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Report

The Rate of Cell Differentiation Controls the *Arabidopsis* Root Meristem Growth Phase

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Summary

Upon seed germination, apical meristems grow as cell division prevails over differentiation and reach their final size when division and differentiation reach a balance. In the *Arabidopsis* root meristem, this balance results from the interaction between cytokinin (promoting differentiation) [1–4] and auxin (promoting division) [2, 5] through a regulatory circuit whereby the ARR1 cytokinin-responsive transcription factor [6] activates the gene *SHY2* [2, 6, 7], which negatively regulates the *PIN* genes encoding auxin transport facilitators [2, 5]. However, it remains unknown how the final meristem size is set, i.e., how a change in the relative rates of cell division and differentiation is brought about to cause meristem growth to stop. Here, we show that during meristem growth, expression of *SHY2* is driven by another cytokinin-response factor, ARR12 [1], and that completion of growth is brought about by the upregulation of *SHY2* caused by both ARR12 and ARR1: this leads to an increase in cell differentiation rate that balances it with division, thus setting root meristem size. We also show that gibberellins selectively repress expression of *ARR1* at early stages of meristem development, and that the DELLA protein REPRESSOR OF GA 1-3 (RGA) [8] mediates this negative control.

Results and Discussion

SHY2 Expression Changes during Meristem Development

In the cytokinin/auxin regulatory circuit that controls root meristem size maintenance, SHY2 is the central switch—the two hormones act on its activity in opposite ways in balancing cell differentiation with cell division [2–4]. Because the relative rates of cell differentiation and division must change during root meristem growth, SHY2's activity should vary over time if it is also crucial in this phase. We analyzed the level of expression of the *SHY2* gene at different times during root meristem growth—at 3 days postgermination (dpg), when the meristem is actively growing, and at 5 dpg, when the meristem reaches its final size—by quantifying *SHY2* mRNA via quantitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR) and analysis of the activity of a *SHY2::GUS* transcriptional fusion [9]. The level of expression of *SHY2* increased during meristem growth, reached a maximum at 5 dpg (Figures 1A, 1G, and 1N), and subsequently remained constant in time (data not shown). Thus, the balance between cell differentiation and cell division, and consequently completion of meristem growth, is reached concomitantly with maximal (steady-state) expression of *SHY2*, suggesting that the latter is involved in meristem growth and in determining its size.

To verify this hypothesis, we transiently expressed at 3 dpg a nondegradable version of the SHY2 protein under control of a heat-shock promoter (*HS::shy2-6*) [10], thus anticipating at 3 dpg the maximum *SHY2* expression. Upon a 30 min heat treatment, the root meristem of *HS::shy2-6* plants stopped growing and remained constant in size during the following days, resulting in smaller meristem compared to wild-type roots (Figure 1M). This indicates that a high level of SHY2 is necessary and sufficient to determine the final size of the root meristem. Longer heat treatments (up to 2 hr) resulted in progressively smaller meristem, but never in its complete differentiation (data not shown), possibly because SHY2 represses auxin signaling and transport on the one hand and controls cytokinin biosynthesis by downregulating the *IPT5* gene [11] on the other, thus balancing its own effects [2]. To further confirm that a high level of the SHY2 protein at 3 dpg is responsible for meristem size stabilization, we analyzed the root phenotype of wild-type and *SHY2* loss-of-function (*shy2-31* [2, 10]) plants harboring the *35S::ARR1ΔDDK:GR* construct [6] after 8 hr of dexamethasone induction at 3 dpg. As in *HS::shy2-6* plants, the root meristem of *35S::ARR1ΔDDK:GR* plants stopped growing and remained constant in size during the following days (Figure 1M), whereas *shy2-31; 35S::ARR1ΔDDK:GR* roots did not show any reduction in meristem size ([2] and data not shown), corroborating the notion that SHY2 is the central switch that controls meristem size.

Different Complements of Cytokinin-Responsive Factors Control *SHY2* during Meristem Growth and Meristem Maintenance

We had previously shown that the *SHY2* gene is positively controlled to maintain meristem size by the cytokinin-responsive ARR1 transcription factor, and that expression of the *ARR1* gene is only detectable at 5 dpg (Figures 2A and 2C; see also Figure S2E available online) [1, 2]. It is therefore unlikely that ARR1 also controls *SHY2* expression and cell differentiation during meristem growth. We had also shown that the gene encoding another cytokinin-responsive transcription factor, *ARR12*, is expressed (as *ARR1*) only in the root meristem transition zone, but its expression is detectable immediately after seed germination and remains constant during root meristem growth (Figures S2A, S2C, and S2F) [1]. The expression pattern of ARR12 and the phenotype of the *arr12-1* mutants, which already display a larger root meristem at 3 dpg (Figures 1C and 1Q; Figure 2H) [1], suggest that ARR12 may be involved in activating *SHY2* during meristem growth. To verify this hypothesis, we compared the expression of *SHY2* at 3 dpg in wild-type and *arr12-1* mutant roots by utilizing the *SHY2::GUS* transcriptional fusion described above. In wild-type meristems, *SHY2* expression at 3 dpg was hardly detectable (Figure 1A) but was strongly induced

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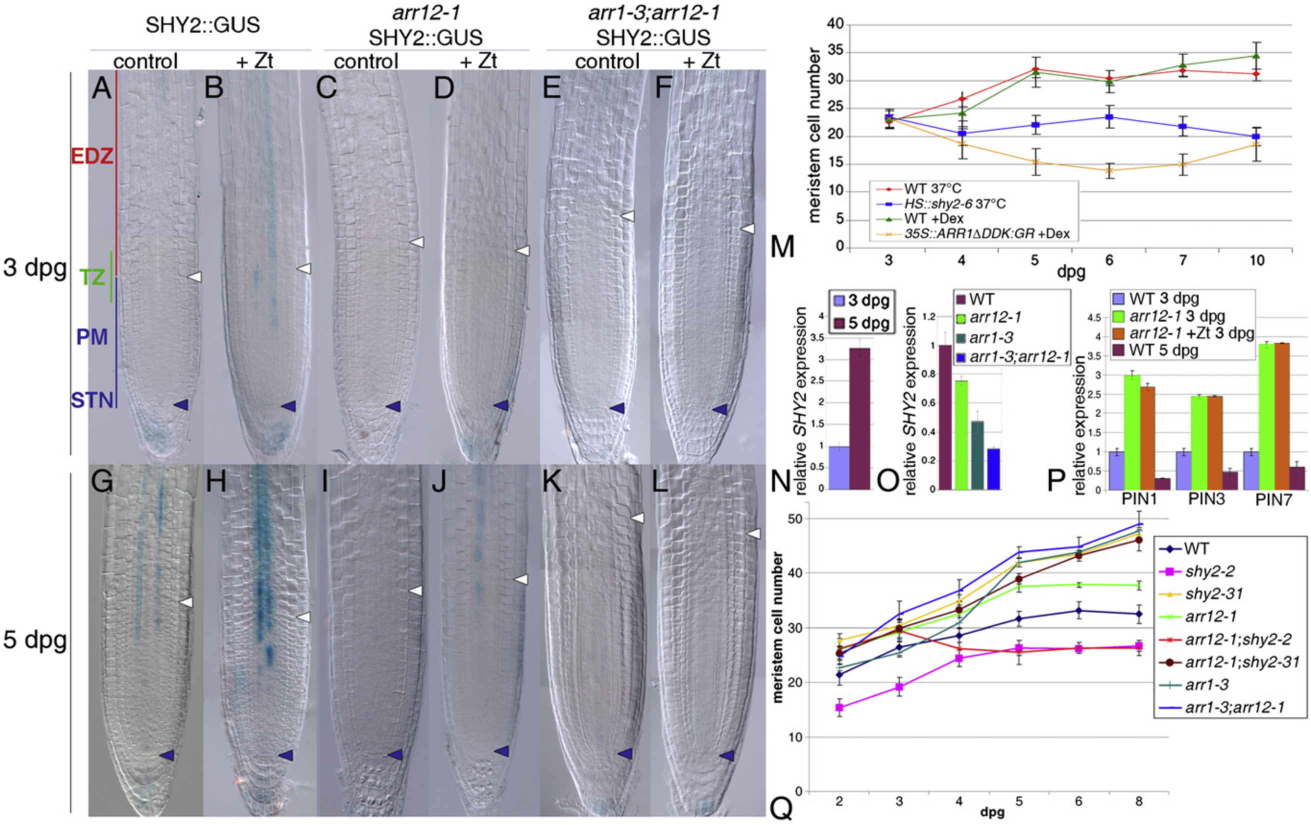

Figure 1. *SHY2* Expression at Early Stages of Root Meristem Development Depends on ARR12 and Increases during Meristem Growth

(A) Longitudinal view of *Arabidopsis* root meristem. EDZ indicates elongation and differentiation zone; TZ, transition zone; PM, proximal meristem; STN, stem cell niche.

(A–L) *SHY2::GUS* expression in root meristems at 3 days postgermination (dpg) (A–F) and at 5 dpg (G–L) of wild-type (A and G), wild-type grown 4 hr on 5 μM transzeatin (Zt) (B and H), *arr12-1* (C and I), *arr12-1* grown 4 hr on 5 μM Zt (D and J), *arr1-3;arr12-1* (E and K), and *arr1-3;arr12-1* grown 4 hr on 5 μM Zt (F and L). Blue and white arrowheads indicate the quiescent center and the first elongated cortex cell (cortex transition zone), respectively.

(M) Root meristem cell number of *HS::shy2-6* plants (grown at 37°C for 30 min) and *35S::ARR1ΔDDK:GR* plants (grown on 2 μM dexamethasone [Dex] for 8 hr) induced at 3 dpg and measured over time. WT indicates wild-type.

(N) qRT-PCR of *SHY2* at 3 dpg and 5 dpg wild-type roots.

(O) qRT-PCR of *SHY2* at 5 dpg in wild-type, *arr12-1*, *arr1-3*, and *arr12-1;arr1-3* roots.

(P) qRT-PCR analysis of *PIN1*, *PIN3*, and *PIN7* at 3 dpg in wild-type, *arr12-1*, and *arr12-1* roots treated for 4 hr with 5 μM Zt, and at 5 dpg in wild-type roots.

(Q) Root meristem cell number of wild-type, *shy2-2*, *shy2-31*, *arr12-1*, *arr12-1;shy2-2*, *arr12-1;shy2-31*, *arr1-3*, and *arr1-3;arr12-1* measured over time.

Error bars indicate standard deviation. For qRT-PCR experiments: Student's t test, $p < 0.05$, n = 3. See also Figure S1.

by cytokinin treatment (Figure 1B). In contrast, in the *arr12-1* mutant background, *SHY2::GUS* activity was not detectable (Figure 1C), nor did it show any increase upon cytokinin treatment (Figure 1D). These data indicate that during meristem growth, when ARR1 is not present, *SHY2* is under the control of ARR12. In order to assess whether at 5 dpg—when *ARR1* is active—both ARR1 and ARR12 are needed to ensure the maximum level of *SHY2* expression, we analyzed *SHY2::GUS* activity in the *arr12-1* and *arr1-3* mutant backgrounds at 5 dpg. In wild-type meristems, *SHY2* expression at 5 dpg was clearly visible in the vasculature of the transition zone (Figure 1G) and was strongly induced by cytokinin (Figure 1H). In contrast, *SHY2* expression was very faint in the *arr12-1* root meristem (Figure 1I) but was partially recovered upon cytokinin treatment (Figure 1J), possibly as a result of the activity of ARR1. *SHY2* expression, as shown previously [2], was hardly detectable in the *arr1-3* mutant background. Upon cytokinin treatment, *SHY2::GUS* activity was visible in 30% of the root meristems after prolonged staining (data not shown), possibly as a result of ARR12 activity, suggesting that ARR1 has a dominant role at 5 dpg in the control of *SHY2*. Only in the root meristem of the *arr1-3;arr12-1* double mutant was *SHY2* expression never detectable (Figures 1E and 1K), nor did it show any increase upon cytokinin treatment at 3 dpg (Figure 1F) or at 5 dpg (Figure 1L). Accordingly, comparison of the wild-type with the single *arr1-3* and *arr12-1* mutants and with the *arr1-3;arr12-1* double mutant by qRT-PCR showed that the double mutant had the lowest level of *SHY2* mRNA at 5 dpg (Figure 1O).

To provide further evidence that *SHY2* is under the control of ARR12 during meristem growth, we analyzed the root meristem phenotype resulting from the *arr12-1* mutation in combination with *SHY2* loss-of-function (*shy2-31*) and gain-of-function (*shy2-2* [2, 7]) alleles. The root meristem size of the *arr12-1;shy2-31* mutant was indistinguishable from that of the *arr12-1* mutant at 3 dpg and 5 dpg, whereas the *arr12-1;shy2-2* root meristem was indistinguishable from that of the *arr12-1* mutant at 3 dpg and displayed a *shy2-2* phenotype from 5 dpg onward upon ARR1 activation (Figure 1Q). These data are in accordance with the SHY2 protein acting

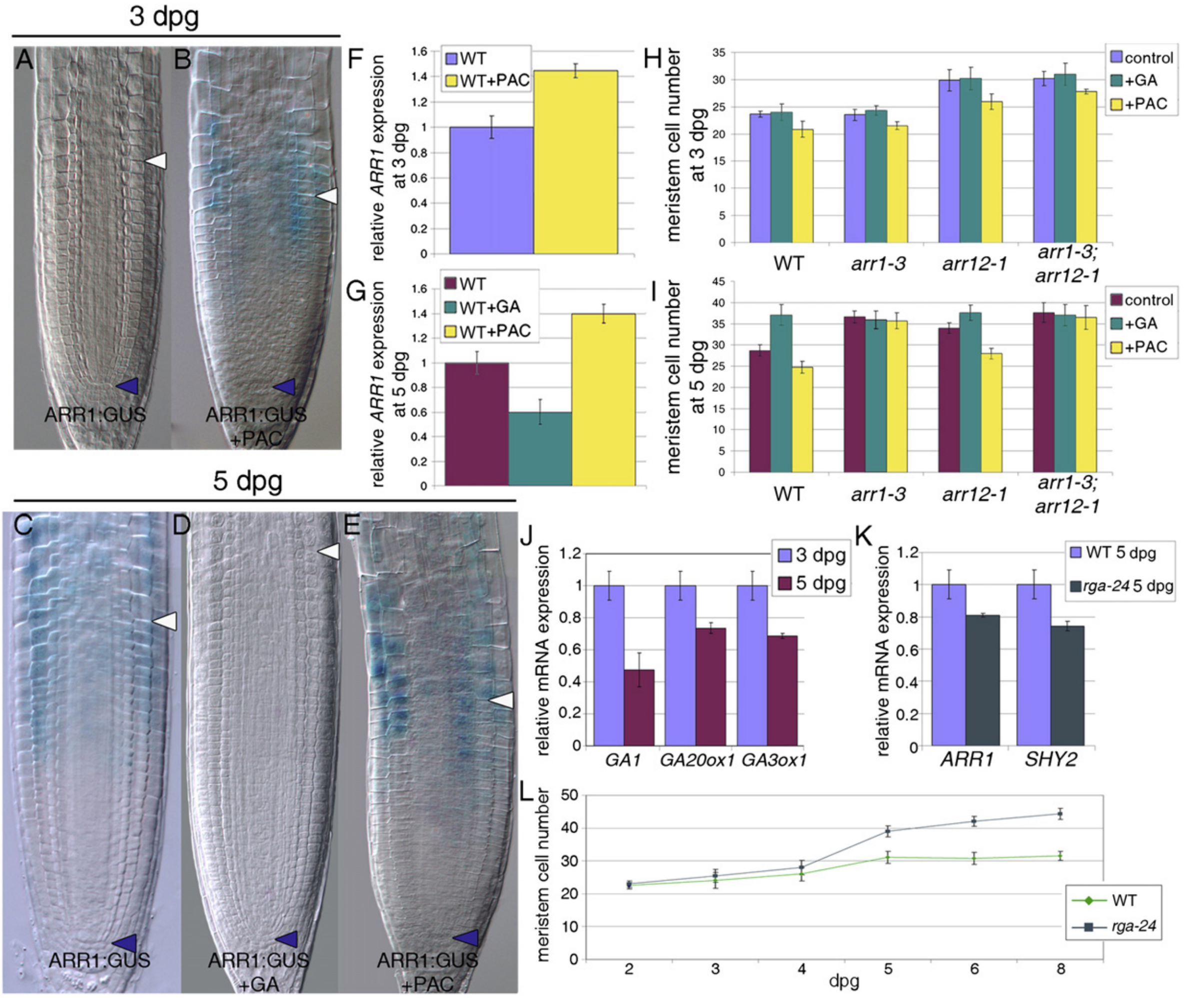

Figure 2. ARR1 Expression Is Controlled by Gibberellin

(A–E) ARR1:GUS expression in root meristems at 3 dpg (A and B) and 5 dpg (C–E) of wild-type (A and C), wild-type grown 16 hr on 10 μM paclobutrazol (PAC) (B and E), and wild-type grown 16 hr on 10 μM gibberellin (GA) (D). Blue and white arrowheads indicate the quiescent center and the cortex transition zone, respectively.

(F) qRT-PCR of *ARR1* in 3 dpg wild-type roots and wild-type roots grown 16 hr on 10 μM PAC.

(G) qRT-PCR of *ARR1* in 5 dpg wild-type roots, wild-type roots grown 16 hr on 10 μM GA, and wild-type roots grown 16 hr on 10 μM PAC.

(H) Root meristem cell number of wild-type, *arr1-3*, *arr12-1*, and *arr1-3;arr12-1* at 3 dpg, grown 16 hr on 10 μM GA or 16 hr on 10 μM PAC.

(I) Root meristem cell number of wild-type, *arr1-3*, *arr12-1*, and *arr1-3;arr12-1* at 5 dpg, grown 16 hr on 10 μM GA or 16 hr on 10 μM PAC.

(J) qRT-PCR of *GA1*, *GA20ox1*, and *GA3ox1* in 3 dpg and 5 dpg wild-type roots.

(K) qRT-PCR of *ARR1* and *SHY2* in 5 dpg *rga-24* roots.

(L) Root meristem cell number of wild-type and *rga-24* measured over time.

Error bars indicate standard deviation. For qRT-PCR experiments: Student's t test, $p < 0.05$, $n = 3$. See also Figure S2.

downstream of the ARR12 transcription factor. Furthermore, the root meristem of the *shy2-31* loss-of-function mutant was indistinguishable from that of the *arr1-3;arr12-1* double mutant, whereas the root meristem size of the latter was larger from 5 dpg onward compared to the *arr1-3* and *arr12-1* single mutants (Figure 1Q), corroborating the notion that both genes are necessary from 5 dpg onward to control meristem size.

These results indicate that expression of *SHY2* is controlled by ARR12 during meristem growth and that both ARR12 and ARR1 are necessary to ensure optimal expression of *SHY2* at 5 dpg.

ARR12 Controls the Activity of the *PIN* Genes

We next asked whether *SHY2* expression driven by ARR12 would result, during meristem growth, in the downregulation of the *PIN* genes [2]. Thus, we compared the level and distribution of *PIN1*, *PIN3*, and *PIN7* mRNAs in the wild-type and *arr12-1* mutant by both qRT-PCR and analysis of the activity of PIN:GFP translational reporter fusions [2]. At 3 dpg, the level of the *PIN* mRNAs was higher (Figure 1P) and the domains of PIN expression were expanded in the *arr12-1* mutant as compared with wild-type roots (Figures S1A, S1B, S1E, S1F, S1I, and S1J). Furthermore, no reduction in meristem size and no downregulation of *PIN1*, *PIN3*, and *PIN7* were observed in the *arr12-1* mutant (Figure 1P; Figures S1C, S1G, and S1K) or in the *shy2-31* mutant at 3 dpg (data not shown) in response to cytokinin treatment. These results indicate that ARR12 controls *PIN* expression via activation of *SHY2*. Thus, the same regulatory circuit is controlled by different complements of factors in controlling meristem growth and in setting and

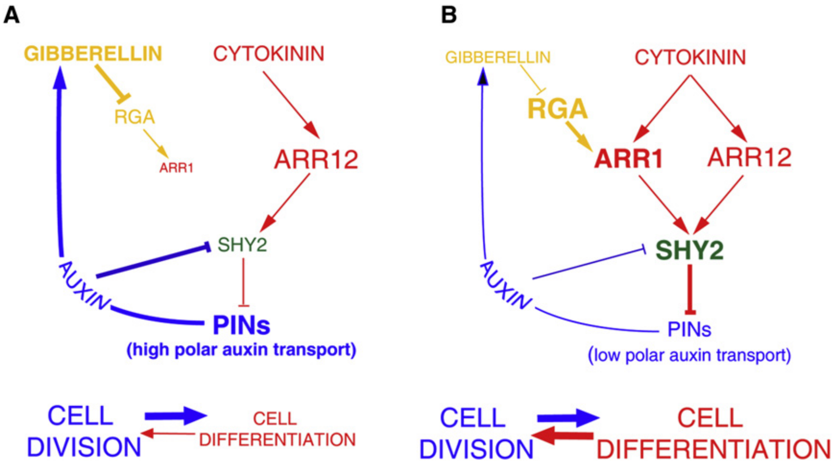

Figure 3. A Model for Gibberellin-Cytokinin Interaction during Root Meristem Growth

(A) The regulatory circuit controlling meristem growth at 3 dpg. High levels of gibberellin repress expression of the *ARR1* gene via RGA. ARR12 drives a low level of *SHY2* expression, sustaining PIN-mediated polar auxin transport, which in turn supports gibberellin biosynthesis [30]. This ensures a prevalence of cell division over cell differentiation.

(B) At 5 dpg, a decrease of gibberellin biosynthesis stabilizes the RGA protein, allowing transcriptional activation of *ARR1*, which eventually joins ARR12 in increasing *SHY2* expression, slowing PIN-mediated polar auxin transport and gibberellin biosynthesis. This results in an increase in cell differentiation that balances it with cell division and stops meristem growth.

maintaining meristem size. Up to 5 dpg, when only ARR12 is present, the level of *SHY2* is relatively low and cell division prevails over differentiation, thus ensuring meristem growth. Upon *ARR1* activation at 5 dpg, the synergistic action of ARR12 and ARR1 increases *SHY2* expression, resulting in a higher differentiation input that balances cell division with cell differentiation and sets meristem size.

One prediction based on this model is that PIN expression should change during meristem growth, being higher at early stages and decreasing at 5 dpg as a result of the high level of *SHY2* activity. Indeed, analysis by qRT-PCR (Figure 1P) and PIN:GFP translational reporter fusions in wild-type root meristems revealed that PIN expression was higher at 3 dpg (Figures S1A, S1E, and S1I) and significantly decreased at 5 dpg (Figures S1D, S1H, and S1L).

Gibberellins Antagonize the Cytokinin Cell Differentiation Input by Repressing *ARR1*

We next asked what represses *ARR1* up to 5 dpg, thus preventing a premature increase in the cell differentiation rate and consequently a premature arrest of meristem growth. It has been shown that gibberellins, in analogy to auxin, positively control root growth [12] and meristem size by sustaining cell division [13, 14]. We observed that exogenous gibberellins increased root meristem size of wild-type plants only when applied at 5 dpg (Figure 2I) and had no effect at 3 dpg or earlier (Figure 2H and data not shown). This suggests that gibberellins may antagonize cytokinin by suppressing the activity of ARR1 (expressed only at 5 dpg) but not ARR12. Indeed, exogenous gibberellin treatment strongly downregulated ARR1:GUS expression at 5 dpg (Figures 2C, 2D, and 2G) without affecting ARR12:GUS expression at either 3 dpg (Figures S2A and S2B) or 5 dpg (Figures S2C and S2D). To further substantiate the specificity of gibberellins in repressing *ARR1* but not *ARR12*, we analyzed the effect of exogenous gibberellins on wild-type and *arr1-3* and *arr12-1* mutant root meristems. As expected, at 3 dpg all meristems were insensitive to gibberellins (Figure 2H). At 5 dpg, wild-type and *arr12-1* meristems increased in size upon gibberellin application, whereas *arr1-3* root meristems were still insensitive (Figure 2I), indicating that gibberellins affect meristem size only through *ARR1*.

To confirm the role of gibberellins in repressing *ARR1* during meristem growth, we treated ARR1:GUS plants at 3 dpg and 5 dpg with paclobutrazol (PAC), an inhibitor of gibberellin biosynthesis [15]. In both cases, PAC treatment resulted in a decrease in meristem size (Figures 2H and 2I) [14]. Concomitantly, anticipation of *ARR1* expression at 3 dpg (Figures 2B and 2F) and *ARR1* overexpression at 5 dpg (Figures 2E and 2G) were observed. Accordingly, *arr12-1* mutant root meristems were responsive to PAC (i.e., reduced their size) both at 3 dpg and at 5 dpg, whereas *arr1-3* meristems were responsive to PAC at 3 dpg but resistant at 5 dpg (Figures 2H and 2I).

These results suggest that a reduction in the level (or signaling) of gibberellins releases repression of *ARR1* at 5 dpg. Accordingly, genes encoding rate-limiting enzymes in gibberellin biosynthesis, such as *GA1* [16, 17]—whose role in controlling root meristem size [13, 14] and root length [18] has already been established—and *GA20ox1* [17, 19] and *GA3ox1* [17, 20], are significantly downregulated at 5 dpg compared to 3 dpg (Figure 2J). Gibberellins promote degradation of DELLA proteins [8, 18, 21–23], which function as growth repressors during *Arabidopsis* seedling development [8, 12, 18, 22, 24–27]. Of the genes encoding the five DELLA proteins [8], *REPRESSOR OF GA 1-3* (*RGA*) [23, 25] is expressed in the root transition zone, and its level is significantly higher at 5 dpg than at 3 dpg (Figures S2G–S2I). This supports the notion that gibberellin activity decreases toward the end of the meristem growth phase, thus releasing repression of *ARR1* and bringing about the increase in cell differentiation rate that balances it with cell division, setting final meristem size. Accordingly, the *RGA* loss-of-function mutant *rga-24* [25, 26] displayed a lower level of *ARR1* and *SHY2* expression at 5 dpg (Figure 2K), mimicking high levels of gibberellin, and an enlarged root meristem (Figure 2L; Figures S2J and S2K) that continued growing after 5 dpg (Figure 2L), as in the *arr1-3* and *shy2-31* loss-of-function mutants (Figure 1Q) [1, 2].

In conclusion, we have shown that in allowing growth of the root meristem after seed germination and for the meristem to reach its final size, the ARR1/SHY2/PIN circuit necessary to maintain the final meristem size [2] is integrated by two additional components: the cytokinin-responsive transcription factor ARR12 and gibberellins (Figure 3). ARR12 drives a low level of expression of *SHY2* during the growth phase to ensure a prevalence of cell division over cell differentiation (Figure 3A). ARR1 eventually joins ARR12 in increasing *SHY2* expression, leading to an increase of cell differentiation that thus balances cell division and stops meristem growth (Figure 3B). Gibberellins, necessary for seed germination and radicle protrusion

[27, 28], repress expression of the *ARR1* gene during postgermination meristem growth, and a subsequent decrease in their activity allows—via the DELLA protein RGA—*ARR1* expression and the consequent upregulation of *SHY2* (Figure 3B).

Experimental Procedures

Plant Material, Growth Conditions, and Treatments

All mutant and transgenic lines utilized in this work were described previously [1, 2], with the exception of the *rga-24* mutant, kindly provided by N. Harberd (Oxford University), and the RGA:GFP lines, kindly provided by M. Tsiantis (Oxford University) with the permission of T.-p. Sun (Duke University). Seeds were sterilized and grown as described previously [29]. Cytokinin, gibberellin (GA_3), and paclobutrazol treatments were performed as specified in the figure legends.

Root Meristem Size Analysis

Root meristem size is expressed as the number of cortex cells in a file extending from the quiescent center to the first elongated cortex cell, as described previously [1]. For each experiment, a minimum of 90 plants were analyzed.

RNA Isolation and qRT-PCR

Total RNA extraction and quantitative RT-PCR analysis were performed as described previously [2]. Gene-specific primers used are described in Supplemental Experimental Procedures.

Image Analysis

GUS histochemical staining of ARR1:GUS, ARR12:GUS, and *SHY2::GUS* transgenic lines was performed and visualized as described previously [1, 2].

Supplemental Information

Supplemental Information includes two figures and Supplemental Experimental Procedures and can be found with this article online at doi:10.1016/j.cub.2010.05.035.

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