperature
142 entrainment. A *prp7 prp9* double mutant cannot be robustly entrained to temperature cycles under
143 continuous light and a PRC reveals insensitivity to phase adjustment of the oscillator to cold
144 temperature pulses in the double mutant (Salomé and McClung, 2005). The temperature sensing
145 pathways for entrainment have not been defined, but it's notable that light signalling components
146 are emerging as key factors in temperature sensing (Jung et al., 2016; Legris et al., 2016; Ma et
147 al., 2016; Park et al., 2017). In particular, the temperature-dependent association of PhyB to clock
148 gene promoters, including *PRR9* and *PRR7* (Jung et al., 2016) presents a potential mechanism for
149 temperature entrainment.

150
151 The mechanism(s) by which temperature compensation of circadian rhythms is achieved are not
152 yet clear. It's possible the robustness of circadian period across ambient temperatures is due to

153 compensation by counteractive components of the oscillator and is thus an emergent property of
154 complexity of the clock. This is supported by the observation that high order combinations of clock
155 mutants have a compromised circadian rhythms specifically at sub-optimal temperatures (Shalit-
156 kaneh et al., 2018). Nevertheless, temperature compensation can be achieved with simple
157 oscillators (Terauchi et al., 2007) and there appears to be specific roles for particular clock-
158 associated proteins. For example, temperature compensation in Arabidopsis requires *GI* because
159 a *gi* mutant has a dramatically short period at elevated temperature (Gould et al., 2006; Salomé et
160 al., 2010). There is also a role for CRY proteins. Temperature compensation requires blue light
161 because it is compromised in red light and in *cry1 cry2* mutants. A mathematical model based on
162 transcript data across varying light and temperature accurately predicted dramatic changes in
163 LATE ELONGATED HYPOCOTYL (LHY) abundance with temperature and mis-regulated LHY in
164 *cry1 cry2* (Gould et al., 2013). Similarly to phytochromes, CRY1 contributes to
165 thermomorphogenesis (Ma et al., 2016) but unlike the model of temperature-regulated dark-
166 reversion to Pfr of PhyB (Jung et al., 2016), a mechanism for temperature sensing by
167 cryptochromes has not been proposed.

168
169 Entrainment by sugar requires *PRR7*, since *prp7* mutants are insensitive to period change by
170 exogenous sucrose and are unable to adjust phase to pulses of sucrose. Depletion of endogenous
171 sugars during the day by inhibition of photosynthesis increases *PRR7* transcript levels and
172 lengthens circadian period (Haydon et al., 2013). Systematic modelling of PRCs to sucrose most
173 accurately recapitulate the experimental PRC when sugar either activates expression of EC
174 components or represses *PRR7* (Ohara et al., 2018). The arrhythmic phenotypes of EC mutants
175 make it difficult to experimentally test the role of EC components in entrainment, but the modelling
176 corroborates the severely compromised sucrose PRC observed in *prp7* mutants (Haydon et al.,
177 2013).

178
179 The effect of sucrose on period also requires *BASIC LEUCINE ZIPPER 63 (bZIP63)*, a
180 transcription factor which is activated by the starvation-responsive kinase Snf1-RELATED
181 KINASE1 (SnRK1) and binds to the *PRR7* promoter (Mair et al., 2015; Frank et al., 2018). Over-
182 expression of *KIN10*, a catalytic subunit of SnRK1 and *bzip63* mutants have attenuated sucrose
183 PRCs, similar to *prp7* mutants (Frank et al., 2018). The precise mechanism by which energy status
184 modulates SnRK1 activity is unresolved (Zhang et al., 2009; Emanuelle et al., 2015), although it's
185 possible there may be several signals. One possible mechanism involves trehalose-6-phosphate
186 (T6P), a signalling sugar which closely tracks sucrose status in Arabidopsis (Figueroa and Lunn,
187 2016) and is reported to inhibit SnRK1 activity (Zhang et al., 2009; Nunes et al., 2013). Null
188 mutants in *T6P SYNTHASE 1 (TPS1)* are embryo lethal (Eastmond et al., 2002; Schluepmann et
189 al., 2003) but hypomorphic alleles are impaired in circadian period adjustment and entrainment by
190 sucrose (Gómez et al., 2010; Frank et al., 2018). Thus, a signalling pathway for circadian

191 entrainment from signal to oscillator has been defined (Frank et al., 2018). This process of
192 modulating the phase of the oscillator by the status of photosynthesis, for example according to
193 light availability, might be important to optimise rhythmic metabolism, growth and physiology in
194 photoautotrophs.

195

196 **1.3 The Arabidopsis circadian oscillator**

197

198 **1.3.1 Transcription-translation feedback loops**

199

200 Since genetic screens identified *timing of cab 1 (toc1)/ prr1*, the first circadian clock mutant in
201 Arabidopsis (Millar et al., 1995a), there has been enormous progress in understanding the
202 transcriptional feedback loops that lie at the core of the circadian oscillator. The current model of
203 the Arabidopsis oscillator is comprised of around 20 genes (Figure 1), which continues to expand
204 as more components of regulatory complexes are revealed.

205

206 *CIRCADIAN CLOCK ASSOCIATED 1 (CCA1)*, *LHY* and *RVE8/LHY- CCA1- LIKE 5 (LCL5)* are
207 expressed around dawn and encode myb-like factors which bind to evening elements (EE) and
208 CCA1-binding sites (CBS), which are *cis*-regulatory sequences in gene promoters, to regulate
209 transcription (Alabadí et al., 2001; Farinas and Mas, 2011; Rawat et al., 2011; Hsu et al., 2013).
210 Their targets include *PRR9*, *PRR7*, *PRR5* and *TOC1* which are expressed during the day and
211 evening, and genes encoding the evening complex (EC) during the night (Alabadí et al., 2001; Hsu
212 et al., 2013; Adams et al., 2015; Kamioka et al., 2016). EEs and CBSs are also present in many
213 circadian-regulated output genes. For example, CCA1 binds to promoter regions of *ca.* 1300 genes
214 in the Arabidopsis genome (Nagel et al., 2015). CCA1 and LHY act to repress these clock genes
215 by recruiting a corepressor, DE-ETIOLATED 1 (DET1) to EEs (Lau et al., 2011). Loss of this
216 repression in mutants of *CCA1*, *LHY* and *DET1* give rise to short-period phenotypes (Millar et al.,
217 1995b; Green and Tobin, 1999). On the other hand, RVE8 and partially redundant homologues
218 RVE4 and RVE6 accumulate during the afternoon and act as an activators of EE-containing genes
219 by recruiting co-activators, LNK1 and LNK2 (Rugnone et al., 2013; Xie et al., 2014; Ma et al.,
220 2018). LNKs interact with the LCL domain of RVE8 and recruited to the promoters of *PRR5* and
221 *TOC1*. LNKs, but not RVE8, interact with RNA Pol II and the histone chaperone FACILITATES
222 CHROMATIN TRANSCRIPTION (FACT) complex and promote transcription initiation and
223 elongation of *TOC1* and *PRR5* (Ma et al., 2018). Association of FACT complex to *TOC1* mRNA is
224 rhythmic and closely matches *TOC1* mRNA abundance (Perales, 2007). Mutants in the activating
225 components, *RVE4*, *RVE6*, *RVE8*, *LNK1* or *LNK2*, have long-period phenotypes (Hsu et al., 2013;
226 Rugnone et al., 2013). The activating and repressive myb-like factors are counteractive, which is
227 evident in the near-wild type period of a quintuple *cca1,lhy,rve4,6,8* mutant (Shalit-kaneh et al.,
228 2018).

229

230 *PRR9*, *PRR7*, *PRR5* and *TOC1* are expressed sequentially through the day in a wave of de-
231 repression by *CCA1/LHY* and activation by *RVE8/6/4* (Matsushika et al., 2000). These PRR
232 proteins bind to promoters of *CCA1* and *LHY* to repress their expression (Nakamichi et al., 2010;
233 Gendron et al., 2012; Huang et al., 2012). *PRR9*, *PRR7* and *PRR5* interact with *TOPLESS* (*TPL*),
234 a member of the Groucho/Tup1 corepressor family, which recruits HISTONE DEACETYLASE 6
235 (*HDA6*) to *CCA1* and *LHY* promoters (Wang et al., 2013). Triple *prp9,7,5* mutants are arrhythmic
236 (Nakamichi et al., 2005) and depletion of *TPL* lengthens period (Wang et al., 2013). *TOC1* also
237 binds to promoters and represses *CCA1/LHY* expression (Gendron et al., 2012; Huang et al.,
238 2012), but it does not interact with *TPL* (Wang et al., 2013). Like other PRRs, *TOC1* has general
239 repressor activity (Gendron et al., 2012) and *toc1* mutants have a short-period phenotype (Millar et
240 al., 1995a). *TOC1* interacts with *CCA1* HIKING EXPEDITION (*CHE*), a TCP transcription factor
241 which also binds to a TCP binding site (*TBS*) in the *CCA1* promoter and contributes to repression
242 (Pruneda-Paz et al., 2009).

243

244 The EC, which is active during the night, is comprised of *EARLY FLOWERING 3* (*ELF3*), *ELF4*
245 and *LUX*, another myb-like factor (Nusinow et al., 2011). Mutants in any one of these components
246 are arrhythmic (Hicks et al., 1996; Doyle et al., 2002; Hazen et al., 2005). Expression of *ELF3*,
247 *ELF4* and *LUX* are repressed by *CCA1/LHY* and activated by *RVE8/6/4* (Hazen et al., 2005; Kikis
248 et al., 2005; Hsu et al., 2013). The EC binds to *LUX* Binding Sites (*LBS*) in the promoter of *PRR9*
249 to repress expression during the night, as well as the *LUX* promoter (Dixon et al., 2011; Helfer et
250 al., 2011; Nusinow et al., 2011; Herrero et al., 2012). Chromatin immunoprecipitation followed by
251 DNA sequencing (ChIP-Seq) identified hundreds of additional EC-binding sites in gene promoters,
252 including *CCA1*, *PRR7* and *GI* (Ezer et al., 2017).

253

254 In addition to de-repression of morning-active genes by the PRRs and the EC, activation of *CCA1*
255 expression involves *LIGHT-REGULATED WD1* (*LWD1*), *LWD2* and at least two TCP transcription
256 factors (Wu et al., 2008; Wang et al., 2011b; Wu et al., 2016). *LWD1*, *LWD2*, *TCP20* and *TCP22*
257 transcript levels peak during the night (Wu et al., 2008; Wu et al., 2016) and mutants have short
258 circadian period (Wang et al., 2011b; Wu et al., 2016). A *lwd1 lwd2* double mutant has a strikingly
259 short ca. 18-h period, similar to *cca1 lhy* double mutants (Wang et al., 2011b). Genetic evidence
260 suggests *TCP20* and *TCP22*, and probably other Class I TCPs, activate *CCA1* expression in a
261 *LWD*-dependent manner (Wu et al., 2016). *LWDs* lack a DNA binding domain, but *LWD1* associate
262 with promoters of *CCA1*, *PRR9*, *PRR5* and *TOC1* (Wang et al., 2011b; Wu et al., 2016). *LWD1*,
263 and probably *LWD2*, physically interacts with *TCP20* and *TCP22* in nuclei and both associate with
264 a *TBS* in the *CCA1* promoter (Wu et al., 2016).

265

266 There is also a role for chromatin remodeling in transcriptional activation of circadian oscillator
267 genes. There are daily rhythms in histone 3 acetylation (H3ac) and trimethylation (H3K4me3) of
268 clock genes. These histone marks are associated with transcriptional activation and peak levels
269 coincide with maximum clock gene expression. Pharmacological inhibition of H3K4me3 or H3ac
270 reduced amplitude and lengthened circadian period of gene expression (Malapeira et al., 2012).
271 Conversely, inhibition of histone deacetylation increased clock gene expression amplitude and
272 delayed phase and/or period (Perales, 2007). Inhibition of H3K4me3 with nicotinamide lead to
273 increased association of transcriptional repressor binding to clock gene promoters (Malapeira et
274 al., 2012). Thus, these histone modifications might contribute to activation of oscillator genes by
275 modulating repressor binding.

276
277 There are distinct roles of histone demethylation in activation of morning and evening expressed
278 clock genes. *JUMONJI DOMAIN CONTAINING 5 (JMJD5/JMJ30)* encodes a putative histone
279 demethylase which is coexpressed with *TOC1*. Mutants have a short circadian period and might
280 act synergistically with *TOC1* in derepression of morning expressed clock genes (Jones et al.,
281 2010; Lu et al., 2011a). *CCA1* and *LHY* bind to the *JMJD5* promoter and repress expression (Lu et
282 al., 2011a), suggesting a possible feedback loop. By contrast, *LYSINE SPECIFIC DEMETHYLASE*
283 *1-LIKE 1 (LDL1)* and *LDL2*, another class of histone demethylase, interact with *CCA1* and *LHY* in
284 a complex with a histone deacetylase *HDA6*. *hda6 ldl1 ldl2* mutants have increased H3ac and
285 H3K4me at the *TOC1* promoter and reduced amplitude of *TOC1* transcript abundance (Hung et al.,
286 2018) consistent with a role in transcriptional activation of *TOC1*.

287

288 **1.3.2 Translational control**

289

290 In contrast to the deep knowledge of the mechanisms of transcriptional control of the circadian
291 oscillator, our understanding of the full extent of translational regulation of circadian clocks is
292 currently limited, particularly in plant cells. There are daily rhythms of ribosome transition into
293 polysomes with the highest rates of translation occurring during the day (Pal et al., 2013).
294 Microarrays of mRNA in polysomes revealed rhythms of translational state in ca. 10-50% of
295 detected transcripts, including numerous oscillator genes. The phase of mRNA abundance and
296 translation states were different for the majority of transcripts and the phase relationships were
297 altered in *CCA1*-overexpressors and/or in continuous light (Missra et al., 2015). These
298 observations suggest a role for the oscillator in regulating translation of a significant proportion of
299 mRNAs, as well as the possibility that there is translational control of the oscillator.

300

301 Several oscillator genes have substantial phase offsets between mRNA and protein abundances,
302 which might represent a contribution from translational control. Comparisons of mRNA and protein
303 phase estimate a 4-8 h offset for the PRR proteins (Fujiwara et al., 2008), 3-6 h for the RVE8

304 (Rawat et al., 2011) and up to 8 h for ELF3 (Nusinow et al., 2011). The precise post-transcriptional
305 mechanism(s) which give rise to these phase differences are unknown but a number of
306 mechanisms of translational control have been linked to circadian rhythms in other organisms and
307 might contribute to regulation of the oscillator in plants.

308

309 Codon usage is correlated with gene expression level and can affect translational efficiency. Sub-
310 optimal codon usage in core clock genes contributes to oscillator function by affecting translation
311 elongation rates in *Drosophila*, *Neurospora* and cyanobacteria (Xu et al., 2013; Zhou et al., 2013;
312 Fu et al., 2016). It seems likely that similar effects of codon bias could contribute to oscillator gene
313 translation in plants.

314

315 Translation of short upstream open reading frames (uORFs) within the 5' of mRNAs can act to
316 repress translation of the main coding ORF. Approximately 35% of *Arabidopsis* transcripts are
317 estimated to contain uORFs (Von Arnim et al., 2014). *LHY* mRNA contains several uORFs and is
318 translationally induced by light (Kim et al., 2003a). Mutants that disrupt eukaryotic initiation factor 3
319 h (eIF3h) are impaired in efficient translation of several uORF containing mRNAs, including *LHY*
320 (Kim et al., 2004). However, it is not yet clear what impact this has on oscillator function.

321

322 1.3.3 Post-translational control

323

324 There are a range of post-translational mechanisms that act on proteins of the core oscillator.
325 These affect protein maturation, subcellular localisation, transcription factor activity and ubiquitin-
326 mediated proteasome degradation (Figure 2). In addition, histone modifications contribute
327 extensively to transcriptional control (see 1.3.1).

328

329 Several circadian oscillator proteins have been shown to move between the nucleus and
330 cytoplasm including ELF3 and GI. ELF4 is required to recruit ELF3, but not LUX, to the nucleus
331 (Herrero et al., 2012). The best described contribution of post-transcriptional control of the
332 oscillator involves an F-box E3 ubiquitin ligase ZEITLUPE (ZTL), which interacts with GI to control
333 light-dependent nucleocytoplasmic partitioning and targets substrates TOC1 and PRR5 for
334 degradation.

335

336 ZTL has properties of a blue-light photoreceptor and blue light strongly promotes its interaction
337 with GI via a LIGHT, OXYGEN VOLTAGE (LOV) domain (Kim et al., 2007). GI is also stabilised by
338 sucrose, which requires *ZTL*, so sugar might similarly promote the GI-ZTL interaction (Haydon et
339 al., 2017). GI is a co-chaperone, which in cooperation with HEAT SHOCK PROTEIN 90 (HSP90),
340 promotes ZTL maturation in the cytoplasm (Kim et al., 2011; Cha et al., 2017). After dusk, GI-ZTL
341 dissociates, GI moves to the nucleus and mature ZTL ubiquitinates TOC1, PRR5 and CHE for

342 degradation (Más et al., 2003; Kiba et al., 2007; Fujiwara et al., 2008; Kim et al., 2013; Lee et al.,
343 2018). In the nucleus, ELF3 promotes interaction of GI with CONSTITUTIVE
344 PHOTOMORPHOGENIC 1 (COP1), another E3 ligase which is required for rhythms of GI protein
345 (Yu et al., 2008). ZTL is also degraded by the proteasome (Kim et al., 2003b) but the identity of the
346 ligase is unknown. *ztl* mutants have a long circadian period (Somers et al., 2000), consistent with a
347 role in protein turnover of oscillator proteins. This is partially redundant with related F-box proteins
348 FLAVIN, KELCH REPEAT F-BOX 1 (FKF1) and LOV KELCH PROTEIN 2 (LKP2) because *ztl fkf1*
349 *lkp2* triple mutants have a further lengthened period (Baudry et al., 2010). Conversely, mutants in
350 *UBIQUITIN SPECIFIC PROTEASE 12 (UBP12)* have a short period (Cui et al., 2013) although the
351 substrates are unknown.

352
353 The ZTL-HSP90 complex also contributes to thermal stability of the circadian clock. Warm
354 temperature promoted the ZTL-HSP90 interaction and the complex associates with insoluble
355 protein aggregates to degrade those damaged proteins through the ubiquitin-proteasome pathway.
356 *ztl* and *HSP90* RNAi seedlings are hypersusceptible to heat stress with respect to growth and
357 robustness of transcriptional circadian rhythms (Gil et al., 2017). Thus, this role for ZTL
358 demonstrates another example of converging light and temperature signals in plants.

359
360 In cyanobacteria, phosphorylation state of the KaiC protein drives a self-sustaining post-
361 translational oscillator (Nakajima et al., 2005; Rust et al., 2007). In Arabidopsis, there are rhythms
362 of phosphorylation state of PRR proteins although the specific kinases are unknown (Fujiwara et
363 al., 2008). PRR5 interacts with TOC1 and promotes its phosphorylation and nuclear localisation
364 (Wang et al., 2010). Phosphorylated TOC1 and PRR5 more readily interact with ZTL and are
365 targeted for degradation. Phosphorylation of PRR3 and TOC1 also promotes their interaction to
366 prevent interaction with ZTL (Fujiwara et al., 2008), but this PRR3-TOC1 complex would be
367 restricted to shoot vasculature (Para et al., 2007). Thus, this counteractive role of phosphorylation
368 of TOC1 to promote both stabilisation and degradation might reflect sequential phosphorylation
369 events controlled by distinct kinases or relate to tissue-specific features of the oscillator (see
370 1.3.5).

371
372 Phosphorylation of CCA1 by CASEIN KINASE 2 (CK2) contributes to alteration of promoter-
373 binding activity (Sugano et al., 1998; Sugano et al., 1999; Daniel et al., 2004). CK2 can
374 phosphorylate CCA1 and inhibit its binding to promoters and thus interfere with the transcriptional
375 repression of CCA1 target genes (Portolés and Más, 2010). CK2 is also phosphorylated
376 preferentially in the light (Perales et al., 2006), which reduces its kinase activity and increases its
377 susceptibility to proteasome-degradation (Hardtke et al., 2000). Thus, the effect of CK2 on CCA1
378 would be diminished during the day and promoted during the night. A triple mutant in CK2 catalytic
379 subunits *ck alpha (cka1) cka2 cka3* has a long period, consistent with hypophosphorylation of

CCA1 (Lu et al., 2011b). Inhibition or overexpression of CK2 impairs temperature compensation of the clock, which has been attributed to effects of warm temperature on CK2 phosphorylation and CCA1 promoter-binding (Portolés and Más, 2010).

1.3.4 Calcium signalling

Calcium is a second messenger which transduces extracellular signals to regulate plant physiological and developmental processes. Environmental stimuli such as cold, salt, hormones and pathogen invasion cause Ca^{2+} influx from external and internal stores to the cytoplasm, which trigger downstream signalling (Dodd et al., 2010). There are also circadian oscillations of cytosolic free calcium concentrations ($[\text{Ca}^{2+}]_{\text{cyt}}$) (Johnson et al., 1995). These are driven by the core oscillator (Xu et al., 2007) but also contribute to regulate the oscillator (Martí Ruiz et al., 2018). In this way, circadian Ca^{2+} signalling could integrate environmental signals to the oscillator.

The precise channel(s) which drive circadian rhythms of cytosolic Ca^{2+} are unknown. Nicotinamide can inhibit the synthesis of cyclic adenosine diphosphate ribose (cADPR), a Ca^{2+} channel agonist in animal cells. Nicotinamide dampens circadian $[\text{Ca}^{2+}]_{\text{cyt}}$ oscillations and lengthens transcriptional circadian rhythms (Dodd et al., 2007; Hearn et al., 2018). There are circadian oscillations of cADPR which correlate with Ca^{2+} rhythms (Dodd et al., 2007) but the cADPR-activated channel(s) in plant cells are not known.

Transcript levels of oscillator genes including *CCA1* and *PRR7* are regulated by cADPR (Dodd et al., 2007) and robust rhythms of *CHE* expression can be driven by an artificially imposed circadian Ca^{2+} oscillation (Martí Ruiz et al., 2018). Input of Ca^{2+} signals to the clock requires a calcium sensor CALMODULIN-LIKE 24 (CML24) because *cm124* mutants have a long circadian period and this effect is diminished in the presence of nicotinamide or sucrose, either of which abolish circadian Ca^{2+} rhythms. Mutants in *CHE* or *TOC1* are epistatic to *cm124* (Martí Ruiz et al., 2018), pointing to a potential feedback loop between Ca^{2+} and the oscillator.

1.3.5 Spatial heterogeneity of circadian oscillators

All plant cells contain a circadian oscillator, and circadian rhythms can be sustained in a cell autonomous manner (Nakamichi et al., 2003). However, there is spatial heterogeneity in the genetic architecture and behaviour of the oscillator in different organs, tissues and cell-types. The circadian period of rhythmic gene expression is lengthened in roots and hypocotyls compared to leaves (James et al., 2008; Takahashi et al., 2015; Bordage et al., 2016). Circadian period is also lengthened in young leaves and the shoot apex compared to old leaves (Takahashi et al., 2015; Kim et al., 2016).

418

419 There is also spatial heterogeneity within organs. Although circadian period is lengthened in whole
420 roots compared to shoots, precise imaging and quantification of CCA1-YFP fluorescence in nuclei
421 of young seedlings indicates that the period of oscillations in roots tips are dramatically shorter
422 (Gould et al., 2018). This phenomenon might also explain the observed rephasing of the oscillator
423 in emerging lateral roots (Voss et al., 2015). There is similar heterogeneity within leaves (Wenden
424 et al., 2012). Transcriptomes of dissected leaves and imaging of cell-type specific luciferase
425 reporters revealed altered phase in leaf vasculature compared to whole leaves (Endo et al., 2014).
426 Cell-type specific expression of aequorin suggest circadian oscillations of cytosolic Ca^{2+} are
427 derived from mesophyll cells (Martí et al., 2013). Thus, there is variation in the circadian oscillator
428 in different tissues and cell-types.

429

430 This variation could be due to tissue-specific differences between oscillator gene expression. For
431 example, the *PRR3* promoter is strongly expressed in shoot vasculature (Para et al., 2007).
432 Similarly, other evening-expressed clock genes cycle more robustly in vascular cells and
433 misexpression of *CCA1*, a morning-expressed gene, in phloem companion cells damps *TOC1*
434 expression (Endo et al., 2014). Distinct PRCs to temperature have been determined for
435 *CATALASE3* (*CAT3*) or *CAB2* rhythms, which might be due to the expression of *CAT3*, but not
436 *CAB2*, in leaf epidermis (Michael et al., 2003). Overexpression of *CCA1* in epidermal cells, but not
437 mesophyll or vasculature, increased sensitivity of hypocotyl elongation to warm temperature
438 (Shimizu et al., 2015), suggesting epidermal cells are required for temperature sensing and/or
439 growth associated with thermomorphogenesis.

440

441 Despite the spatial heterogeneity and cell autonomy of oscillators in plant cells, there is clear
442 evidence of coupling between cells. Spatial waves of circadian gene expression have been
443 observed in mature leaves (Wenden et al., 2012) and roots and shoots of young seedlings (Gould
444 et al., 2018), which implies localised coupling between cells. Coupling of cellular oscillators would
445 aid a plant to coordinate effective circadian-mediated environmental responses. At least two waves
446 can be detected in young seedlings, each originating at the shoot and root apex, implying a
447 hierarchy of cell type-specific oscillators (Gould et al., 2018). Indeed, circadian rhythms in roots of
448 decapitated plants are specifically compromised in continuous light, suggesting a role for a shoot-
449 derived signal (Bordage et al., 2016). Ablation of shoot apices lead to advanced phase in leaves
450 and damped rhythms in roots, whereas removal of cotyledons or leaves had no effect.
451 Micrografting of shoot apices between genotypes demonstrated that circadian rhythms can be
452 largely restored in both roots and shoots by a wild-type shoot apex on a mutant plant (Takahashi et
453 al., 2015). The mechanisms by which neighbouring cells are coupled, or the signals derived from
454 shoot or root apices, are yet to be defined.

455

1.4 Outputs of the plant circadian system

Since the core oscillator is comprised of a network of rhythmically expressed transcriptional regulators, it is straightforward to understand how the circadian system drives rhythmic physiological and developmental processes. ChIP-seq experiments have revealed the large number of direct promoter targets of oscillator proteins in the Arabidopsis genome. Over 1000 promoters are bound by each of CCA1, PRR7 or PRR5, about 150 by PRR9, over 700 by TOC1 or LHY and nearly 900 by LUX (Huang et al., 2012; Nakamichi et al., 2012; Liu et al., 2013; Nagel et al., 2015; Liu et al., 2016; Ezer et al., 2017; Adams et al., 2018). There are significant overlaps between target genes but also specific targets for each oscillator component, which would be required to generate specific phases of expression of target genes. For example, pairwise comparisons show 15-50% overlap between PRR protein targets (Liu et al., 2016) and about one third of CCA1 targets are also bound by LHY (Adams et al., 2018). In addition to direct targets, these circadian regulators will feed into transcription factor hierarchies that have been shown to be important in environmental responses (Song et al., 2016). Thus, the basis for circadian rhythms of over a third of the transcriptome becomes evident. Furthermore, oscillator proteins also bind to promoters of non-rhythmic genes. For example, about one third of CCA1 targets (Nagel et al., 2015) and nearly half of LHY targets are not rhythmically expressed in continuous light (Adams et al., 2018). This might suggest the circadian clock also contributes to regulating non-rhythmic processes. CCA1 and LHY might also regulate a number of genes that only have detectable rhythms of expression in light-dark cycles. The latter would imply that the contribution of the circadian clock to rhythmic expression in light-dark cycles has been underestimated.

1.4.1 Phytohormone signalling

Phytohormones modulate most aspects of growth, development and physiology. There is evidence the circadian clock contributes to control of biosynthesis and/or signalling of most phytohormones (Thain et al., 2004; Lee et al., 2006; Covington and Harmer, 2007; Michael et al., 2008a; Goodspeed et al., 2012). Among these, several play a central role in mediating responses to various environmental challenges including drought, cold, salinity, pathogens and herbivory (Figure 3).

LHY functions prominently in the control of abscisic acid (ABA) signalling. There is significant enrichment of ABA-responsive elements (ABRE) in promoters of genes bound by LHY but not CCA1 (Adams et al., 2018). ABA levels peak late in the day (Lee et al., 2006; Adams et al., 2018), consistent with a role of LHY as a repressor of ABA pathways. Induction of *LHY* represses ABA-related target genes and overexpression of *LHY* dramatically damps rhythmic accumulation of ABA under drought stress. However, rhythms of ABA levels were unaltered in *lhy* or *LHY*

overexpressors in well-watered plants. ChIP-seq did not identify LHY bound to promoters of ABA biosynthesis genes. LHY might bind to biosynthesis gene promoters only under stress conditions or circadian rhythms of ABA might be controlled indirectly by LHY *via* a distinct oscillator component (Adams et al., 2018). The latter is supported by a role for TOC1 in ABA-mediated responses to drought. TOC1 binds to the promoter of a putative ABA-signalling gene, *ABA-BINDING PROTEIN/GENOMES UNCOUPLED 5 (ABAR/GUN5)*, and *toc1* mutants and *TOC1* overexpressors have altered responses to ABA and drought (Legnaioli et al., 2009) but it is not known if these genotypes have altered rhythms of ABA.

There are circadian rhythms of two defense hormones, jasmonic acid (JA) and salicylic acid (SA), which are antiphased and peak during the day and night, respectively. Circadian rhythms of defense responses are important for resistance to herbivory because *Arabidopsis* seedling that lack a functional oscillator, or wild-type seedlings that are grown antiphased to an herbivorous caterpillar, have reduced herbivory resistance. This is likely to require rhythmic JA, which triggers plant responses to wounding, because mutants in either JA biosynthesis or JA signalling lack enhanced herbivory resistance conferred by resonant circadian rhythms (Goodspeed et al., 2012). Similarly, there is temporal variation in susceptibility of *Arabidopsis* to the fungal pathogen *Botrytis cinerea*, which is lowest during the morning. This effect is diminished in arrhythmic *elf3* mutants or in mutants of *JA ZIM 6 (JAZ6)*, encoding a transcriptional repressor of JA-mediated defense responses (Ingle et al., 2015).

Circadian rhythms of SA are regulated by CHE (Zheng et al., 2015). CHE binds to the promoter of *ISOCHORISMATE SYNTHASE 1 (ICS1)* encoding a key enzyme in SA biosynthesis. In *che* mutants, circadian rhythms of SA levels were damped but also systemic induction of SA and pathogen-triggered defense responses were diminished revealing a crucial role for the circadian oscillator in regulating SA-mediated defense.

Exogenous application of SA can alter expression of oscillator genes. Long term application of SA increased clock gene expression, whereas short-term application reduced amplitude and delayed phase (Zhou et al., 2015; Li et al., 2018). The latter effect was phenocopied by localised *Pseudomonas syringae* infection, giving rise to systemic damping and period delay in non-infected tissues (Li et al., 2018), possibly representing a SA-mediated effect of pathogen infection on the circadian oscillator. NON-EXPRESSOR OF PATHOGENESIS-RELATED 1 (NPR1) is a transcriptional activator of SA-mediated immune responses and of *TOC1* (Zhou et al., 2015), revealing at least one mechanism by which SA adjusts the oscillator.

Leaf senescence can be triggered by both developmental environmental cues, and can be activated by JA *via* MYCs, a subgroup of bHLH transcription factors. The EC acts to inhibit JA-

532 induced leaf senescence by directly binding to the *MYC2* promoter to repress expression. Mutants
533 in EC genes have accelerated JA-mediated senescence, which is suppressed in *myc2* mutants, as
534 well as precocious leaf senescence phenotypes (Zhang et al., 2017). TIME FOR COFFEE (TIC),
535 which interacts with the EC (Huang et al., 2016) also contributes to regulate MYC2. TIC interacts
536 with MYC2 and promotes its degradation, affecting circadian rhythms of MYC2 expression and
537 plant responses to JA (Shin et al., 2012).

538

539 PRR9 also contributes to age- and dark-induced leaf senescence and directly regulates
540 *ORESARA1 (ORE1)*, a positive regulator of ageing. *prp9* mutants have delayed senescence
541 phenotypes (Kim et al., 2018). It is not clear if or how this pathway involves phytohormones, but
542 *ORE1* is also regulated by ethylene signalling (Kim et al., 2009). There are circadian rhythms of
543 ethylene emission in Arabidopsis, with levels peaking towards dusk (Thain et al., 2004). These are
544 likely driven by direct PIF-mediated repression of *AMINOCYCLOPROPANE-1-CARBOXYLIC*
545 *ACID (ACC) SYNTHASE (ACS)* genes during the night (Song et al., 2018a). Exogenous
546 application of ACC, an ethylene precursor, shortens circadian period and *ethylene insensitive 3*
547 (*ein3*) mutants have lengthened period (Haydon et al., 2017). Since circadian period shortens with
548 leaf age (Kim et al., 2016), there might also be a role for circadian-mediated ethylene signalling in
549 ageing and senescence.

550

551 **1.4.2 Rhythmic metabolism**

552

553 As photoautotrophs, plant metabolism must be tightly coordinated with the light-dark cycle. In this
554 way, plant metabolism is inextricably linked to the environment. This is highlighted by the
555 contribution of photosynthetic metabolism to circadian entrainment (Haydon et al., 2013; Frank et
556 al., 2018). There is circadian regulation of net CO₂ assimilation and stomatal conductance in
557 Arabidopsis (Dodd et al., 2005). This is, in part, driven by circadian rhythms of photosynthesis-
558 associated transcripts, which are upregulated before dawn and peak during the middle of the day
559 (Harmer et al., 2000). Photosynthetic genes are direct targets of circadian oscillator proteins.
560 Based on ChIP-seq data, there is enrichment of photosynthesis-related genes specifically among
561 targets of morning expressed components CCA1, PRR9 and PRR7 and the EC (Nagel et al., 2015;
562 Liu et al., 2016; Ezer et al., 2017). Consistent with this, comprehensive metabolite profiling in
563 circadian clock mutants revealed greater changes in primary metabolites in *cca1 lhy*, *prp7 prp9* and
564 *elf3* mutants compared to *toc1* or *gi* (Flis et al., 2018). Furthermore, the contributions of CCA1,
565 PRRs and the EC to regulation of rhythmic metabolism are also distinct from each other because
566 the metabolic profiles of the mutants are starkly different, despite similar circadian phenotypes
567 (Nakamichi et al., 2009; Flis et al., 2018). Thus, the role of the circadian oscillator in controlling
568 rhythmic metabolism is complex, and challenging to decipher.

569

570 An elegant example of circadian regulation of metabolism is that of starch metabolism. In
 571 Arabidopsis, starch is synthesized from assimilated carbon and accumulates approximately linearly
 572 during the day. At night, starch is degraded to sustain metabolism and growth at a rate that will
 573 utilise almost all of the starch by dawn (Gibon et al., 2004; Lu et al., 2005). This pattern is
 574 maintained across a range of photoperiods, even in the event of an unpredictable early onset of
 575 dusk (Graf et al., 2010; Sulpice et al., 2014). In this way, the control of starch biosynthesis and
 576 degradation are critical to ensure that metabolic rhythms are matched to the rhythmic environment.
 577 The circadian system controls the timing of starch exhaustion because patterns of starch
 578 metabolism match the period of circadian clock mutants (Graf et al., 2010; Flis et al., 2018).
 579 However, precisely how this is achieved is unknown.
 580
 581 Mathematical modelling has proposed two distinct hypotheses for control of rhythmic starch
 582 metabolism. One of these models proposes two chloroplast-localised molecules: *S*, which
 583 measures the amount of starch; and *T*, which measures the time to dawn (Scialdone et al., 2013).
 584 The model supposes that these molecules interact at the surface of starch granules and
 585 approximate a division computation to calculate the rate of starch degradation required to nearly
 586 exhaust starch around dawn. The model accurately predicts a range of experimental data and a
 587 possible mechanism for *S* has been proposed based on phosphorylation state of starch granules.
 588 However, there is currently no candidate for *T* and so the model cannot be fully tested.
 589
 590 An alternative model is based on homeostatic maintenance of sucrose levels and integrates the
 591 effect of sucrose to adjust the phase of the circadian oscillator (Seki et al., 2017). This model
 592 suggests that circadian phase adjustment is not required to alter rates of starch degradation in
 593 response to an unexpected early night, because this is determined by sucrose demand. However,
 594 the model predicted that circadian phase adjustment is required to adjust rates of starch
 595 accumulation during the day according to photoperiod. Consistent with the model's predictions a
 596 *prp7* mutant, which is unable to adjust phase according to sucrose, over-accumulates starch during
 597 the day. Since circadian phase adjustment to sucrose depends on a trehalose-6-phosphate (T6P)-
 598 dependent pathway (Frank et al., 2018), which correlates closely with sucrose concentration
 599 (Figueroa and Lunn, 2016) and regulates starch metabolism (Martins et al., 2013), a possible
 600 mechanism for integrating these signals into the model emerges. Nevertheless, the precise
 601 mechanism by which starch metabolism is controlled by the clock is not yet defined and could
 602 involve either or both of the proposed models.
 603
 604 Rhythmic metabolism is associated with cycles of redox states and production of reactive oxygen
 605 species (ROS). In plants, these are tightly associated with the availability of light to drive
 606 photosynthetic metabolism. There are circadian rhythms of H₂O₂ levels in Arabidopsis, which peak
 607 during the day and are phased similarly with catalase activity (Lai et al., 2012). There are also

608 circadian rhythms of the reduction-oxidation coenzymes NADPH and NADP⁺, which are
609 antiphased (Zhou et al., 2015), and of oxidation state of peroxiredoxins (PRX) (Edgar et al., 2012).
610 Circadian rhythms of PRX oxidation are conserved across all kingdoms of life (Edgar et al., 2012).
611 These can be sustained in the absence of transcription and translation (O'Neill et al., 2011), which
612 supports an intriguing hypothesis that a metabolic oscillator might have established the basis for
613 evolution of circadian oscillators.

614

615 The oscillator directly regulates ROS pathways and ROS can affect the state of the oscillator. *CAT*
616 genes were among the earliest transcriptional reporters for circadian rhythms in Arabidopsis
617 (Zhong et al., 1994) and are directly regulated by the oscillator (Michael and McClung, 2002).
618 Furthermore, CCA1 binds to promoters of ROS-regulated genes and overexpression of *CCA1*
619 attenuates their transcriptional response to superoxide production and suppresses H₂O₂
620 accumulation (Lai et al., 2012). Transient application of H₂O₂ can delay phase (Li et al., 2018)
621 suggesting that ROS signals might also regulate the oscillator. The effects of the immune signal,
622 SA, on the oscillator have also been attributed to redox balance and ROS signalling (Zhou et al.,
623 2015; Li et al., 2018). Application of SA disrupts NADPH/NADP⁺ balance (Zhou et al., 2015) but is
624 also known to trigger extracellular ROS production by RESPIRATORY BURST OXIDASE
625 HOMOLOG (RBOH) proteins. The effects of SA on the phase of the oscillator were absent in an
626 *rboh* mutant (Li et al., 2018) suggesting a contribution of extracellular ROS production on
627 circadian rhythms. Redox and ROS signals could therefore provide additional mechanisms by
628 which metabolism adjusts the circadian system. However, since these signals can also be derived
629 from various environmental challenges, they are likely involved in a wider range of circadian-
630 mediated responses.

631

632 **1.4.3 Gating of environmental responses by the circadian clock**

633

634 The benefit of the circadian network is not only to regulate the timing of rhythmic outputs, but also
635 to control responsiveness of circadian outputs to stimuli according to the time of day. This
636 important phenomenon is termed gating. The simplest mechanism by which gating can be
637 controlled is through rhythmic activity of a repressor or activator. Rhythms of activity can be
638 controlled by light or temperature, but circadian gating must be controlled by the oscillator and, by
639 definition, must persist in constant conditions. Examples of stimuli that are gated by the clock are
640 light, sugar, phytohormones, cold and pathogens. In many cases, circadian gating is likely
641 achieved by direct regulation by the oscillator because core clock genes bind to the promoters of
642 thousands of genes in the Arabidopsis genome.

643

644 *CAB2* expression is induced by pulses of light in continuous dark and responsiveness is gated, so
645 that the effect is limited during subjective night and maximal during the subjective day (Millar and

646 Kay, 1996). This circadian control might be important to limit the response of the oscillator to false
647 light cues, such as moonlight. Gating of this acute response to light requires ELF3 (McWatters et
648 al., 2000). Induction of *CAB2* by light in etiolated *elf3* mutants and *ELF3* overexpressors is
649 enhanced and suppressed, respectively, suggesting ELF3 represses this acute response to light
650 during the night. These genotypes are also compromised in phase re-setting as shown by
651 aberrant PRCs to red and blue light, particularly with respect to phase advances during the
652 subjective night (Covington et al., 2001). Thus, this repressive role of ELF3 in light signalling likely
653 contributes to entrainment.

654

655 There is also circadian gating of phytochrome-mediated shade responses in Arabidopsis. Induction
656 of *PHYTOCHROME INTERACTING FACTOR (PIF) 3-LIKE 1 (PIL1)* expression and hypocotyl
657 elongation by pulses of far-red light are greatest towards dusk (Salter et al., 2003). PIL1 interacts
658 with TOC1 and gating is severely compromised in a *toc1* mutant (Makino et al., 2002; Salter et al.,
659 2003).

660

661 Hypocotyl growth is promoted by temperature, a process called thermomorphogenesis. EC
662 components have been identified as repressors of this PIF-mediated process (Box et al., 2015;
663 Raschke et al., 2015; Jung et al., 2016). But thermomorphogenesis is also gated by the clock
664 through TOC1 and PRR5 (Zhu et al., 2016). TOC1 and PIF4 interact and bind to an overlapping
665 set of promoters, including a number of confirmed thermoresponsive genes. These target genes
666 are least responsive to pulses of warm temperature in the evening when TOC1 is most highly
667 expressed and they are de-repressed in *toc1* and *toc1 prr5* mutants. Thus, TOC1 likely interacts
668 with PIF4 to inhibit activation of target genes in the evening to gate thermoresponsive growth.

669

670 There is circadian gating of responses to phytohormones, including ABA (Legnaioli et al., 2009).
671 Exogenous ABA induces *TOC1* expression in the evening and this requires ABAR. Since TOC1
672 directly regulates *ABAR*, this suggests a feedback loop. Stomatal closure in *TOC1 RNAi* plants is
673 hyper-responsive to ABA and these lines are tolerant to dehydration, which is consistent with
674 gating of ABA-responses late in the day by TOC1.

675

676 There is circadian gating of defense responses of Arabidopsis to bacterial and fungal pathogens.
677 Susceptibility of Arabidopsis to *P. syringae*, *B. cinerea* or *Hyaloperonospora Arabidopsidis* (downy
678 mildew) is greater at subjective dusk than subjective dawn (Bhardwaj et al., 2011; Wang et al.,
679 2011a; Ingle et al., 2015). Gating of immune responses to downy mildew requires CCA1. Promoters
680 of transcripts regulated by downy mildew infection are enriched for EEs and mutants in *CCA1*, but
681 not *LHY*, have reduced susceptibility to infection at dawn but not at dusk (Wang et al., 2011a). Gating
682 of susceptibility to *B. cinerea* might depend directly on rhythmic JA signals because temporal
683 variation is diminished in a *jaz6* mutant (Ingle et al., 2015).

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1.5 Conclusion

The circadian system is complex. This complexity is crucial to integrate environmental cues into coherent physiological and developmental responses that enhance fitness. Exponential progress is being made to understand the mechanisms by which environmental signals are incorporated into the circadian system. Yet there are many questions about how diverse signals converge on the oscillator, and are ultimately decoded. This is particularly important as we transfer experimental systems into the context of real environments rather than controlled laboratory conditions (Annunziata et al., 2017; Song et al., 2018b). Finally, although circadian traits have been frequently selected for (or against) in domestication and breeding of many of our staple crops (Bendix et al., 2015), there is an urgent need to accelerate the transfer of our deepening knowledge of the circadian system into the field.

Figure legends

Figure 1. Transcriptional control of the Arabidopsis circadian oscillator. A summary of the current model of the components contributing to transcriptional control of the oscillator. See section 1.3.1 in the main text for details. Phases of expression for each protein (blue) are represented by their position on the circle. Overlapping genes indicate protein interactions. Activating and repressive interactions are shown by red and green connections, respectively. Dashed lines indicate putative interactions.

Figure 2. Post-translation control of the Arabidopsis circadian oscillator. A summary of post-translational modifications of oscillator proteins. See section 1.3.2 in the main text for details. Modifications of circadian oscillator proteins (blue) that promote or inhibit protein activity are shown by green or red connections, respectively. Protein phosphorylation (circles) can affect protein interactions, nuclear localisation or protein activity. Ubiquitination (pentagons) precedes protein degradation. Known modifications directed by unknown proteins are shown. Phases of events and protein localisation are represented by their position on the circle.

Figure 3. Phytohormones integrate environmental cues in the circadian system. The phase of circadian-regulated levels of jasmonic acid (JA), abscisic acid (ABA), ethylene and salicylic acid (SA) are represented by their position on the perimeter of the circle. The defined interactions between these phytohormones, circadian oscillator components (blue), other genes and proteins (grey) and plant responses to environment are shown. Green and red connections represent positive and negative interactions, respectively.

722

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728 References

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Figure 1. Transcriptional control of the Arabidopsis circadian oscillator. A summary of the current model of the components contributing to transcriptional control of the oscillator. See section 1.3.1 in the main text for details. Phases of expression for each protein (blue) are represented by their position on the circle. Overlapping genes indicate protein interactions. Activating and repressive interactions are shown by red and green connections, respectively. Dashed lines indicate putative interactions.

Figure 2. Post-translational control of the Arabidopsis circadian oscillator. A summary of post-translational modifications of oscillator proteins. See section 1.3.2 in the main text for details. Modifications of circadian oscillator proteins (blue) that promote or inhibit protein activity are shown by green or red connections, respectively. Protein phosphorylation (circles) can affect protein interactions, nuclear localisation or protein activity. Ubiquitination (pentagons) precedes protein degradation. Known modifications directed by unknown proteins are shown. Phases of events and protein localisation are represented by their position on the circle.

Figure 3. Phytohormones integrate environmental cues in the circadian system. The phase of circadian-regulated levels of jasmonic acid (JA), abscisic acid (ABA), ethylene and salicylic acid (SA) are represented by their position on the perimeter of the circle. The defined interactions between these phytohormones, circadian oscillator components (blue), other genes and proteins (grey) and plant responses to environment are shown. Green and red connections represent positive and negative interactions, respectively.