MicroRNAs regulated cell differentiation in plants: Case Study

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Abstract— *MicroRNAs (miRNAs) function on post-transcriptional gene silencing and regulate the gene expression by degrading the transcripts of their targets, leading to down-regulation of the target genes. Plant miRNAs have been reported to play important roles in developmental control, hormone secretion, cell proliferation, and response to environmental stresses. In this review, we have reviewed miRNA expression and its potential role in regulating cell differentiation in Arabidopsis and summarized the miRNAs regulated cell differentiation during root, shoot, leave, and embryo development. We have further described practical application of expression of miRNAs in plant molecular breeding.*

Keywords— Cell differentiation, gene expression, microRNAs, post-transcriptional gene silencing, root, shoot, leave, embryo development.

I. INTRODUCTION

MicroRNAs (miRNAs) the gene expression by base-pairing with the transcripts of their targets, leading to post-transcriptional gene silencing and down-regulation of the target genes (Ross and Davis 2011, Vashisht and Nodine 2014, Wang, et al. 2011a). Different expression of miRNAs is associated with many human diseases and has been shown to affect the hallmarks of cancer through regulating proliferative signaling, resisting cell death, evading growth suppressors, enabling replicative immortality, and activating metastasis (Duggal, et al. 2012, Ross and Davis 2011). Recent evidence suggests that nutrients and dietary factors modify miRNA expression and their mRNA targets through cell cycle regulation, differentiation, and stress response (Duggal, et al. 2012, Ross and Davis 2011). Resveratrol (3,5,4'-trihydroxystilbene) is a plant phenolic phytoalexin that has been reported to have antitumor properties by exerting anti-proliferative effects against A549 human non-small cell lung cancer cells (Bae, et al. 2011, Lancon, et al. 2012). Results from microarray analysis demonstrated that resveratrol treatment altered miRNA and its target gene expression and lead to changes of cell proliferation and differentiation, indicating that the effects of resveratrol on microRNA populations in humans may present a novel approach for studying the anticancer mechanisms, metabolism, and muscle differentiation (Bae, et al. 2011, Lancon, et al. 2012).

Plant miRNAs have been reported to play important roles in developmental control, hormone secretion, cell differentiation, and response to environmental stresses (Borges, et al. 2011, Liu, et al. 2012, Vashisht and Nodine 2014, Wang, et al. 2011a). In Arabidopsis, complementary sites within predicted targets identified with near complementarity are conserved in rice and most of the targets are members of transcription factor gene families involved in developmental patterning, suggesting that many plant miRNAs act similarly to small interfering RNAs in directing mRNA cleavage and many plant miRNAs function during cellular differentiation to clear key regulatory transcripts (Rhoades, et al. 2002, Wang, et al. 2011a, Zhang, et al. 2009). An online database for *Arabidopsis thaliana* miRNA function annotations that integrated miRNA-target interactions, transcription factor and their targets, expression profiles, genomic annotations, and pathways has been developed and the associated terms may provide valuable insight for the functions of each miRNA (Liu, et al. 2012).

Regulatory activations of miRNAs in development of plant embryos, proliferation of plant stem cells, modulation of immune response to macrophages, and development of plant male germ line have been well documented (Borges, et al. 2011, Dweep, et al. 2013, Vashisht and Nodine 2014, Wang, et al. 2011a). Compared to targets of animal miRNAs, targets of plant miRNAs can be easily identified by computational prediction because plant miRNAs always bind their targets with near perfect complementarity (Dweep, et al. 2013, Liu, et al. 2012). Recently, great progress of regulatory activations of miRNAs in plant cell differentiation has been made (Borges, et al. 2011, Dweep, et al. 2013, Vashisht and Nodine 2014,). In this review, we have focused miRNA expression and its potential role in regulating cell differentiation in Arabidopsis and

summarized the miRNAs regulated cell differentiation during root, shoot, leave, and embryo development based on the previously published investigations (Table 1). We have further described practical application of expression of miRNAs in plant molecular breeding.

TABLE 1
PLANT SPECIES AND MICRORNAS KNOWN TO REGULATE CELL DIFFERENTIATION

Organs	Species	MicroRNAs	References
Root	Mediterranean orchid (*Orchis italic*)	miR172	(Salemme, et al. 2013)
	Arabidopsis (*Arabidopsis thaliana*)	miR396, miR165, miR166, miR160	(Hewezi, et al. 2012, Miyashima, et al. 2011, Wang, et al. 2005)
Leave	Tomato (*Solanum lycopersicum*)	miR166, miR319	(Hu, et al. 2014, Ori, et al. 2007)
	Mediterranean orchid (*Orchis italic*)	miR172	(Salemme, et al. 2013)
	Arabidopsis (*Arabidopsis thaliana*)	miR396. miR398, miR164	(Grigg, et al. 2005, Koyama, et al. 2010, Miura, et al. 2010, Wang, et al. 2011b)
Shoot	Arabidopsis (*Arabidopsis thaliana*)	miR166b, miR394, miR164	(Grigg, et al. 2005, Knauer, et al. 2013, Koyama, et al. 2010, Liu, et al. 2013)
	Barley (*Hordeum vulgare*)	miR156, miR171, miR172	(Curaba, et al. 2013)
	Hybrid aspen (*Populus tremulaxPopulus alba*)	miR166	(Ko, et al. 2006)
Embryo	Sweet orange (*Citrus sinensis*)	miR156a/b, miR164b and 171c	(Vashisht and Nodine 2014, Wu, et al. 2015)
	Rice (*Oryza sativa*)	53 microRNA	(Chen, et al. 2011)
	Arabidopsis (*Arabidopsis thaliana*)	miR156	(Nodine and Bartel 2010, Vashisht and Nodine 2014, Zhang, et al. 2009)

1.1 MicroRNAs regulated cell differentiation in Arabidopsis

During sporophytic generation, male reproductive cells are differentiated into multicellular male gametes in the gametophytic generation (Zhang and Yang 2014). However, the mechanism controlling the specification of the tapetum and microsporocyte cell fate within the anther is not fully understood. Recent investigations demonstrated that both miRNAs related molecular switches and signaling pathways play a role in both the establishment of somatic and reproductive cells and the specification of tapetum and microsporocytes in plants (Borges, et al. 2011, Zhang and Yang 2014). In Arabidopsis, microRNA activity in the male germline has been widely investigated (Borges, et al. 2011). Hundreds of miRNA sequences processed in the Arabidopsis sporophyte have been discovered through next-generation sequencing technologies (Borges, et al. 2011). Comparative analysis of miRNAs identified in sperm cells demonstrated that variations in the sequence length of known miRNAs might be associated with a putative germline-specific Argonaute complex (Borges, et al. 2011). For example, ARGONAUTE 5 (AGO5), a homology of AGO1 that localizes preferentially to the sperm cell cytoplasm in mature pollen, may be part of the complex (Borges, et al. 2011).

In Arabidopsis inflorescence stems, class III homeodomain-leucine zipper transcription factors regulate cell differentiation through microRNA-directed cleavage (Kim, et al. 2005). For example, miR166-mediated ATHB15 (a transcription factor exclusively expressed in vascular tissues) mRNA cleavage may be a principal mechanism for the regulation of vascular differentiation (Kim, et al. 2005). MicroRNA166 mediated ATHB15 mRNA cleavage occurred in wheat germ extracts, Arabidopsis, and *Nicotiana benthamiana* cells, suggesting that miR166-associated ATHB15 down-regulation may be a conserved mechanism in all vascular plants (Kim, et al. 2005). The simple unicellular trichomes of Arabidopsis is an excellent model to study molecular mechanism of cell differentiation in plants (Pattanaik, et al. 2014). Transcription factors

R2R3 MYB, basic helix-loop-helix (bHLH), and WD40 repeat (WDR) proteins form a transcriptional network to regulate trichome development through microRNAs directed cell differentiation in Arabidopsis (Pattanaik, et al. 2014).

Plant-derived antioxidant carnosic acid and vitamin D analog doxercalciferol participate in microRNAs regulated cell differentiation (Duggal, et al. 2012). For example, microRNA181a is involved in differentiation and cell cycle arrest by partially inhibited the effect of CA/1-D2 on the differentiation, suggesting that miR181a has a role in CA/1-D2- induced differentiation and cell cycle arrest (Duggal, et al. 2012). Some miRNAs can highly affect plant agricultural traits, including fruit development, biomass yield, and flower development through microRNA directed cell differentiation, suggesting that miRNAs may be a resource for the genetic improvement of crops (Zheng and Qu 2015). MicroRNAs can exert their effects at distant sites as well as within the cells of origin during the process of cell differentiation and stress responses, indicating their potential roles in various biological processes (Ross and Davis 2011).

1.2 MicroRNAs regulated cell differentiation in root

Recent investigation demonstrated that endodermis-derived microRNA 165/166 regulated xylem cell differentiation by suppressing the expression of the Class III HD-ZIP transcription factor PHABULOSA (PHB) in the peripheral stele of the Arabidopsis root meristem (Miyashima, et al. 2011). MicroRNA165 acts in a dose-dependent manner to control cell differentiation in the Arabidopsis root (Miyashima, et al. 2011). In the Mediterranean orchid *Orchis italica*, microRNA172 regulates the activity of plant-specific AP2/ERF transcription factors at the post-transcriptional level by targeting their conserved target site (Salemme, et al. 2013). For example, the OitaAP2_ISO isoform is expressed in the root and stem (Salemme, et al. 2013). The expression profile of miR172 is complementary to that of the OitaAP2 isoforms, suggesting the existence of OitaAP2 inhibitory mechanisms in these tissues (Salemme, et al. 2013).

In vitro rooting is a multifactorial response leading to formation of new roots at the base of plant stem cuttings (da Costa, et al. 2013). A complex microRNA circuitry is involved in response factors essential for gene expression in in vitro rooting (da Costa, et al. 2013). After root establishment, microRNA directed auxin response factors are required for root meristem maintenance and cytokinins needed for root tissue differentiation (da Costa, et al. 2013). The syncytium is a unique plant root organ and its formation involves the re-differentiation of hundreds of root cells (Hewezi, et al. 2012). In *Arabidopsis thaliana*, microRNA396 up-regulates the development of syncytium and has a role in the transition from one phase to the other (Hewezi, et al. 2012), indicating that miR396 represents a key regulator for the reprogramming of root cells (Hewezi, et al. 2012).

There are increased evidences supports that microRNAs control cell differentiation through regulating expression of transcription factors and auxin response factors in plants (Salemme, et al. 2013, Wang, et al. 2011a). In *Arabidopsis thaliana*, microRNA160 regulates the root cap cell formation by repressing expression of auxin response factors ARF10 and ARF16 (Wang, et al. 2005). ARF10 and ARF16 have been reported to play a role in restricting stem cell differentiation in an indispensable way for root development (Wang, et al. 2005). MicroRNA160 regulated expression of ARF10 and ARF16 genes suggests that miR160 plays an essential role in regulating cell differentiation in Arabidopsis root (Wang, et al. 2005).

1.3 MicroRNAs regulated cell differentiation in shoot

Shoot regeneration requires the presence of specific miRNAs (Liu, et al. 2013). Results from the β-glucuronidase (GUS) expression domains for miR165a/166b demonstrated that GUS activity of miR166b was detected within the shoot apical meristem, suggesting that GUS activity for miR166b was concentrated in the stem apical meristem and that miR166b might play a distinct role in shoot regeneration (Liu, et al. 2013). Using a sensitized mutant screen, miR394 was identified as a mobile signal that confers stem cell competence to the distal meristem during shoot meristem formation in *Arabidopsis thaliana* (Knauer, et al. 2013). This repression is required to potentiate signaling from underneath the stem cells, suggesting that a mechanistic framework of how stem cells are localized at the tip of the meristem (Knauer, et al. 2013). In additional, microRNA regulated expression of auxin transporters and compounds in auxin catabolism may play important role in early stages of cell differentiation (da Costa, et al. 2013).

MicroRNAs, such as miR156 and miR172, play important role during the transitions from juvenile to adult in the life cycle of plants (Curaba, et al. 2013). In Arabidopsis and barley, miR171 over-expression alters the vegetative to reproductive phase transition by activating the miR156 pathway, suggesting that some of the roles of miR171 and its target genes are conserved (Curaba, et al. 2013). It is becoming increasingly clear that microRNA molecules are participants in plant stem cell control and in positioning the stem cell niches in plants (Wang, et al. 2011a). Transgenic *Populus* expressing a microRNA-resistant form of a *Populus* class III HD ZIP gene presents unstable phenotypic abnormalities affecting both primary and secondary

growth, suggesting that the *Populus* class III HD ZIP gene plays a fundamental role in the initiation of the cambium and in regulating the patterning of secondary vascular tissues (Robischon, et al. 2011).

Results from whole-genome tiling arrays showed that the H3K27me3 (a gene associated with mitotically stable gene repression) target genes were in undifferentiated cells of the shoot apical meristem and in differentiated leaf cells (Lafos, et al. 2011). H3K27me3 indirectly activates specific transcription factors through H3K27me3-mediated silencing of microRNA genes, suggesting that H3K27me3 is one of the major determinants of tissue-specific gene expression during the process of cell differentiation in plants (Lafos, et al. 2011). A tightly controlled balance between cell proliferation in the center and cell differentiation at the periphery of the shoot meristem maintains its integrity and microRNA regulated expression of LOM1 and LOM2 transcripts in the peripheral and basal zones of the SAM promotes cell differentiation at the periphery of shoot meristems (Schulze, et al. 2010).

Coordination and promotion of cellular differentiation are essential for the development of plant shoots (Koyama, et al. 2010). Transcription factors are involved in this coordination via the negative regulation of specific genes, which regulate the formation of shoot meristems and the specification of organ boundaries (Koyama, et al. 2010). Gain of function of these genes suppressed the formation of shoot meristems, whereas their loss of function induced ectopic expression of specific genes, indicating that miR164 and its targeted genes have important roles in the signaling pathways that generate different leaf forms, without having any lethal effects on shoots (Koyama, et al. 2010). Class III homeodomain leucine-zipper (HD-Zip) proteins have been shown to play a regulatory role in vascular differentiation (Ko, et al. 2006). Expression of the hybrid aspen (*Populus tremula x Populus alba*) class III HD-Zip transcription factor (PtaHB1) and microRNA 166 (Pta-miR166) family demonstrated that wood formation was regulated both developmentally and seasonally, suggesting seasonal and developmental regulation of microRNA in this perennial plant species (Ko, et al. 2006).

1.4 MicroRNAs regulated cell differentiation in leave

Shoot apical meristems determine leave formation that differentiates an adaxial side specialized for light capture and an abaxial side specialized for gas exchange in plants (Grigg, et al. 2005, Salemme, et al. 2013). Relationship between meristem activity and the differentiation of adaxial leaf fate has been recognized (Grigg, et al. 2005). In *Arabidopsis thaliana*, the zinc-finger protein SERRATE acts in a microRNA gene-silencing pathway to regulate expression of the HD-Zip III gene PHABULOSA (PHB) while also limiting the competence of shoot tissue to respond to KNOX expression, suggesting that SERRATE acts to coordinately regulate meristem activity and leaf axial patterning (Grigg, et al. 2005). The AP2/ERF proteins are plant-specific transcription factors involved in leave development to response to various environmental stresses and their activities are controlled by the miR172 at the post-transcriptional level (Grigg, et al. 2005, Salemme, et al. 2013). The expression profile of miR172 is complementary to that of the OitaAP2 isoforms, suggesting the existence of OitaAP2 inhibitory mechanisms involving miR172 (Salemme, et al. 2013).

In plants, CIN-like TCP genes, such as TCP3, directly activates the expression of genes for miR164 and acts dose dependently in the differentiation of leaves, suggesting CIN-like TCPs have important roles in the signaling pathways that generate different leaf forms, without having any lethal effects on shoots (Koyama, et al. 2010). Chicken interferon-gamma is both an inhibitor of viral replication and a regulator of numerous immunological functions and the mechanism of transgenic ChIFN-gamma tobacco resistance involves RPS20 and other genes that induce microRNA-based gene regulation (Wu, et al. 2014). Overexpression of a microRNA166-resistant version of SlREV not only resulted in vegetative abnormalities, but also caused dramatic reproductive alterations and ectopic fruit formation, suggesting novel roles of SlREV in tomato (Hu, et al. 2014). It has been reported that microRNA396-targeted growth-regulating factors are required for leaf adaxial-abaxial polarity and reduction of the expression of growth-regulating factor genes by transgenic miR396 overexpression in leaf polarity mutants resulted in plants with enhanced leaf adaxial-abaxial defects, indicating that miR396 negatively regulates cell proliferation by controlling entry into the mitotic cell cycle and suggesting that cell division activity mediated by miR396-targeted growth-regulating factors is important for polarized cell differentiation during leaf morphogenesis (Wang, et al. 2011b).

Investigation on the Arabidopsis yellow variegated2 mutant demonstrated that this mutant is a typical leaf-variegated mutant and whose defect results from the lack of FtsH2 metalloprotease in chloroplasts (Miura, et al. 2010). Up-regulation of Cu/Zn superoxide dismutase 2 appears to be partly attributable to the lack of a miR398 in tissues with abnormal chloroplast differentiation (Miura, et al. 2010). In *Arabidopsis thaliana*, 17 miRNAs showed pollen-enriched expression compared with leaves, suggesting pollen not only utilises many miRNAs and trans-acting siRNAs expressed in the somatic tissues, but also

expresses novel miRNAs (Grant-Downton, et al. 2009). In the partially dominant mutation Lanceolate (La) of tomato (*Solanum lycopersicum*), the reduced sensitivity to miRNA regulation leads to elevated LA expression in very young La leaf primordia and down-regulation of several LA-like genes using ectopic expression of miR319 resulted in larger leaflets and continuous growth of leaf margins, suggesting that regulation of LA by miR319 defines a flexible window of morphogenetic competence that is required for leaf elaboration (Ori, et al. 2007).

1.5 MicroRNAs regulated cell differentiation in embryo

The basic plant body plan is established during early embryogenesis and miRNAs play pivotal roles during embryonic pattern formation (Vashisht and Nodine 2014; Wu et al. 2015). Multiple miRNAs appear to specifically repress transcription factor families during early embryogenesis and have a large influence on the gene regulatory networks that contribute to the earliest cellular differentiation events in plants (Vashisht and Nodine 2014). The genome wide profiles of miRNAs/siRNAs and their target genes in nonembryogenic and embryogenic tissues of sweet orange identified 50 known and 45 novel miRNAs, and the conserved csi-miR156a/b, miR164b and 171c directed suppression of specific transcription factors, providing new clues for future investigation of mechanisms that control somatic embryogenesis (Wu, et al. 2015).

In cultured rice embryogenic calli, 50 known microRNA families, representing one third of annotated rice microRNAs have been identified and 53 microRNAs appear to vary in expression between differentiated and undifferentiated calli, suggesting a role of microRNAs in meristem development (Chen, et al. 2011). To assess the functions of embryonic miRNAs in Arabidopsis, the developmental and molecular consequences of DCL1 loss has been determined (Nodine and Bartel 2010). In dcl1 eight-cell embryos, the two most up-regulated targets are SPL10 and SPL11 transcription factors and miR156-mediated repression of zygotic SPL transcripts prevents premature accumulation of transcripts from genes normally induced during the embryonic maturation phase, suggesting that miRNAs enable proper embryonic patterning by preventing precocious expression of differentiation-promoting transcription factors (Nodine and Bartel 2010). In plants, the co-expressed miRNA clusters are pivotal in coordinately regulating embryonic development, cell cycles, and cell differentiation (Zhang, et al. 2009).

II. CONCLUSION

Functional consequences of miRNAs and miRNA clusters in plant genomes have been reported to be associated with developmental control, hormone secretion, cell proliferation, and response to environmental stresses. In this review, we have reviewed miRNA expression and its potential role in regulating cell differentiation during root, shoot, leave, and embryo development in plants. Cell differentiation regulated by miRNAs during root, shoot, leave, and embryo development and regulation of expression of miRNAs may have practical application in plant molecular breeding.

AUTHORS' CONTRIBUTIONS

WT wrote the manuscript. All authors participated, contributed to design of research, performed, and evaluated the experiments. All authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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