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GIGANTEA Integrates Photoperiodic and Temperature Signals to Time When Growth Occurs

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Abstract:	Circadian clocks synchronize internal physiological responses to occur at the most optimal time of the day. In plants, hormone signaling is one process under the control of this clock. It has been previously shown that the circadian clock moderates the plant's sensitivity to gibberellin by regulating the expression of GA receptors. Two papers by Nohales & Kay (2019) and Park et al., (2020) have revealed that post-translational regulation of DELLA proteins by the circadian clock also contributes in timing when the plant is most sensitive to GA.
Suggested Reviewers:	
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We thank the reviewer for their comments on the manuscript. As requested, we have made the following changes to document.

- *"Thermomorphogenic growth is shifted to midday (ZT 4-12) but not early morning under long days"*

To provide clarity to the reader, we have had ZT times in brackets following the text to explain when the growth occurs. This has been done for short days (line 104) and long days (105). The suggestion to add midday for long days was also incorporated into the text (line 105).

- *"GI protein is relatively unstable at night under short days than long days, leading to the pronounced thermomorphogenic growth at nighttime under short days"*

This text has been added as verbatim, replacing the original text.

- *I recommend the authors to revise Figure B by incorporating the following suggestions.*

All the recommend changes have been made to the figure. We hope this provides more clarity for the reader.

GIGANTEA Integrates Photoperiodic and Temperature Signals to Time When Growth Occurs

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Circadian clocks synchronize internal physiological responses to occur at the most optimal time of the day. In plants, hormone signaling is one process under the control of this clock. It has been previously shown that the circadian clock moderates the plant's sensitivity to gibberellin by regulating the expression of GA receptors. Two papers by Nohales & Kay (2019) and Park *et al.*~~,~~ (2020) have revealed that post-translational regulation of DELLA proteins by the circadian clock also contributes in timing when the plant is most sensitive to GA.

Circadian clocks regulate growth to occur at the most optimal time

The daily rotation of the Earth around the sun generates predictable diurnal changes in light and temperature. Across all domains of life, networks known as circadian clocks have independently evolved. Circadian rhythms are generated either by transcriptional/translational feedback loop(s) or a post-translational mechanism (McClung, 2019). Circadian clocks regulate the sensitivity of internal responses to daily environmental fluctuations, resulting in adaptable and rhythmic oscillations in physiology. Organisms more in sync with their external environment have been shown to have enhanced fitness. In plants, the circadian clock involves morning and evening expressed genes arranged into a series of interconnected loops (McClung, 2019).

The plant circadian clock has a regulatory role in nearly all physiological responses, including hormone signaling. So far, the circadian clock has been shown to regulate components of auxin, jamonate, brassinosteroids, cytokinin, GA, and abscisic acid (Singh and Mas, 2018). Additionally, hormones reciprocally regulate the pace and robustness of circadian rhythms generating a feed-back mechanism that adjusts the activity of the oscillator (Hanano et al., 2006). GA has a major role throughout the lifecycle of the plant (Daviere and Achard, 2016). The circadian clock has been shown to regulate the expression of GA biosynthesis and catabolism enzymes and the expression of the GA receptor *GA-INSENSITIVE DWARF1a* (*GID1a*) and *GID1b* (Arana *et al.,* 2011*;* Blázquez *et al.,* 2002*)*. The diurnal regulation of *GID1a*/*b* was proposed to underpin how the clock controls when GA signaling occurs, a process termed gating. However, the work of Nohales and Kay (2019) and Park *et al.*~~,~~ (2020) has revealed a post-translational mechanism also contributes to the gating of GA signaling.

GIGANTEA Represses GA Signaling by Stabilizing DELLA

GIGANTEA (GI) is a plant specific protein with no known functional domains. It has been previously shown to be involved in the circadian clock, flowering time, growth, and stress tolerance (Mishra and Panigrahi, 2015). GI has multiple proposed functions; the best characterized of these is as a co-chaperone with HEAT SHOCK PROTEIN90 (HSP90) to promote protein maturation and stability (Cha et al., 2017). Nohales and Kay (2019) found that GI could interact with the DELLA proteins

REPRESSOR OF GA1-3 (RGA), GIBBERELLIC ACID INSENSITIVE (GAI) and RGA-LIKE PROTEIN3 (RGL3). DELLA proteins are transcriptional regulators that repress the expression of GA responsive genes. DELLA proteins directly interact with GA receptors through their DELLA domain, leading to their degradation via the 26S-proteasome pathway (Davière and Achard, 2016). Circadian regulation of *GID1a/b* causes diurnal accumulation of RGA protein, with RGA levels peaking in the mid-afternoon before declining in the evening. Nohales and Kay found that the oscillations in RGA were dependent on GI. In the absence of *gi*, RGA levels remained low and did not oscillate, while the overexpression of *GI* increased DELLA stability across the night (Nohales and Kay, 2019). The binding of GID1a to RGA was disrupted by the presence of GI, but GI did not bind to the DELLA domain of RGA. Therefore, it is unlikely that GI directly competes with the GID1a-DELLA interaction and instead stabilizes DELLA via a separate, unknown mechanism. As with RGA, GI has diurnal changes in protein accumulation. In the evening, GI is degraded by the circadian protein EARLY FLOWERING3 (ELF3) and the E3 ligase CONSTITUTIVE PHOTOMORPHOGENIC1 (COP1) (Yu et al., 2008). The degradation of GI coincides with maximal expression of *GID1a/b*. Thus, the circadian clock can precisely time when GA signaling occurs through transcriptional and post-translational mechanisms that converge on the stability of DELLA proteins.

Park *et al.,* (2020) found the same GI-DELLA interaction is required for gating growth in response to elevated temperature. Such warmth initiates a range of physiological changes, including elongated hypocotyls, leaf span, and leaf angle. Park *et al.,* found the *gi-2* mutant had an enhanced thermomorphogenic growth at 28°C compared to wild-type plants (Park et al., 2020). This response was not found to be caused by genes downstream of GI in flowering time, circadian, or stress signaling pathways. The transcription factor PHYTOCHROME INTERACTING FACTOR4 (PIF4) is a central hub for the thermomorphogenic growth (Quint et al., 2016). The *gi-2* mutant had elevated expression of PIF4 targets and introducing the *pif4-101* mutant into the *gi-2* background suppressed the *gi-2* thermomorphogenic phenotype (Park et al., 2020). However, the *gi-2* mutant did not have dramatically elevated *PIF4* transcription. Therefore, GI was proposed to regulate PIF4 through a post-translational mechanism.

GA has been previously shown to promote thermomorphogenesis by inhibiting DELLA mediated sequestration and degradation of PIF4 (Quint et al., 2016). As found by Nohales and Kay, Park *et al.,* showed that GI could interact and stabilize DELLA proteins. The stabilization of DELLA by GI was not dependent on HSP90, indicating that GI stabilizes DELLA independently of its known chaperone function. Whether GI uses a shared mechanism to stabilize DELLA at ambient and elevated temperatures remains to be seen. In the absence of GI stabilizing DELLA, PIF4 protein levels became elevated in the night triggering a stronger thermomorphogenic response.

The expression and activity of *PIF4* is controlled by the circadian clock to precisely time when thermomorphogenesis occurs (Quint et al., 2016). It has been previously shown that under short day (SD) photoperiods, thermomorphogenesis occurs prior to dawn (ZT16-24), while under long days (LD) thermomorphogenesis is shifted to the early morning and midday (ZT4-12). The work of Park *et al.,* revealed that GI confers photoperiodic information and alters the timing of thermomorphogenesis. Elevated temperatures during LD nights promoted the stability of GI, leading to prolonged DELLA activity (Park et al., 2020). The prolongment of DELLA activity subsequently reduced the activity and stability of PIF4, shifting the thermomorphogenic response from the night into the morning. In the absence of *gi*, thermomorphogenesis ~~in~~ under LD was no longer precisely timed and occurred in both the morning and evening. Under SD, GI protein is relatively unstable at night under short days compared to long days, leading to the pronounced thermomorphogenic growth at night-time under short days ~~elevated temperatures did not stabilize GI in the evening, leading to the window of thermomorphogenic growth occurring prior to dawn~~ (Park et al., 2020). Therefore, GI integrates photoperiodic and temperature signals to time the initiation of growth by regulating the stability of DELLA.

Concluding Remarks

It has been previously shown that GI and DELLA are molecular hubs in Arabidopsis, integrating external and internal cues to control an array of processes. Here the work of Nohales and Kay and Park *et al.,* has revealed that these two molecular hubs are interconnected, with GI stabilizing DELLA proteins. The integration of temporal and

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Formatted: Font: Font color: Custom Color(RGB(34,34,34)) thermal sensitivity into GI provides a mechanism to precisely gate growth under ambient and elevated temperatures. In both studies, hypocotyl development in Arabidopsis seedlings was used as the output to measure and understand the importance of the GI-DELLA interaction. However, GA has a critical role in many other processes throughout the lifecycle of Arabidopsis as well as in other plants. For example, the induction of flowering time in barley is dependent on GA signaling, with improper accumulation of GA leading to early flowering under non-inductive photoperiods (Boden et al., 2014). It is possible that photoperiodic information transmitted through GI to DELLA could contribute to the timing of flowering to occur only under favorable conditions.

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Figure: Illustrations of the Signaling Activity leading to Growth via GI-DELLA Interactions.

Approximate protein levels over a 24 hour period of GID1 (solid pink), GI (solid orange), DELLA (thick solid red) and PIF4 (dotted thick green) under (A) short day (SD) photoperiods and (B) long day (LD) photoperiods under warmer temperatures, Green arrows indicate growth induction and black blunt arrows lines indicate inhibition highlighted in the color of the protein inhibiting. Under short days suppression of growth is limited to light periods and early night due to low accumulation of GI during the day and rapid degradation at night. Under LD the growing period is shifted to the very end of the night and early morning as longer accumulation of GI during the day results in higher levels at night and longer GI-DELLA interactions to inhibit PIF4 activity. A simplified signaling pathway of (C) growth suppression and (D) growth are also shown, clock symbols indicate clock signaling pathways and clock signaling regulation when on a molecules, sun symbols indicate light signaling pathways, red thermometer's indicate warm temperature signals, flower symbols indicate flower pathway signaling regulation and proteasome symbols indicates degradation.

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