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Report

Synergism of Red and Blue Light in the Control of *Arabidopsis* Gene Expression and Development

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Summary

The synergism between red and blue light in the control of plant growth and development [1, 2] requires the coaction of the red light photoreceptor phytochrome B (phyB) and the blue light and UV-A receptor cryptochromes (cry) [3]. Here, we describe the mechanism of the coaction of these photoreceptors in controlling both development and physiology. In seedlings grown under red light, a transient supplement with blue light induced persistent changes in the transcriptome and growth patterns. Blue light enhanced the expression of the transcription factors *LONG HYPO COTYL 5* (*HY5*) and *HOMOLOG OF HY5* (*HYH*) [4] and of *SUPPRESSOR OF PHYA 1* (*SPA1*) and *SPA4* [5]. HY5 and HYH enhanced phyB signaling output beyond the duration of the blue light signal, and, contrary to their known role as repressors of phyA signaling [5], SPA1 and SPA4 also enhanced phyB signaling. These observations demonstrate that the mechanism of synergism involves the promotion by cry of positive regulators of phyB signaling. The persistence of the light-derived signal into the night commits the seedling to a morphogenetic and physiological program consistent with a photosynthetic lifestyle.

Results and Discussion

Synergism between phyB and cry1 Generates Hysteretic Gene Expression and growth Patterns

Although several points of convergence between phy and cry signaling have been reported [6–9], none of them has been causally linked to the coaction between phy and cry. To investigate the mechanisms of phyB-cry1 coaction, we cultivated wild-type (WT), *cry1*, and *phyB* seedlings of *Arabidopsis thaliana* for 3 days under continuous red light, a treatment that activates phyB but not cry. On the third day, the seedlings were given supplementary blue light for 3 hr, to activate cry, then returned to red light (Figure 1A). Seedlings were harvested, and the processed RNA was hybridized to ATH1 Affymetrix microarrays. As a control, one set of seedlings was never subjected to the 3 hr blue light treatment.

To select the genes specifically controlled by cry1 in response to blue light, we searched our database and identified 324 genes showing a significantly reduced response to the blue light treatment in the *cry1* mutant ($p < 0.005$, $q < 0.1$) [10] (Table S1, available online). These genes were then further classified with the use of two different criteria: (1) whether the cry1-mediated response to blue light either disappears or persists beyond the duration of the blue light treatment, and (2) whether the cry1-mediated response to blue light is either reduced or not reduced in the absence of active phyB (i.e., in the *phyB* mutant background). The combination of these criteria defines four groups of genes (Figure 1B). Most of the genes that show a cry1-mediated response to blue light belong to the group in which the response was persistent beyond the blue light treatment and required phyB (Figure 1B). In turn, the genes of this group formed two major clusters (Figure 1C and Table S1): Cluster 1, with expression repressed by blue light, contains genes such as *CULLIN 4* [11], *ARGO NAUTE1* [12], *AINTEGUMENTA* [13], *CYCLIN-DEPENDENT KINASE C;2* [14], and *SYNTAXIN 23* [15], which have known function in the regulation of development (e.g., leaf development, photomorphogenesis) and could shape plant body form and function in response to the blue light signal. Cluster 2, with expression promoted by blue light, contains several chloroplast-related genes, including two FtsH protease genes [16], suggesting that transient blue light perceived by cry1 might trigger acclimation of the photosynthetic apparatus.

In some cases, the response to a transient signal can persist well beyond the duration of the signal, a phenomenon called hysteresis [17, 18]. A brief exposure to red light, for instance, shifts phyB to its active stage that persists many hours in darkness. The hysteresis in gene expression can also have its origin in the transcriptional networks, and the system design principles of these networks are under intense research, given their particular importance for the transformation of short signals into developmental decisions [17, 18]. Given that 3 hr of blue light generated changes that persisted 6 hr after the termination of the blue light, we conclude that the synergism between phyB and cry1 generates hysteresis in gene expression.

The inhibition of the rate of stem (hypocotyl) growth by light is a key feature of the photomorphogenic pattern of development. Prompted by the results of transcriptome studies, we used the same light protocol to investigate hypocotyl growth responses. The experiments were done in the Columbia background for the subsequent analysis of signaling mutants, and we used the *cry1 cry2* double mutant because of the fact that in Columbia, cry2 makes a contribution to the blue light response that is not obvious in Landsberg *erecta* [3] (see below). In WT seedlings exposed to continuous red light, blue light reduced hypocotyl extension growth and the rate of growth did not recover after termination of the blue light treatment (Figure 1D). In the *phyB* mutant and the *cry1 cry2* double mutant, blue light failed to inhibit the rate of hypocotyl elongation (Figure 1D). We conclude that the synergism between phyB and cry generates hysteresis in the inhibition of hypocotyl growth.

We also used a variation of the protocol shown in Figure 1A, in which at the 3 hr mark, the seedlings were given a pulse of far-red light, followed by darkness, which reduced the amount of active phyB to a minimum. In comparison to the results of red light controls (never exposed to blue light), the persistence

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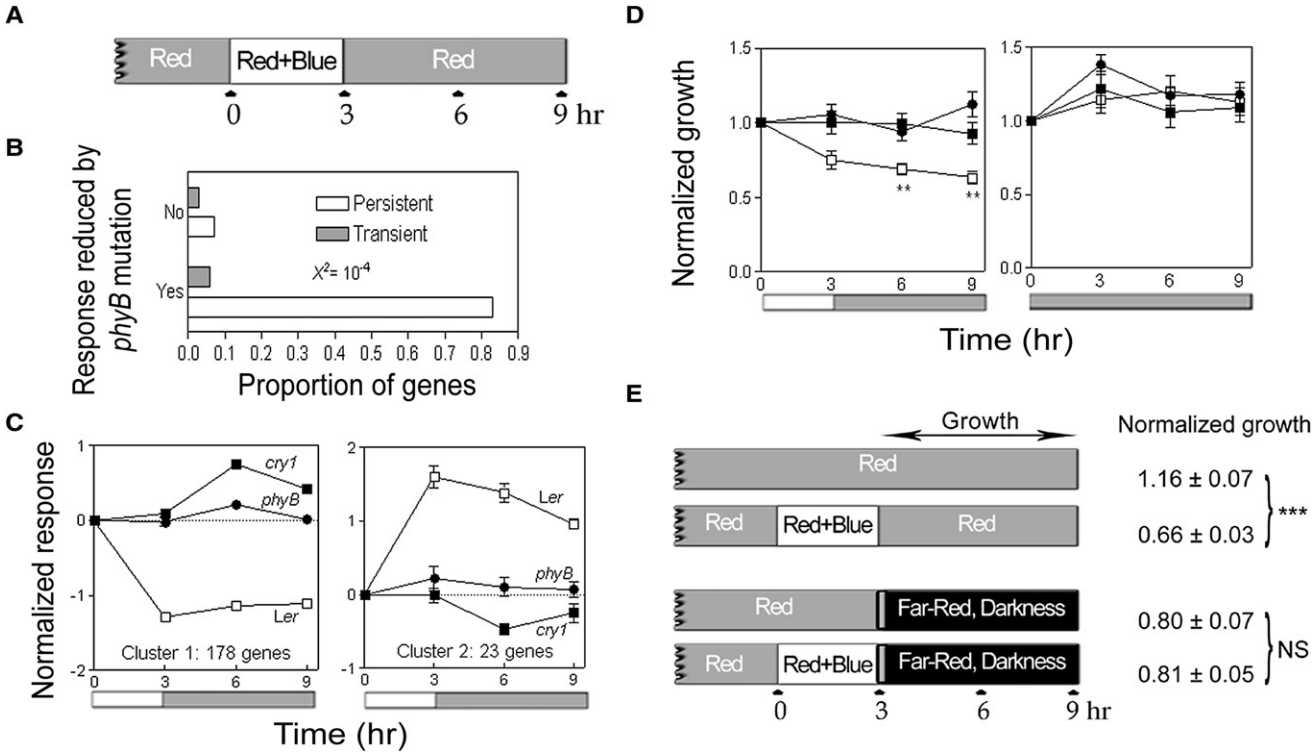

Figure 1. The Coaction between cry1 and phyB Generates Hysteresis in Gene Expression and Stem Growth

(A) Experimental protocol. Three-day-old seedlings grown under continuous red light (11 μmol . m^{-2} . s^{-1}) were exposed to 3 hr of blue light (5 μmol . m^{-2} . s^{-1}) added to the red light background and then harvested immediately after blue light (3 hr), 3 hr and 6 hr after the end of blue light (6 hr and 9 hr harvest time, respectively), or without a blue light supplement as red light controls (0 hr). Light sources are described in Supplemental Experimental Procedures.

(B) Proportion of genes that show either transient or persistent responses to blue light perceived by cry1 as affected by the dependence of the blue light response on phyB. The result of the χ^2 contingency test incorporating the correction of Yates is indicated.

(C) Average normalized expression and (standard error) SE of the genes corresponding to clusters containing at least 20 genes (other clusters are listed in Table S1). Both clusters correspond to the genes in which the cry1-mediated response to blue light is persistent and depends on phyB.

(D) Persistent stem (hypocotyl) growth response to blue light in the WT but not in the *phyB* or *cry1 cry2* mutants. Three-day-old seedlings grown under continuous red light were exposed to 3 hr of blue light added to the red light background (between time 0 and time 3 hr). Rates are plotted at the end of the relevant 3 hr period. Data are means and SE of at least 25 (red + blue) or 11 (red) seedlings. Data were analyzed by two-way ANOVA and Bonferroni posttests, with time = 0. Double asterisk indicates $p < 0.01$; all of the other differences with time = 0 are not significant ($p > 0.05$).

(E) The hysteresis is caused by a persistent enhancement of phyB-mediated output by transient cry1 activation. Red-light-grown seedlings were exposed to 3 hr of red + blue light or left as red light controls and then transferred either back to red light (data from Figure 1D) or to a pulse of far-red light followed by darkness. Data are means and SE of 14–32 seedlings and were analyzed by two-way ANOVA and Bonferroni posttests. Triple asterisk indicates $p < 0.001$, NS denotes not significant.

of growth inhibition beyond the presence of blue light was observed if the seedlings returned to red light at the 3 hr mark but not if the seedlings were exposed to far-red followed by darkness (Figure 1E). This indicates that phyB has to be active *after* cry activation, even if phyB had been active under red light before and during blue light. The duration of cry in its signaling stage after the termination of blue light is not established. Green light appears to return cry to its inactive state [19]. Therefore, green light given after the blue light treatment is predicted to reduce the levels of active cry eventually present after the end of blue light. This green light treatment did not reduce the synergism (Figure S1). We can therefore establish a sequence in which cry enhances phyB-mediated signaling and not vice versa.

cry1 Activity Recruits New Genes under phyB Control

The comparison of expression in red light controls of WT versus *phyB* mutant seedlings identified 551 genes with expression affected by phyB ($p < 0.005$, $q < 0.1$) [10] (Table S2). However, only 6% of the genes showing synergism between cry1 and phyB had expression levels already affected by phyB under red light alone (Table S2). This very restricted overlap indicates that activation of cry1 recruits new genes to the control by phyB, genes that were not affected by phyB in the absence of cry1 activity.

cry1 Activity Recruits New Genes to phyB Signaling

Consistent with previous reports, blue light promoted the expression of several genes with known function in photomorphogenesis, including *SPA1*, *SPA4*, *HY5*, and *HYH* [4, 20] (Figure S2). SPA1, which forms complexes with E3 ligase activity [21], is a negative regulator of phyA signaling [5]. HY5 and HYH are basic leucine zipper transcription factors that mediate photomorphogenesis [4].The induction of these genes showed no synergism between phyB and cry1, because the promotion by blue light was reduced by the *cry1* but not by the *phyB* mutation (Figure S2). The lack of hysteresis in the expression of these genes is consistent with the absence of synergism. However, the products of these genes could be involved in the generation of coaction; therefore, we tested this possibility.

The *spa1* mutation (tested in the *phyA* mutant background for the avoidance of phyA-mediated effects) and the *hy5 hyh*

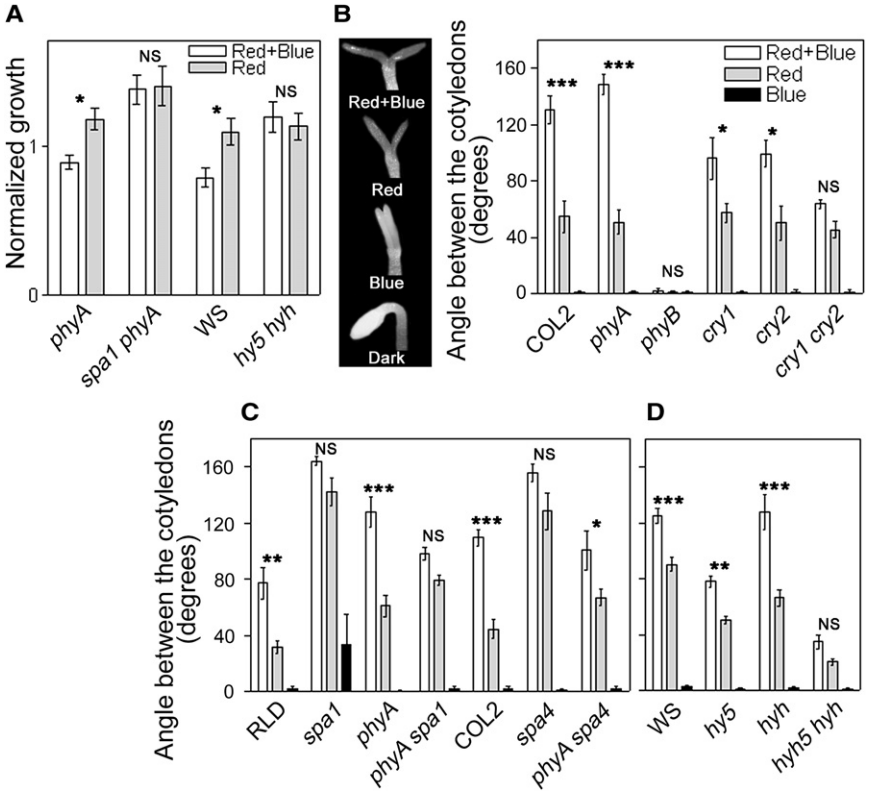

Figure 2. Synergism between phyB and Cryptochromes Requires SPA1, SPA4, HY5, and HYH

(A) The growth response to blue light requires SPA1, HY5, and HYH. The average growth rate during 9 hr is presented for the seedlings that received blue light + red light during the first 3 hr of this period and for red light controls. Data are means and SE of at least 14 seedlings. The difference between red and red + blue was analyzed by two-way ANOVA and Bonferroni posttests. NS denotes not significant ($p > 0.05$), asterisk indicates $p < 0.05$.

(B) Cotyledon unfolding depends on the coaction between phyB and cry. Cotyledon unfolding under continuous red light is enhanced by a daily supplement of 3 hr blue light, a treatment that is not effective if provided without the red light background. The seedlings were grown under continuous red light daily supplemented with 3 hr of blue light, continuous red light, daily blue light (3 hr) without a continuous red light background, or in darkness. Data are means and SE of at least ten boxes of seedlings. The difference between red and red + blue was analyzed by two-way ANOVA and Bonferroni posttests. NS indicates not significant ($p > 0.05$), single asterisk indicates $p < 0.05$, double asterisk indicates $p < 0.01$, and triple asterisk indicates $p < 0.001$.

(C and D) The coaction between phyB and cry requires SPA1, SPA4, HY5, and HYH. Data are means and SE of at least six boxes of seedlings. The difference between red and red + blue was analyzed as in B.

mutations eliminated the inhibition of hypocotyl growth by blue light, shown in Figure 2A compared to the control seedlings under continuous red light. Thus, SPA1, which is a negative regulator of phyA signaling [5], appears here as a positive regulator of phyB signaling. This indicates that the hysteresis in the inhibition of hypocotyl growth generated by the combined action of phyB and cry requires SPA1, HY5, and HYH. SPA1, HY5, and HYH did not inhibit hypocotyl growth immediately before blue light (absolute growth rates, means ± SE, mm h^{-1}, *phyA*: 0.22 ± 0.02; *phyA spa1*: 0.21 ± 0.02; WS: 0.26 ± 0.01; *hy5 hyh*: 0.21 ± 0.01), but they were required for growth inhibition after blue light (Figure 2A). This suggests that the expression of *SPA1*, *HY5*, and *HYH* is below a threshold under red light and that the promotion of their expression by blue light perceived by cry is necessary for triggering the persistent growth inhibition.

To investigate the long-term consequences of the synergism, we used the aforementioned light protocol (Figure 1A) repeated during three days, including controls in darkness and controls for which daily exposure to 3 hr of blue light terminated with a pulse of long-wavelength far-red light followed by darkness for activation of cry without activation of phyB. Without the red light background to activate phyB, blue light had no significant effects on cotyledon unfolding. However, 3 hr of blue light added to a continuous red light background that activates phyB did promote cotyledon unfolding (Figure 2B). Both the *phyB* and the *cry1 cry2* mutants failed to respond to blue light (Figure 2B). The unfolding response depends on the coaction between phyB and cry. In the *spa1* and *spa4* mutants, 3 hr of blue light had no effect when added to red light (Figure 2C). The failure of the *spa1* and *spa4* mutants to respond to blue light added to red light was also evident in the *phyA* mutant background (Figure 2C). Therefore, SPA1 and SPA4 enhance phyB-mediated responses independently of phyA when the seedlings are exposed to blue light. The latter is a novel function of *SPA* genes, which could involve the degradation of negative regulators of phyB signaling. SPA proteins work in concert with COP1, and the *cop1* mutants failed to show the synergism between cry and phyB (data not shown). COP1 also acts as a positive regulator of photomorphogenesis mediated by phyB [22].

The *hy5* mutant showed reduced cotyledon unfolding under red light but apparently normal responses to supplementary blue light (Figure 2D). The *hyh* mutant showed normal unfolding under red light [4, 20] and apparently larger synergism between red and blue light than that of the WT (strong cotyledon unfolding in *hyh* has recently been reported [23]). However, the *hy5 hyh* double mutant failed to respond to the blue light supplement (Figure 2D). This indicates that HY5 and HYH are redundantly required for the coaction between phyB and cry. Interestingly, 27% of the genes promoted (cluster 2, Figure 1C) and 11% of the genes inhibited (cluster 1) by blue light in a phyB-dependent manner are direct targets of HY5 [24], which matches the proportion of direct targets of HY5 in microarrays comparing WT and *hy5* seedlings (26% of the genes promoted and 12% of the genes inhibited by HY5 are their direct targets) [24]. Although a significant proportion of the genes that show hysteresis in their expression patterns are direct targets of HY5, the *HY5* and *SPA1* promoters are not direct targets of HY5, and *HYH* and *SPA4* are direct targets, but their expression is unaffected by the *hy5* mutation [4, 24]. In principle, this could account for the lack of hysteresis in the expression of *HY5*, *HYH*, *SPA1*, and *SPA4* (Figure S2).

Light and circadian signals that control flowering and hypocotyl growth have a common model of convergence, because in both cases one signal (the clock) controls mRNA levels and the other signal (light) controls the stability of the protein derived from this mRNA (CONSTANS in the case of flowering

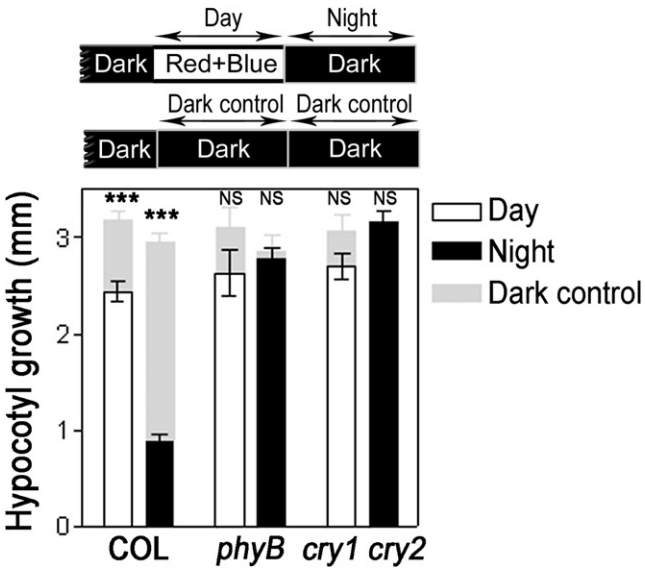

Figure 3. The Synergistic Action between phyB and cry1 Maintains Reduced Growth Rates during the Night

Seedlings were grown against vertical agar in darkness for 2 days and then transferred to light (red + blue) for 12 hr (day) followed by 12 hr of darkness (night). Hypocotyl length increments were recorded during the light exposure and during the subsequent night period, as well as in seedlings that remained in darkness (dark controls). Data are means and SE of at least 16 seedlings. The difference between light and darkness was analyzed by two-way ANOVA and Bonferroni posttests. NS denotes not significant ($p > 0.05$), triple asterisk indicates $p < 0.001$.

[25], PIF4 and PIF5 in the case of growth [26]). Given that cry controls *HY5* expression and light is known to downregulate COP1-mediated degradation of HY5 protein in the proteasome [4], we investigated whether phyB was necessary for stabilizing HY5 in the temporal frame when phyB is necessary for the persistent output of cry excitation. Shifting phyB to its inactive stage by far-red light abolished the persistent effect of blue light on hypocotyl growth (Figure 1E) but had no effect on HY5 stability (Figure S3). We conclude that phyB is necessary for the response to HY5 but not for stabilization of HY5. Cry could enhance the expression of *HY5*, *HYH*, *SPA1*, and *SPA4* by inactivating COP1 and consequently stabilizing transcription factors [27] acting upstream of these genes. However, blue light did not enhance stability of HY5 (one of the known targets of COP1 [27]) within the time frame in which the synergism is observed (Figure S3), probably because red light in itself is able to stabilize HY5 [27].

The Synergism between phyB and cry Reinforces Seedling Commitment to Photomorphogenesis

The combined action of phyB and cry generates hysteretic responses that persist beyond the presence of the blue light treatment required for activation of cry. Given that phyB remains active during the first part of the night [28, 29], we speculated that this synergism could help the plant to maintain the inhibition of hypocotyl growth during darkness. Seedlings of *Arabidopsis* were grown in darkness for 2 days and then transferred to light (red plus blue) for 12 hr, followed by 12 hr of darkness. In the WT seedlings, hypocotyl growth was partially reduced during light exposure and largely arrested during the subsequent night (Figure 3). The *phyB* or *cry* mutations had little effect during light exposure (their contribution can be stronger in older seedlings or at higher irradiances), but mutations affecting either phyB or cry were enough to eliminate the persistent inhibition of hypocotyl growth in subsequent darkness (Figure 3). The synergism between phyB and cry is necessary for the specification of the developmental fate of the seedling, and if one of the two photoreceptor types is missing, growth returns to the values observed before the light stimulus.

Conclusions

Understanding the mechanisms involved in the integration of dynamic signals is one of the challenges of modern biology [30]. The convergence between circadian cues and light typically involves the control of mRNA abundance by the clock and the control of its protein product by light [25, 26]. The convergence between phyB and cry signaling follows a model that is at least partially different. Blue light perceived by cry enhances the expression of *SPA1*, *SPA4*, *HY5*, and *HYH* independently of phyB. Then, *SPA1*, *SPA4*, *HY5*, and *HYH* enhance phyB-mediated signaling independently of cry (i.e., after the termination of the blue light signal) (Figure S4). Cry recruits new genes to phyB control, and a significant proportion of these genes are direct targets of HY5. Thanks to the action of phyB, the effects triggered by cry persist well beyond the blue light signal that activates cry, creating a hysteretic switch. Because phyB can remain active in darkness, the synergism helps to maintain the commitment to a photoautotrophic lifestyle during the night.

Experimental Procedures

Microarray Experiments

The *cry1-1* (formerly *hy4-2.23n* [31]) and *phyB*-5 (formerly *hy3* [31]) mutants and the WT seedlings used for microarray experiments are in the Landsberg *erecta* background. Seedlings were grown in boxes with agar as described [3]. Samples were harvested in liquid nitrogen, and total RNA was extracted with the RNEasy Plant Mini Kit (QIAGEN). For each time point, samples were pooled, obtaining three (WT) or two (*phyB*, *cry1*) biologically independent replicates. cDNA and cRNA synthesis and hybridization to ATH1 Affymetrix *Arabidopsis* Gene Chips were performed in accordance with Affymetrix instructions. Expression data (Table S3) were normalized, restricted by presence criteria, and used for ANOVA to identify the genes showing expression responses to blue light perceived by cry1. These genes were then used for investigating the dependence of the response to blue light on phyB and the transient or persistent nature of the response to blue light by means of contrasts based on partition of the sum of squares of the ANOVA, in accordance with criteria established a priori. These procedures are described in detail in the Supplemental Experimental Procedures.

Measurements of Hypocotyl Growth and Cotyledon Angle

For physiological experiments, we used *phyB-9* [32], *phyA-211* [33], *cry1-304*, *cry2-1* [34], and *spa4-1* [5] in Columbia; *hy5-KS50*, *hyh*, and *hy5KS50-hyh* [4] in Ws; *spa1*-2 and *phyA-101* [35] in RLD; and *phyA-101 spa4-1* in a mixed Columbia and RLD background. Seedlings were grown in boxes with agar as described previously [3]. Measurements of hypocotyl growth are based on the analysis of successive photographs as described in Supplemental Experimental Procedures, and cotyledon angle was measured with a protractor.

Supplemental Data

Supplemental Data include Supplemental Experimental Procedures, four figures, and three tables and can be found with this article online at http://www.cell.com/current-biology/supplemental/S0960-9822(09)01198-1

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