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Plant developmental transitions: the role of microRNAs and sugars

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What determines the rate at which a multicellular organism ages is a mystery in biology. In plants the changes in morphological and physiological traits serve as markers for the developmental transitions. Mutant characterizations and genetic analyses in *Arabidopsis thaliana* delineate an evolutionarily conserved, microRNA156 (miR156)-guided timing mechanism that temporally regulates many aspects of biological processes during development. Recent studies now reveal that sugar metabolites, the products of photosynthesis, feed into this developmental timer by regulating miR156 levels, thereby ensuring that each developmental transition occurs under favorable conditions.

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Introduction

Understanding the reproducibility of developmental programs between individuals of the same multicellular organism is a fundamental challenge in biology. This developmental precision reflects the conserved and intrinsic mechanisms that temporally regulate all the aspects of biological processes during development. The cues that guide these developmental events can also include extrinsic inputs, such as nutrients, light and temperature.

By contrast to animals, plants utilize different developmental programs from juvenility to maturity. After seed germination, the shoot apical meristem (SAM), a population of pluripotent stem cells at the shoot apex, begins to produce leaves. The plant reaches maturity when it becomes competent to exogenous or endogenous floral-inducing signals such as hormones, light and temperature [1]. Upon the transition to reproductive growth, the SAM gives rise to flowers. Although different plants have dramatically different morphology, the program deployed to time developmental transitions is well conserved, which offers us an excellent system to study the reproducibility of developmental programs between individuals.

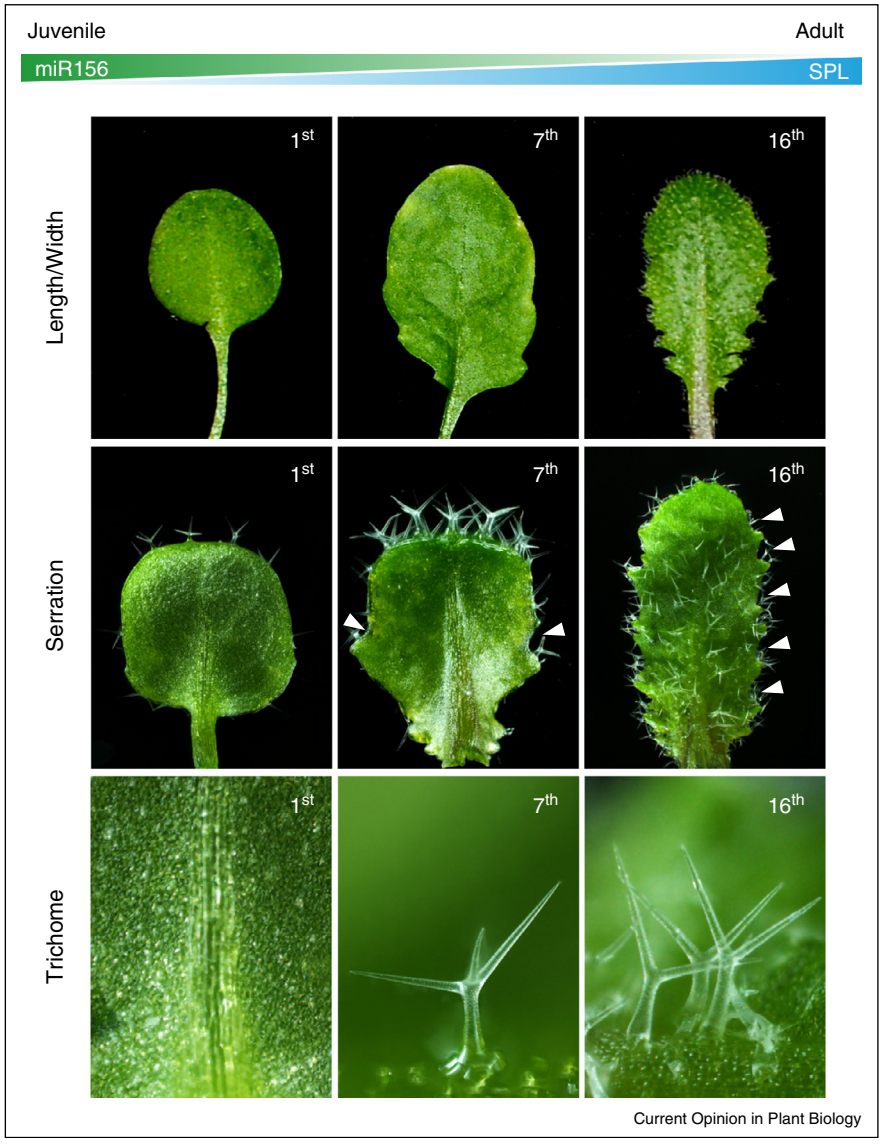
The plant developmental transitions are under genetic regulation and can be defined by the morphology of lateral organs [2]. In principle, the mutations that affect developmental timing do not appreciably accelerate or retard the life cycle of the plant. Nor do they alter organ identity *per se*. Rather, they change the temporal identity of lateral organs to one normally expressed at a different time within the same lineage, but usually restricted to a distinct developmental stage. The observed temporal transformations in developmental timing mutants have been likened to the floral homeotic mutants, in which floral organ identities are spatially, rather than temporally, transformed [3].

The past decade has seen a great advance in our understanding of the molecular basis of plant developmental transitions. Mutant characterizations and genetic analyses in *Arabidopsis thaliana* reveal a central timing module governed by microRNA156 (miR156) and its regulator, sugar. In this review, we first describe the hallmarks of plant developmental transitions and then turn to summarize the roles of miR156 and sugars in plant developmental transitions. The related unanswered questions and future directions are then discussed.

The hallmarks of plant developmental transitions

Plants continuously produce different types of lateral organs such as leaves and flowers during development. As such, the changes in morphological and anatomical traits of these organs serve as visible markers of developmental transitions. In the annual *A. thaliana*, the transition from juvenile to adult stage is marked by changes in the initiation of trichomes (leaf hairs) on the abaxial surface of the leaf, an increase in the length/width ratio of the leaf blade and the production of serrations on the leaf margin [4–6] (Figure 1). When an *Arabidopsis* plant enters the reproductive phase, flowers are produced in commitment

Figure 1



The visible markers for the juvenile-to-adult phase transition in *Arabidopsis*. Juvenile leaves differ from adult leaves in blade length/width ratio, leaf serrations (arrowheads) and trichomes on the abaxial side.

with internode elongation. It has to be noted that the changes during the juvenile-to-adult phase transition vary in different plants. For instance, the number of leaflets is progressively increased in *Cardamine hirsuta* [7], but decreased in *Acacia confusa* [8]. Eucalyptus species exhibit striking and abrupt change from juvenile to adult phase [9], whereas a similar transition in *Arabidopsis* is gradual [10].

In addition to the above visible phenotypes, the changes in physiology and the responsiveness to environmental signals also act as markers for developmental transitions. For example, the biosynthesis of secondary metabolites such as monoterpene is changed during development [11]. The adult plants have lower regenerative capacity than juvenile plants [12,13]. Moreover, only the adult plants have reproductive competence and can be induced to flower in response to exogenous cues such as light and temperature [14,15].

The central role of miR156 in plant developmental timing

miRNAs are a class of short, single-stranded non-coding RNAs that regulate target gene expression at post-transcriptional level in both plants and animals [16,17]. The first miRNA described, *lin-4*, in concert with another

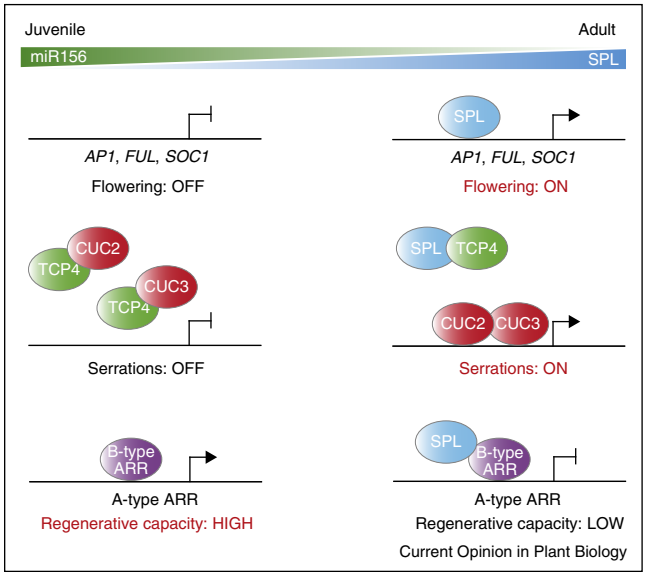
miRNA, *let-7*, acts as a developmental switch that programs stage-specific cell identities in the nematode *Caenorhabditis elegans* [18,19]. Expression analyses reveal that the sequential activation of these two miRNAs is a crucial event, such that the corresponding change in expression level modulates the progression of a cell to its next temporal fate. In mammals, the role of *let-7* is specified; it has been shown that *let-7* exerts important functions in neuronal regeneration, stem cell function and tissue repair during aging [20–22].

As in animals, studies in maize and *Arabidopsis* have revealed that miR156 plays a crucial role in plant developmental transitions. miR156 is extremely conserved in land plants [23]. It accumulates at a high level in seedlings and subsequently declines as plants age [24,25]. This expression pattern is not only observed in *Arabidopsis*, but also in other species such as *Arabis alpina*, *Cardamine flexuosa*, Chinese cabbage, maize, rice, tobacco, tomato and poplar [26–31,32••,33••]. miR156 is both necessary and sufficient for the maintenance of the juvenile phase; overexpression of miR156 prolongs the juvenile phase and delays flowering, while blocking the function of miR156 by a 'target mimicry' strategy (*MIM156*) results in a premature phenotype [25,34,35]. In *Arabidopsis*, the developmental and physiological programs timed by miR156 include leaf shape (length/width ratio of the blade and leaf size), leaf initiation rate, leaf complexity, shoot regenerative capacity, secondary metabolites accumulation, trichome initiation, stress response, innate immunity, embryonic patterning and flowering [34–36,37•,38,39,40•,41–44,45•,46,47]. For instance, overexpression of *MIM156* causes temporal leaf transformation; the first two leaves in a *MIM156* overexpression line resemble the adult leaves in wild type [34].

The biological function of miR156 is exerted by its targets, *SQUAMOSA PROMOTER BINDING PROTEIN-LIKEs* (*SPL*s). *SPL*s encode a family of transcription factors with conserved SBP DNA-binding domain at the amino terminus [48]. Based on sequence similarities and domain structure, miR156-targeted SPLs can be divided into five groups [49]. Functional analyses demonstrate that different *SPL*s have different functions. An increased level of *SPL3* causes early flowering without any other evident phenotypes, suggesting a specific role of SPL3 in floral transition. Among the other *SPL*s, *SPL9* and *SPL15* play predominant roles. Although *spl9* and *spl15* mutants behave as wild type, the *spl9 spl15* double mutant displays weaker but similar precocious phenotype to a miR156 overexpression line [42,50].

Identification of the events downstream of SPL9 in *Arabidopsis* has revealed that the miR156-SPL9 timer is integrated into diverse developmental and metabolic pathways through either transcriptional activation or repression (Figure 2). For example, SPL9, as a canonical

Figure 2



SPL9 times diverse developmental events by distinct molecular mechanisms. SPL9 promotes flowering through activating miR172 and MAD-box genes such as *FUL* and *SOC1*. SPL9 could also act as a transcriptional repressor, where it represses cytokinin response by binding with B-type ARRs. In addition, SPL9 could license the CUC2–CUC3 complex for serration production by binding with TCP4.

transcription activator, induces flowering through activating MADS-box genes *APETALA1* (*AP1*), *FRUITFULL* (*FUL*) and *SUPPRESSOR OF OVEREXPRESSION OF CO1* (*SOC1*) [25,35], or promotes terpene biosynthesis through the activation of terpene synthase *TPS21* [40•]. By contrast, SPL9 represses cytokinin response and anthocyanin production through binding with the B-type ARABIDOPSIS RESPONSE REGULATORs (ARRs), the master regulators in the cytokinin signaling pathway, or PAP1, the MYB transcription factor in the anthocyanin biosynthetic pathway [36,38]. In a recent study, SPL9 was found to license the CUP-SHAPED COTYLEDON2 (CUC2)-CUC3 transcription complex that instructs leaf serration formation through binding with TCP4 (TEOSINTE BRANCHED1/CYCLOIDEA/PCF) [37•]. In the future, genome-wide identification of SPL9 targets and its interacting partners will thus shed light on the complex regulatory network governed by SPL9.

In addition to MADS-box genes, the role of SPL9 in flowering is also mediated by another conserved miRNA, miR172 [51,52]. The miR172 level increases with age [27,53]. It has been shown that one of the miR172 coding loci, *MIR172B*, is the direct target of SPL9 [34]. As a result, miR172 levels are elevated in the absence of miR156 but reduced when miR156 is overexpressed. In the *A. thaliana* genome, miR172 targets five *AP2*-like genes which act as flowering repressors through inhibition

of the expression of the florigen gene *FT* [15]. The high level of miR172 leads to early flowering and suppresses the late flowering phenotype caused by miR156 overexpression [54,55]. Interestingly, the same regulatory circuit is recruited for timing abaxial trichome production [34]. Thus, the miR156-SPL-miR172 module is reminiscent of the *lin-4-let-7* cascade in *Caenorhabditis elegans*, suggesting an evolutionarily conserved timing mechanism in multicellular organisms.

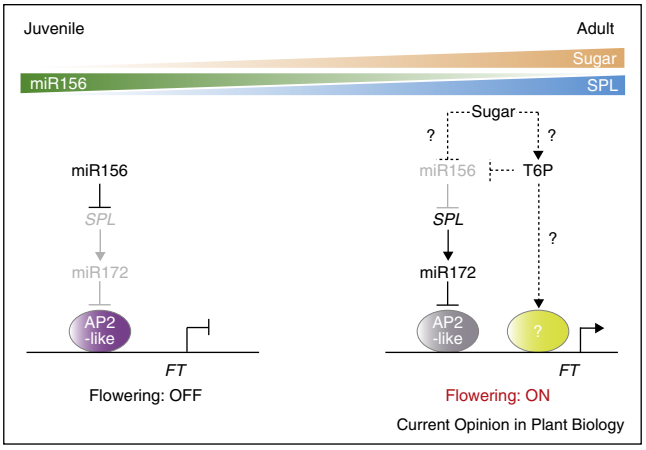
The role of sugar in plant developmental transitions

How the miR156 level is regulated by age is mysterious. Previous physiological experiments give us some valuable hints. In 1953, Allsopp reported that *Marsilea drummondii* plants grown on sugar-free media produced juvenile leaves [56]. The supplement with metabolizable sugars accelerates the production of adult leaves. Consistently, the reduction in photosynthesis rate by suppression of *RUBISCO SMALL SUBUNIT* (*RBCS*) results in a prolonged juvenile phase in tobacco [57]. Moreover, it is known that exogenous sucrose promotes flowering in a number of plant species [58]. In line with these observations, defoliation and severe pruning increase the production of juvenile leaves in both the herbaceous plant, *Ipomoea caerulea* [59] and woody plants such as *Pinus radiata* [60,61], raising the possibility that sugar may accelerate plant developmental transitions by modulating miR156 level.

Indeed, several lines of evidence now reveal a direct link between sugar and miR156 abundance (Figure 3). First, removal of pre-existing leaves causes an increase in miR156 expression and delays plant maturation [62,63••]. Second, miR156 level is reduced in response to exogenous glucose or sucrose treatment, accompanied with an acceleration of juvenile-to-adult phase transition [62,63••,64••]. Third, *chlorina1* (*ch1*), the photosynthetic mutant which shows impaired photosynthesis, prolongs the juvenile phase, in commitment with a high level of miR156 [62,63••,64••]. Moreover, the repression of miR156 by sugar is conserved among different plant species [63••].

The regulation of developmental transitions by sugar is not solely mediated by miR156. A recent intriguing study reveals that trehalose-6-phosphate (T6P) regulates flowering through a distinct genetic pathway [65••] (Figure 3). Trehalose-6-phosphate synthase1 (TPS1) converts glucose-6-phosphate and UDP-glucose to T6P [66,67]. The mutation in *TPS1* causes embryonic growth arrest. Analyses of the conditional complemented or weak *tps1* mutants demonstrate a positive role of TPS1 in flowering [68,69]. Transgenic plants and expression analyses further reveal that T6P is sufficient to trigger flowering when it is produced in the SAM and that T6P contributes to the production of florigen FT in leaves.

Figure 3



The role of sugars in flowering time. In the juvenile phase, the expression of *FT* is repressed by miR172-targeted AP2-like transcription factors. Sugar promotes flowering through activating miR172 by repressing miR156. In addition, T6P could induce floral transition through modulating miR156 level and activating *FT* in leaves. Question marks and dotted lines indicate unknown molecular mechanisms or transcription factors. Gray color: not expressed or inactivated.

Thus, the biosynthesis of T6P ensures plants flower at the correct time when carbohydrate levels are appropriate.

Future directions

Although considerable progress has been made in elucidating the molecular components deployed to time plant developmental transitions, several fundamental questions need to be resolved. First, what determines the rate at which a plant ages? Identification of sugar as the upstream regulator of miR156 suggests that plants might use carbohydrates as a timer. However, it remains unclear how sugar temporally regulates miR156 abundance. Additionally, how is TPS1 activity connected to *FT* expression? Therefore, the identification of the sugar sensor and establishing the molecular link between sugar sensing and the regulators for plant developmental transitions will be important next steps.

Another unanswered question is whether miR156 can be regulated by factors other than sugar. Indeed, functional analyses demonstrate that two mediator (MED) subunits, MED12 and MED13, act as global regulators of developmental timing by fine-tuning the expression of temporal regulatory genes including miR156 [70]. In addition, genome-wide binding assays reveal that FUSCA3 (FUS3), a B3 domain transcription factor regulating seed development, and two MADS-box proteins, AGAMOUS-LIKE 15 (AGL15) and AGL18, are associated with regulatory regions of two miR156-coding loci [71,72]. Whether histone modification and DNA methylation also play a

role in regulating the temporal expression pattern of miR156 awaits further investigations.

The rate of plant maturation can be also influenced by environmental factors such as nutrients, light, stress and temperature. For example, cellular carbohydrates synthesized in leaves and nitrogen nutrients such as nitrate and ammonium assimilated by roots are tightly coordinated to sustain optimal plant growth [73]. Although it is well known that increased levels of nitrogen delay flowering [58,74], insights into the molecular mechanism by which this pathway functions are still lacking.

Still unclear is the molecular basis of the developmental transitions in polycarpic plants. Polycarpic perennials flower repeatedly and can live more than two years [75,76]. By contrast to annuals, polycarpic perennials maintain a supply of vegetative meristems to sustain their growth for another life cycle. Thus, understanding of the preservation of vegetative meristems and how these meristems confer resistance to senescence signals will be a challenge for the future.

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