The Control of Developmental Phase Transitions by microRNAs and Their Targets in Seed Plants

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Abstract: Seed plants usually undergo various developmental phase transitions throughout their lifespan, mainly including juvenile-to-adult and vegetative-to-reproductive transitions, as well as developmental transitions within organ/tissue formation. MicroRNAs (miRNAs), as a class of small endogenous non-coding RNAs, are involved in the developmental phase transitions in plants by negatively regulating the expression of their target genes at the post-transcriptional level. In recent years, cumulative evidence has revealed that five miRNAs, miR156, miR159, miR166, miR172, and miR396, are key regulators of developmental phase transitions in plants. In this review, the advanced progress of the five miRNAs and their targets in regulating plant developmental transitions, especially in storage organ formation, are summarized and discussed, combining our own findings with the literature. In general, the functions of the five miRNAs and their targets are relatively conserved, but their functional divergences also emerge to some extent. In addition, potential research directions of miRNAs in regulating plant developmental phase transitions are prospected.

Keywords: plant development; phase transitions; miRNAs; target genes; regulatory role

1. Introduction

The life cycle of seed plants is composed of a succession of distinct developmental phases, mainly including vegetative growth, reproductive growth, seed/embryo set [1]. The vegetative growth can be further divided into juvenile and adult phases [2], and the reproductive growth entails the vegetative-to-reproductive transition and the development of floral organs [3]. The seed/embryo set, as a unique development process of seed plants, also includes multiple developmental phases [4]. In addition, storage organ formation is also a special development process, which involves various developmental transitions such as underground stolon-to-tuber and aerial stem-to-rhizome transitions [5–7]. The transitions between developmental phases involve changes in morphological and physiological traits, which may be reflected in organ/tissue size and shape, meristem identity or activity, premature or late-maturity, early or late flowering, etc. [2,8–10]. For instance, the juvenile-to-adult transition is featured by the formation of leaf abaxial trichomes and increased leaf length/width ratio and serration in Arabidopsis [11]; the vegetative-to-reproductive transition is characterized by the conversion of vegetative shoot apical meristem (SAM)-to-flower meristem, and then flower meristem-to-floral meristem, thereby determining flowering [1].

Cumulative data show that developmental phase transitions can be genetically regulated by microRNAs (miRNAs), which participate in complex genetic networks controlling the development
of plants [12,13]. MiRNAs are an extensive class of small endogenous non-coding RNAs of around 21–22 nucleotides in length [13]. The first miRNA to be identified was lin-4 RNA, which is a key regulator controlling the developmental timing in Caenorhabditis elegans [14]. Since the discovery of plant miRNAs in Arabidopsis [15], a large number of miRNAs have been continuously identified in plants in recent years [16]. Plant genomes typically possess several hundreds of miRNA genes, many of which exist as families [17–19]. MiRNA genes are first transcribed by DNA-dependent RNA polymerase II into primary miRNAs and then cleaved by Dicer-like proteins to generate precursor miRNAs, which are further processed by the Dicer enzyme to form mature miRNAs with potential regulatory functions on the expression of genes [19–21]. Current research has revealed that miRNAs usually negatively regulate their target genes by post-transcriptional mRNA cleavage or translational repression [3,22–25].

In recent years, significant progress has been made in exploring the molecular regulation of miRNAs in the developmental phase transitions of plants. It is worth noting that miRNAs were first discovered to be involved in the aerial stem-to-rhizome transition of Gynostemma pentaphyllum in one of our recent studies. In this review, we focus on the relatively well-studied miR156, miR159, miR166, miR172, and miR396, and discuss the roles of these five miRNAs and their targets in plant developmental phase transitions, combining our own findings with literature (Figures 1–3). Simultaneously, we emphasize the effects of these five miRNAs and their targets on developmental transitions in the formation of storage organs (Figure 2). We also discuss the functional conservation and divergence of these miRNA-target modules in regulating the developmental phase transitions of plants.

**Figure 1.** MiRNAs and their targets regulate the developmental phase transitions in plants. MiRNA-target modules not only regulate the juvenile-to-adult and vegetative-to-reproductive transitions, but also control the normal transitions within the formation of tissues/organs, including SAM, root, stem, leaf, flower and embryo/seed/fruit. The functions of the miRNAs, included in Figure 1, have been demonstrated in many plant species.
Figure 2. MiRNAs and their targets regulate the formation of storage organs. (a) MiR156 and miR172-RAP1 (AP2 homolog) module regulate the stolon-to-tuber transition in potato. (b) MiR159-MYB29, miR166-ECH2/SGT-like, miR156-SPL6/13A, and miR396-GRF5-like modules are involved in the aerial stem-to-rhizome transition of Gynostemma pentaphyllum. In G. pentaphyllum, the subapical regions of some aerial stems swell and then drill into the soil to form rhizomes that produce new plants in the next year, which is an adaptive regenerative strategy that enables it to survive during winter.
miR159 family, involved in stress tolerance, has been widely known, but it has also been found to play an important role in the developmental phase transitions of plants [26–28]. The members of the miR159 family regulate developmental phase transitions by targeting MYB transcription factor genes in plants [15,29]. The MiR159-MYB33 module was originally found to control the transition from vegetative to reproductive in Arabidopsis, and elevated miR159 expression of the down-regulated gibberellin (GA)-specific MYB33 level, which reduced a flowering promoter LEAFY activity and thus delayed flowering time [30]. A similar finding was detected in transgenic gloxinia plants overexpressing miR159a, where increased expression of miR159a down-regulated a GA-specific MYB gene and exhibited significantly late flowering [31]. In monocot rice, the overexpression of miR159 also silenced an MYB gene and resulted in delayed flowering [32]. These findings suggest that miR159 seems to act as a negative regulator in vegetative-to-reproductive phase transition. However, there are several conflicting reports on the involvement of miR159 in the regulation of GA-mediated flowering. In Arabidopsis, the overexpression of miR159a had no effect on flowering time but caused anther defects, and the expression of MYB33 in flowers did not change [33]. Surprisingly, the mir159ab double-mutant also delayed flowering, like transgenic plants overexpressing miR159a, but the mutations of their two targets (MYB33/MYB65) did not affect flowering time in Arabidopsis [34]. In a recent report, the decreased miR159 level regulated by miR167 up-regulated the expression of an MYB33-like gene, which was in line with the late flowering of tobacco [35]. Considering these findings, should miR159 be termed as negative or positive regulator in controlling the vegetative-to-reproductive transition? These conflicting reports might be explained if we assume that miR159 has multiple targets that are involved in different regulatory pathways, controlling flowering time, and the downstream targets of miR159 could be negative or positive regulators of flowering. miR159 was also involved in flower, embryo, seed and fruit development in plants. In Larix kaempferi, miR159 and its target MYB33 showed opposite expression trends during somatic embryo maturation, suggesting that miR159 regulates the developmental transition of the embryo by repressing MYB33 expression [36]. In Brassica napus, miR159 was strongly expressed at later stages of seed development, and its target, MYB101, exhibited a contrasting expression trend that was expressed at very low levels throughout seed maturation [37].
which shows that the miR159-MYB101 module is involved in the developmental transition of seeds. The miR159-MYB101 module also controlled stress-induced premature transition to the reproductive phase in Arabidopsis [38]. In tomato, miR159-overexpressing plants exhibited precocious fruit initiation and obligatory parthenocarpy accompanied by MYB1/2 silencing, which reveals that miR159-MYB1/2 modules regulate the transition from flowering to fruit production, which is crucial to ensure successful sexual plant reproduction [39]. Moreover, MYB1/2 silencing in miR159-overexpressing plants resulted in abnormal fruit development [39]. A recent report revealed that the miR159-MYB module was involved in the development of pollen in B. campesbris, and the overexpression of miR159a caused pollen abortion, accompanied with the downregulation of two targets (MYB101/120) [40].

MiR159 has also been demonstrated to be involved in the transition of the juvenile-to-adult phase, independently of GA. In Arabidopsis, the mir159ab double mutant had a significantly faster rate of leaf initiation and much smaller leaves than wild-type plants [41]. mir159ab also produced abaxial trichomes later than wild-type plants, whereas miR159a-overexpressing plants produced abaxial trichomes significantly earlier than normal [41]. These findings suggest that miR159 could act as a positive regulator in the juvenile-to-adult transition of plants. However, the miR159 was identified as a post-transcriptional negative regulator in the root growth of Arabidopsis [42]. The mir159ab double-mutant generated a larger meristem in root than wild type and formed longer roots, accompanied by the increased expression of three targets, MYB33, MYB65 and MYB101 [42].

In one of our recent studies, miR159 targeted MYB29 and the upregulation of miR159 expression corresponded well to the downregulation of MYB29 expression during the aerial stem-to-rhizome transition of G. pentaphyllum (unpublished data). A previous report indicates that the overexpression of a B. oleracea MYB29 enhanced the accumulation of aliphatic glucosinolates (GSLs) in Arabidopsis [43]. GSLs contain three classes of aromatic, aliphatic, and indolic GSLs that are regulated by different members of the MYB family, and MYB29 is responsible for the biosynthesis of aliphatic GSLs [44]. GSLs’ profiles differ extensively within and across plant tissues [45]. In B. rapa ssp. Pekinensis, aliphatic GSLs were mainly accumulated in the stem, whereas aromatic GSLs were mainly accumulated in the roots, which correlated well with the much higher expression of MYB29 in the stem than in the other organs [44]. The variation in the level and composition of GSLs can affect plant growth, fitness, and yield [46], implying that different GSLs have different regulatory mechanisms to adapt developmental and environmental changes. Considering that the stem could acquire the characteristics of the root during the aerial stem-to-rhizome transition of G. pentaphyllum, it is thus suggested that the upregulation of miR159 expression reduced the level of aliphatic GSLs by repressing MYB29 expression, to adjust growth in response to aerial stem-to-rhizome transition in G. pentaphyllum.

3. miR166

To date, cumulative data suggest that miR166 is primarily involved in the developmental transitions within vegetative or reproductive growth, but not in the vegetative-to-reproductive transition in plants. MiR166 regulates various developmental processes, such as SAM maintenance, root, stem, leaf, flower, and seed development, as well as rhizome formation [7,47–50].

In Arabidopsis, the miR166 family has multiple members, and all the family members (except for miR166g) were highly expressed in the SAM and root–hypocotyl junctions, and moderately expressed in the cotyledon vasculatures of young seedlings. As the plant grows, the expression regions were rapidly spread to the leaf veins and root tissues, with the highest expression in the root tip. In contrast, miR166g was not detected in the SAM, but highly expressed in rosette leaf trichomes and moderately expressed in root tissues [48]. These findings suggest that miR166 family members have spatiotemporal specificity in regulating plant development. MiR166 was found to target several members of Homeodomain Leucine Zipper Class III (HD-ZIP III) gene family, including PHABULOSA (PHB), PHAVOLUTA (PHV), REVOLUTA (REV), ARABIDOPSIS THALIANA HOMEobox 8 (ATHB8) and ATHB15 in Arabidopsis [50]. The overexpression of miR166g significantly reduced the expression of PHB, PHV and ATHB15, resulting in enlarged shoot meristems, radialized leaves, vascular defects
and reduced gynoecia [51], suggesting that miR166g affected the normal transitions within organ development. The elevated miR166a level also reduced PHB, PHV and ATHB15 expression, leading to growth retardation at seedling stage and even the absence of SAM in Arabidopsis [48], indicating that miR166a and its targets inhibited the transition of juvenile-to-adult phase. The phenotypic differences between transgenic Arabidopsis overexpressing miR166a and miR166g were probably due to their spatiotemporal specificity, mentioned above. In Medicago truncatula, the overexpression of miR166a decreased the ability of the root to form lateral root by repressing MtCNA1, MtCNA2, and MtHB8, the three homologs of ATHB15 and ATHB8 [52], suggesting that miR166a could be a regulator of lateral organogenesis in plants. Moreover, the miR166a-dependent regulation of the three targets controlled vascular bundle patterning in the root [52]. In poplar, miR166 was found to be involved in the development of stem vascular cambium [53]. The populus POPCORONA (PCN) gene is a homolog of ATHB15. The transgenic poplar overexpressing a miR166-resistant PCN delayed the differentiation of secondary xylem and phloem fiber [53], implying that miR166 could promote the secondary growth of woody stems by inhibiting PCN expression, and thus regulate the transition from the primary growth phase to the secondary growth phase. In the secondary growth of woody plants, the production of vascular tissue is derived from the activity of vascular cambium [54]. MiR166 transcripts were found to change in vascular cambium from dormancy to active growth in Cunninghamia lanceolata [55], suggesting that miR166 could regulate the transition of vascular cambium activity and thus affect wood formation. MiR166-regulated developmental transition of leaves was subsequently found in monocot plants. In rice, the downregulation of miR166 and the up-regulation of its several targets (HD-ZIP III genes) caused by the overexpression of a trans-acting siRNA (siR2141) disturbed leaf polarity and vascular development, and thus retarded growth stage transition [56]. In wheat, the silencing of miR166 led to the upregulation of its target gene HD-ZIP HOX33-like, and generated a leaf-twist phenotype in seedlings [57]. In maize, miR166h was significantly upregulated in the elongation zone of young leaves, suggesting that miR166h possibly control the transition of cell division-to-cell expansion during leaf development [58]. MiR166-mediated developmental transition was further confirmed in the formation of reproductive organs in Arabidopsis and other dicot plants. In developing anthers of Arabidopsis, miR166 promoted the expression of SPOROCYTELESS/NOZZLE (SPL/NZZ), a regulator of sporocyte development, by inhibiting the expression of PHB, to allow floral cells into sporocytes [59]. MiR166 was also found to be involved in the developmental transition of embryo. In Pinus taeda, the expression of miR166 reached its highest level in the female gametophyte during zygotic embryo development, when expanded cotyledons enclosed the SAM, which is a critical transition point where somatic embryo maturation often stops, indicating that miR166 played an important role in sustaining a maturing embryo [4]. Also, in transgenic L. leptolepis, miR166a was significantly upregulated as the somatic embryo matured, suggesting that miR166 regulated the transition from early to late development phases of embryo [60]. Considering these observations, miR166 appears to be an activator of embryo maturation. However, the specific loss of miR166 and ectopic expression of two miR166 targets, PHB and PHV, activated related seed maturation genes to promote seed maturation in Arabidopsis [49], implying that miR166 seems to be an inhibitor of embryo maturation. These conflicting reports imply that, besides HD-ZIP genes, miR166 might target other genes to regulate the developmental transitions during embryo maturation.

In our studies, two members of miR166 family, miR166b and miR166e, were found to be involved in the aerial stem-to-rhizome transition in G. pentaphyllum [7]. MiR166b was predicted to target an enoyl-CoA hydratase 2 (ECH2) gene and they exhibited significantly opposite expression trends during the aerial stem-to-rhizome transition [7]. ECH2 was revealed to participate in IBA-to-IAA conversion by promoting β-oxidation of IBA in Arabidopsis [61]. The long-standing acid growth theory postulates that IAA could enable cell expansion in shoots by triggering cell-wall acidification, and thus activating cell wall-loosening enzymes [62]. ECH2 likely promoted post-mitotic cell expansion during the cotyledon development in Arabidopsis [63]. The target of miR166e was a putative scopoletin glucosyltransferase (SGT)-like gene, and the downregulation of miR166e well corresponded to the
upregulation of its target [7]. SGT enzyme catalyzes the formation of scopolin [64], which inhibited IAA catabolism during tobacco seedling development [65]. Thus, it was hypothesized that the miR166b-ECH2 and miR166e-SGT-like modules probably synergistically promote cell expansion by converting IBA to IAA and preventing the degradation of IAA during the aerial stem-to-rhizome transition of G. pentaphyllum [7].

4. miR156

MiR156 is highly expressed at seedling stage and downregulated with age, acting as a master negative regulator of juvenile-to-adult and vegetative-to-reproductive transitions in plants [1,10,66,67]. In plants, the function of miR156 to regulate developmental phase transitions was originally confirmed in Arabidopsis, which was achieved by targeting the expression of SQUAMOSA PROMOTER BINDING PROTEIN LIKE (SPL) genes [33,68]. SPL was first identified in Antirrhinum majus, encoding a plant-specific transcription factor with a conserved SBP domain, by which SPL can recognize and bind specifically to the promoter region of downstream target genes to regulate plant development [69–71]. The SPL family contains multiple members, such as 16, 19, 35, 28, 13 members in Arabidopsis [72], rice [73], switchgrass [74], poplar [75], and Cleistogenes songorica [76], respectively. Some of them were found to be involved in the transition of developmental phases mediated by miR156. In Arabidopsis, the overexpression of miR156b produced more leaves and delayed flowering, accompanied by the downregulation of multiple SPL genes (SPL2/3/4/5/6/9/10/11/13/15) [33]. Contrarily, the decrease in the level of miR156a/miR156 caused the upregulation of several SPL genes, thereby producing less leaves and promoting juvenile-to-adult transition as well as flowering [68,77]. A recent research revealed that the mutation of miR156c or double mutation of miR156a/c upregulated the expression of seven SPL genes (SPL2/3/9/10/11/13/15), thus accelerating the production of leaf trichomes and promoting the juvenile-to-adult transition in Arabidopsis [10]. In monocot rice, the miR156-SPL14 module was found to be involved in the control of developmental phase transitions [78–82]. The overexpression of a miR156-resistant SPL14 caused a decrease in tiller number, but an increase in plastochron and an acceleration of floral transition [80]. In transgenic rice overexpressing miR156f, the decreased expression of SPL14 together with SPL3 and SPL12 produced more tillers and displayed dwarfism [81]. Another report indicated that the overexpression of two miR156 genes (miR156b/h) resulted in reduced panicle size, and, in particular, delayed flowering. Contrary to the expression trend of the miR156b/h, SPL2/12/13 and SPL6/18 showed decreased mRNA levels in the flag leaves and panicles of transgenic plants, respectively, while SPL14 was downregulated in both flag leaves and panicles of transgenic rice [82]. The tissue-specific expression of miR156-targeted SPL genes was further confirmed in Arabidopsis. For example, SPL9 was expressed in young leaf primordia, whereas SPL15 was only expressed during early stages of inflorescence development in Arabidopsis [67,83]. The MiR156-SPL module regulates the developmental phase transitions that have successively been confirmed in other herbaceous plants, such as tomato, switchgrass, potato, alfalfa and G. pentaphyllum [6,74–86]. A similar mechanism for miR156-mediated developmental phase transitions was also found in perennial woody plants. In poplar, the overexpression of miR156 reduced the expression of SPL3/9, which drastically prolonged the juvenile phase [87]. Several members of miR156 family were downregulated in the vascular cambium from dormancy to activity in tree species C. lanceolata [35], suggesting that miR156 could regulate the dormancy-to-activity transition of vascular cambium in conifers. In the tree species Fortunella hindsii, the overexpression of miR156a significantly enhanced the somatic embryogenesis (SE) competence, accompanied by the downregulation of multiple SPL genes (SPL3/5/6/13/14), indicating that miR156-SPL module regulated the initial phases of SE induction [88]. A recent report indicated that miR156 was downregulated in the floral transition of the tree species Castanea mollissima, and most of the miR156-targeted SPL genes, particularly SPL6/9/10/13/16, were significantly upregulated [89]. These findings suggest that miR156 and its targets are evolutionarily conserved in regulating the developmental phase transitions in both annual herbaceous plants and perennial tree species.
It is worth noting that the overexpression of miR156 produced aerial tubers but reduced underground tuber yield under short day (SD) condition in potato, which was suggested to be associated with a threshold level of miR156 [6]. In wild-type potato, all axillary meristems have the capacity to form tubers, but this potential is suppressed except in underground stolons [90]. MiR156, as a phloem-mobile signal, is thought to be transported to the stolon through phloem to promote tuberization when the level of miR156 exceeds a certain threshold, which in turn reduces the miR156 accumulation in aboveground meristems [6]. Thus, it was suggested that the overexpression of miR156 resulted in levels above the threshold in all the aboveground axillary meristems, and thus produced aerial tubers under SD conditions; however, the reduced underground tuber yield was possibly attributable to the prolonged juvenile phase of these plants [6]. In our research, miR156a was first found to promote the aerial stem-to-rhizome transition by repressing the expression of SPL6 and SPL13A in *G. pentaphyllum* [7].

Some regulatory factors have been found upstream of miR156 to regulate its expression, such as transcription factors, hormones, and light [2,7,41,89,91]. A photoperiod-related transcription factor, *PETER PAN SYNDROME* (*PPS*), regulated the onset of the adult phase and the time of flowering by promoting the expression of miR156 in rice [2]. Our recent studies have shown that the miR156a upstream sequence contains several light-regulated motifs, and the light-mediated regulation of miR156a is probably involved in the aerial stem-to-rhizome transition in *G. pentaphyllum* [7]. It was also found that *AGAMOUS-like AGL15*/*AGL18* and *MYB33* promoted the transcription of miR156a and miR156c by directly binding to the promoters of the two miRNAs in *Arabidopsis* [41,91]. A recent report revealed that GA, as an important hormone, significantly increased the expression level of miR156 and decreased the expression of the targeted SPL genes in *C. mollissima* [89].

5. miR172

In contrast to miR156, miR172 expression is up-regulated as plants age and acts as a positive regulator to control the juvenile-to-adult and vegetative-to-reproductive transitions [1,6]. MiR172 regulates these developmental phase transitions, through targeting *APETALA2* (*AP2*) family members, including *AP2* itself, *TARGET OF EAT 1* (*TOE1*), *TOE2*, *TOE3*, *SCHLAFMUTZE* (*SMZ*) and *SCHNARCHZAPFEN* (*SNZ*) in *Arabidopsis* [1,92]. The overexpression of both miR172a and miR172b promoted the juvenile-to-adult transition and flowering by repressing the expression of their targets in *Arabidopsis* [83,92,93]. Conversely, the loss-of-function mutation in miR172 delayed the formation of adult characteristics such as leaf trichomes, thereby inhibiting the juvenile-to-adult transition in *Arabidopsis* [83]. A recent report revealed that miR172 and its two AP2 targets were involved in the maintenance of stem cells in the shoot apex and regulated the juvenile-to-adult transition in woody poplar [94]. Accumulating evidence indicate that miR172 and its targets not only regulate the vegetative-to-reproductive transitions but also control developmental transitions in the formation of vegetative organs. In transgenic wheat overexpressing miR172d, the expression level of AP2-5 homologs were decreased and resulted in earlier flowering and a longer stem internode than wild-type [95]. In tree species *Jatropha curcas*, the overexpression of miR172a not only resulted in early flowering but also affected the development of vegetative organs, including altered leaf morphology, enhanced xylem development and reduced phloem development [93]. The gain-of-function and loss-of-function of miR172a promoted or delayed flowering and also altered leaf morphology by down- or upregulating the expression of an AP2-like gene in *Sinningia speciosa* [96]. It was also found that miR172 can regulate the normal transition within reproductive organ development. The loss-of-function of miR172 by mimicry technology reduced fruit size and affected fruit valve growth in *Arabidopsis* [97]. In barley, the increased level of AP2 homologs resulted in an abnormal, indeterminate spikelet in the *mir172* mutant [98]. Generally, the functions of miR172 and its targets are relatively conservative between herbaceous plants and perennial tree species.

MiR172 and its targets has also a role in promoting underground tuber formation. In transgenic potato, the upregulation of miR172 promoted tuberization under long day (LD) but had no significant
effect on tuber induction under SD [99]. This finding could be explained by a model for the control of tuberization by several factors, including *Phytochrome B* (*PHYB*), miR172, *RELATED TO APETALA2 1* (*RAP1*) and *BEL5* (*BEL5*) [99]. In the model, miR172 could promote the expression of a tuberization promoter *BEL5*, by targeting a homolog of *AP2, RAP1*. Under LD conditions, *PHYB* might repress the movement of miR172 and *BEL5* mRNA from leaves to stolon, and thus inhibit the tuberization in wild-type potato. However, in the transgenic potato, the increased miR172 and *BEL5* levels override the inhibition caused by LD, thereby promoting tuberization. Under SD, this repression of *PHYB* would be released and allow miR172 and *BEL5* into stolon to induce tuberization [99]. These findings imply that miR172 and *BEL5* could promote tuberization only when their expression levels reach a certain threshold level under LD, but the tuberization could not be enhanced continually with the increase in miR172 and *BEL5* levels under SD.

The promoters of several miR172 family members were found to contain auxin response elements (AuxREs), in which miR172b, miR172c and miR172d contained 2, 2, 1 AuxREs, respectively, in *Arabidopsis* [97,100]. The Auxin Response Factors (ARFs) could recognize the AuxREs in the miR172c promoter to activate the expression of miR172c and thus promote fruit growth in *Arabidopsis* [97]. Another research indicated that ARF was significantly up-regulated during the stolon-to-rhizome transition in lotus [101]. Rhizome is derived from modified stems (stolon) and used for asexual propagation, the predominant propagation way in lotus. Taken together, this suggests that miR172 promotes the developmental transition of organ formation by upstream regulation of ARF in plants.

MiR172 seems to indirectly regulate the expression of miR156-targeted SPL genes to control the developmental transitions in plants. In the miR172d-overproducing *Arabidopsis*, the SPL3/4/5 genes were up-regulated, which led to early flowering [102]. However, the expression of several SPL genes (*SPL3/13/15/23*) was also increased in barley *mir172* mutant and affected the normal development of spikelets [98]. These findings imply that there are positive and negative regulators that regulate SPL expression between miR172 and SPL, and miR172 could mediate these positive and negative regulators to regulate SPL expression, thus controlling vegetative-to-reproductive transition and organ development. MiR156, in turn, could regulate the expression of miR172 via SPL genes. An miR156-mediated *SPL9* bound directly to the miR172b promoter to activate the expression of miR172b in *Arabidopsis* and potato [6,83]. It was further confirmed in rice that miR156-mediated *SPL14* bound the promoters of miR172b and miR172d to positively regulate inflorescence meristem and spikelet transition and negatively control tillering [103].

6. miR396

MiR396 has been shown to play multiple roles during various developmental phases of plants by inhibiting different targets, including *GROWTH-REGULATING FACTOR* (*GRF*), *BASIC HELIX-LOOP-HELIX* (*bHLH*), and *SHORT VEGETATIVE PHASE* (*SVP*) genes [104–106].

*GRF1-3* primarily promotes the leaf and cotyledon growth by regulating cell expansion and also negatively regulates flowering and male fertility to some extent in *Arabidopsis* [104]. In transgenic plants overexpressing miR396a and miR396b, the expression of six *GRF* genes (*GRF1/2/3/7/8/9*) was reduced and the most prominent phenotype was the reduced leaf width [107]. Another report revealed that the overexpression of miR396 (a/b/c/e/h/i/k) not only produced smaller leaves, but also resulted in dwarf, shorter roots, smaller and fewer siliques and seeds, with the down-regulation of *GRF1/2/3/7/8/9* expression in *Arabidopsis*. However, only the overexpression of miR396a/i led to abnormal flower development [108]. These findings indicate that miR396 family members have redundant functions but exhibit functional divergence to a certain degree. A recent research revealed that miR396-GRF module was involved in the embryogenic developmental transition in *Arabidopsis*, and the transcripts of five *GRF* genes (*GRF1/4/7/8/9*) were significantly up-regulated in the *mir396a/b* mutants, but were down-regulated in the miR396b overexpressor line during SE induction via an auxin-related pathway [109]. MiR396 family members played similar roles in other dicot plants, such as tobacco and tomato. In tobacco, the overexpression of miR396a down-regulated three *GRF-like*
genes and resulted in narrow leaves, the abnormal development of stamens and pistils, and declined fertility with little or no seed production [110]. In tobacco, the overexpression of a P. trichocarpa miR396c repressed the expression of several GRF genes (GRF1/3/8) and led to a lack of SAM, as well as altered floral organ specification [111]. In tomato, the significant downregulation of miR396a and miR396b corresponded to a general upregulation of three GRF genes (GRF1/2/5), and produced bigger flowers, in particular, sepals and fruits [112]. These findings suggest that miR396 family members primarily regulate developmental transitions during the growth of vegetative and reproductive organs in dicot plants. Similar findings were also observed in monocot plants such as rice and maize. The overexpression of miR396d in rice significantly reduced the expression of several GRF genes (GRF1/2/3/4/5/6/7/8/10), and gave rise to defects in floral organ development, including open husks, long sterile lemmas similar to the phenotype of the grf6 mutant [113]. In maize, miR396 expression was gradually decreased with advancing grain filling, which was significantly negatively correlated with the increased expression of GRF genes (GRF1/6) [114]. Later, the miR396-GRF module was found to not only control the normal transition of reproductive organ development but also regulate the vegetative organ development in rice. The overexpression of rice miR396a significantly downregulated several GRF genes (GRF1/2/6/8), resulting in dwarf, smaller leaves, abnormal panicles and spikelets, especially a large proportion of rare conjoined-twin florets [115]. These findings demonstrate the functional conservation of the miR396-GRF module across dicot and monocot plants. Recently, our study revealed that the expression of miR396a was up-regulated, whereas its target GRF3-like gene was down-regulated during the aerial stem-to-rhizome transition of G. pentaphyllum (unpublished data), suggesting that miR396 could promote rhizome formation by inhibiting its target GRF expression in plants. MiR396 and miR166 were speculated to interact through their targets, GRF and HD-ZIP genes. The target of miR166, HD-ZIP genes, can specify the adaxial differentiation of organs [116,117]. Interestingly, GRF genes, as the target of miR396, were found to have higher expression levels in the adaxial side of the leaf in Arabidopsis. Moreover, the expression level of GRF genes changed in the leaves with polar defects [118]. These findings suggest that GRF genes are downstream of genes involved in the dorsoventral axis formation, such as HD-ZIP genes [118]. In maize, miR396 and miR166 were found to have similar expression patterns, in that their expression levels were gradually decreased whereas the levels of their target genes, GRF and HD-ZIP homologs, were gradually increased during grain filling [114]. Taken together, the hypothesis that miR396 and miR166 might interact through their target genes seems to make sense.

SVP, as one of the target genes of miR396, was found to negatively regulate flowering, like GRF in Arabidopsis. The overexpression of SVP reduced the expression of a floral promoter FLOWERING LOCUS T (FT) and delayed flowering, whereas the svp mutant showed early flowering [119]. It is worth noting that the decreased expression of both SVP and GRF1 also resulted in a late-flowering phenotype, with curved sepals and petals and enlarged stigmas in the transgenic Arabidopsis overexpressing AtmiR396a and Catharanthus roseus miR396 [105]. Thus, it is suggested that miR396 regulates the normal development of floral organs by targeting SVP and GRF, while it probably controls flowering time by regulating other targets.

MiR396 also regulates developmental transitions in the formation of vegetative organs by targeting bHLH genes. In Arabidopsis, bHLH74 repression by miR396 was found to be required for leaf margin and vein pattern formation, and the overexpression of a miR396-resistant bHLH74 gene resulted in alterations in leaf development, especially in the vein pattern and shape [106]. Further research revealed that the miR396-bHLH module was involved in root development. In M. truncatula, the overexpression of miR396b downregulated the expression of two bHLH79-like genes, resulting in a shorter root [120]. On the contrary, the overexpression of an miR396-resistant bHLH74 produced longer roots in Arabidopsis seedlings [121]. These findings suggest that miR396 could repress the root growth by targeting bHLH genes. In a recent study, an mir396b mutant produced the first leaf with abaxial trichomes earlier than the wild type and exhibited early flowering in Arabidopsis, whereas the miR396a/b overexpression line showed opposite phenotypes [122]. Moreover, the expression of bHLH74 and
several SPL genes were significantly upregulated in the mir396a/b mutant [122]. Given that bhlh74 showed a moderate late flowering phenotype [122] and SPL is a flowering activator, as mentioned above, it is suggested that miR396 could inhibit juvenile-to-adult and vegetative-to-reproductive transitions by directly targeting bHLH74 and indirectly repressing SPL expression.

7. Conclusions

In recent years, molecular genetic analysis regarding miRNAs controlling plant developmental transitions has produced significant advances, and five miRNA families (miRNA159/166/156/172/396) have been demonstrated to be key regulators in the developmental transitions of plants (Figures 1–3; Table S1). MiR156, miR172, and miR159 specifically target the members of SPL, AP2, MYB family, respectively. MiR172 promotes juvenile-to-adult and vegetative-to-reproductive transitions, whereas miR156 shows opposite regulatory roles. Recent research reveals that the two miRNAs, in particular miR172, also play a role in the normal transitions within the growth of vegetative or reproductive organs. Similar to miR172, miR159 can also promote juvenile-to-adult transition, but controlling flowering time is controversial. Unlike the above-mentioned three miRNAs, miR166 and miR396 have multiple targets, which mainly regulate the developmental transitions in organ formation. However, miR166-targets regulatory modules are functionally less conservative than miR396-targets modules. It is worth noting that the five miRNAs all regulate the developmental transition in the formation of storage organs (Figure 2). Among them, miRNA156, miR159, miR172, and miR396 are found to positively regulate aerial stem-to-rhizome or underground stolon-to-tuber transitions. while miR166 negatively controls these transitions. In general, the functions of the five miRNAs and their targets are relatively conserved, at least in seed plants, but functional divergences also emerge to varying degrees.

Current researches reveal that miRNAs usually negatively regulate their downstream targets to affect the developmental process of plants. Thus, it is possible to hypothesize that plants could break the existing developmental status through the negative regulation of miRNAs on their target genes, to achieve developmental phase transitions. However, it is still poorly understood how miRNAs themselves are spatiotemporally regulated. More researches about the complex interplay of these miRNAs with other regulatory factors, in particular, acting upstream of miRNAs, would not only help address this issue but would also probably clarify some existing controversial issues, such as miR159-mediated flowering time and miR166-mediated embryo maturation. In addition, much still remains to be discovered about miRNAs-regulated developmental transitions in the formation of storage organs and vascular tissues, which would be an important molecular basis for improving crop yield and tree biomass through genetic manipulation. It is worth noting that, although gene overexpression helps to understand the role of the gene-of-interest in many plants, especially in non-model plants, the transgenic plants overexpressing a gene can present pleiotropic phenotypes and sometimes may not well elucidate the function of the gene. Therefore, more mutant analysis and the application of gene editing technology, such as CRISPR-Cas9, might provide new insights into plant developmental phase transitions regulated by miRNAs and their targets in the future.

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**Abbreviations**

- miRNAs: MicroRNAs
- SAM: Shoot apical meristem
- GA: Gibberellin
- GSLs: Glucosinolates
- HD-ZIP III: Homeodomain leucine zipper class III
- PHB: Phabulosa
- PHV: Phavoluta
- REV: Revoluta
- ATHB8: *Arabidopsis thaliana* homeobox 8
- ATHB15: *Arabidopsis thaliana* homeobox 15
- PCN: Popcorona
- SPL/NZZ: Sporocyteless/Nozzle
- ECH2: Enoyl-CoA hydratase 2
- SGT: Scopoletin glucosyltransferase
- SPL: Squamosa promoter binding protein like
- SD: Short day
- PPS: Peter pan syndrome
- AP2: Apetala2
- TOE1: Target of eat 1
- SMZ: Schlafmutze
- SNZ: Schnarchzapfen
- LD: Long day
- PHYB: Phyochrome B
- RAP1: Related to apetala2 1
- BEL5: Bell5
- AuxREs: auxin response elements
- ARF: Auxin response factors
- GRF: Growth-regulating factor
- bHLH: Basic helix-loop-helix
- SVP: Short vegetative phase
- FT: Flowering locus T

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