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MicroRNAs as central regulators of plant developmental processes.

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Abstract.

MicroRNAs (miRNAs) are a subset of small non-coding RNAs that have a vital role in controlling gene expression at the post-transcriptional level within plants. Initially found in nematodes, miRNAs have now become recognized as pivotal regulators across various facets of plant growth, encompassing root development, shoot meristem development, vascular development, flowering development, and phase transition. By precisely cleaving target mRNAs and producing secondary small interfering RNAs (siRNAs), miRNAs coordinate intricate gene regulatory networks that oversee both plant development and the response to environmental stimuli. This comprehensive analysis sheds light on the current comprehension of how miRNAs function in different phases of plant development, underscoring their significance in shaping the morphology and physiology of plants. Moreover, it is essential to recognize the existing gaps in knowledge and put forth prospective research avenues that aim to unveil the complex regulatory networks overseen by miRNAs, thereby progressing our insights into plant development and potentially aiding in the formulation of innovative strategies for enhancing crop productivity.

Introduction.

RNA is a vital macromolecule in gene regulation. It can be categorized as coding and non-coding RNAs. In plants, small interfering RNAs (siRNA) and microRNAs (miRNA) are prominent non-coding RNAs. siRNAs were first identified in plants and play roles in gene silencing pathways in both plants and animals. (Hamilton et al., 1999) miRNAs were initially discovered in nematodes (Caenorhabditis elegans) by Victor Ambros and colleagues in collaboration with Gary Ruvkun's research group. Their findings confirmed the involvement of a specific miRNA (Lin-4) in the regulation of the temporal development of nematode larvae. (Lee et al., 1993) In plants, a 22-nucleotide miRNA has the capability to cleave the target mRNA, leading to the generation of a cleavage product that can undergo further processing by RNA-DEPENDENT RNA POLYMERASE 6 (RDR6) and DICER-LIKE 4, resulting in the production of secondary 21 nucleotide siRNA. Moreover, the miRNA/miRNA* with symmetrical features can be processed by DCL2, giving rise to secondary 22 nucleotide miRNAs. These siRNAs are referred to as phased siRNAs (PhasiRNAs) due to their innate characteristic of having a phase arrangement structure. (Borges et al., 2015) MicroRNAs have a crucial role in the plants from influencing them during developmental stages and enabling control over plant growth and their involvement in responses to biotic and abiotic stresses.This review aims to shed light on how different miRNAs play a crucial role in the overall development of plants.

miRNA	**Species**	**Target**	**Target Function**	**References.**
miRNA159	*Arabidopsis*	*GAMYB or GAMYB* like gene	Vegetative tissues, seed development, reproductive development	Allen et al., 2007; Millar et al., 2019
miRNA156	*Arabidopsis* and *Zea mays*	*SPL* family	Leaf development, root development, secondary metabolism and abiotic stress.	Aukerman and Sakai, 2003; Chuck et al., 2007a, 2010; Wang et al., 2008; Xu et al., 2016b; Dai et al., 2018
miRNA164	*Arabidopsis, Zea mays, Orzya.*	*NAC* family	Auxiliary meristem formation, leaf and flower development, lateral root initiation and meristem boundary identity.	Li et al., 2003; Laufs et al., 2004; Hibare et al., 2006; Raman et al., 2008; Zheng et al., 2019; Wang et al., 2021b
miRNA160	*Arabidopsis, Medicago truncatula, Zea mays,*	*ARF*s	Hypocotyl elongation, embryo, leaf and root development	Bustos-Sanmamed et al., 2013; Lopez-Ruiz et al., 2019; Yang et al., 2019; Dai et al., 2021

miRNA167	*Arabidopsis and Oryza*	*ARF*s	Male organ development, root, leaves, stem and flowers development. Stress response and defense aganist pathogen	Wu et al., 2006; Liu et al., 2012; Yao et al., 2019; Caruana et al., 2020
miRNA 165/166	*Arabidopsis*	*HD-ZIP III*	Maintaining meristematic cells, adaxial identity of leaves and lateral root growth	Williams et al., 2005; Jia et al., 2015; Merelo et al., 2016; Yan et al., 2016
miRNA169	*Arabidposis, Antirrhiummajus*and *Zea mays*	*CBF* and *NF-YA* family	Enhancer of C homeotic gene transcription and root architecture.	Cartolano et al., 2007; Sorin et al., 2014 Xu et al., 2014; Xing et al., 2021
miRNA172	*Arabidopsis, Zea mays, Oryza, H.vulgare, S. tuberosome*	*AP2* family	the suppression of flowering regulates the identity and arrangement of flower meristem, transition from vegetative to reproductive phase, as well as the development of carpels and stamens. Furthermore, it controls the process of flower opening, tuber formation, and adaptation to high salt levels.	Chuck et al., 2007b; Martin et al., 2009; Wu et al., 2009; Nair et al., 2010; Wollmann et al., 2010; Zhu and Helliwell 2011; Cheng et al., 2021a; Lian et al., 2021; Werner et al., 2021
miRNA171	*Arabidopsis, barley*	*SCL*	biosynthesis of chlorophyll, transitions between phases, and the determination of floral meristem.	Curaba et al., 2013; Ma et al., 2014; Li et al., 2021
miRNA390	*Arabidopsis*	*TAS3*	siRNA production for ARF inhibition and indirect miRNA165/166 control, side root development and leaf design	Fahlgren et al., 2006; Marin et al., 2010; Endo et al., 2013; Dastidar et al., 2019
miRNA319	*Arabidopsis, Solanum lycopersicum*	*TCP* family	leaf growth and aging, organ bending, production and communication of hormones.	Ori et al., 2007; Schommer et al., 2014; Koyama et al., 2017; Bresso et al., 201%
miRNA394	*Arabidopsis*	*LCR*	Meristematic identity subduing by WUS downregulation, leaf	Baumann, 2013; Knauer et al., 2013; Quet al., 2019

			proclivity and architecture,	
miRNA393	*Arabidopsis and Orzya*	*TIR1* and *AFB*	Side root growth, leaf shape and number, auxin homeostasis	Parry et al., 2009; Chen et al., 2011; Windels and Vazquez, 2011; Lu et al., 2018; Wang et al., 2018
miRNA397	*Oryza*	*OsLAC*	Panicle branches, grain yield	Zhang et al., 2013
miRNA396	*Arabidopsis, Medicago and Oryza*	*GRF*	Cell expansion in leaves, somatic embryogenesis, disease resistance, panicle branching and grain size	Debernardi et al., 2012; Bazin et al.,2013; Liu et al., 2014a; Chandran et al. 2018; Szczygiel-Sommer and Gaj, 201§ Liebsch and Palatnik, 2020; Zhang et al., 2020
miRNA828 and miRNA858	Cotton and grapes	*MYB*s	Fiber development, anthocyanin and flavanol accumulation	Guan et al., 2014; Tirumalai et al., 2019
miRNA824	*Arabidopsis*	*AGL*16	Stomatal patterning	Bergmann and Sack, 2007
miRNA857	*Arabidopsis*	*LACCASE*7	Secondary growth	Abdel-Ghany and Pilon, 2008; Zhao et al., 2015
miRNA847	*Arabidopsis*	*IAA28*	Side root formation	Wang and Guo, 2015
TAS3	All land plants	*ARF3/4* (in mosses) and *AP2 like*	Phase transition, Vasculature development and leaf polarity	Fahlgren et al., 2006; Jing et al., 2017

Table 1: MicroRNAs, their targets and the role they play in plant development.

Biogenesis of miRNA.

MicroRNA (MIR) genes undergo transcription by RNA polymerase II (Pol II), leading to the generation of a primary miRNA (pri-miRNA) transcript. The conversion from pri-to-pre-miRNA and the followed processing of mature miRNA in plants are controlled by DCL1 (Dicer like 1).This pri-miRNA molecule subsequently undergoes self-folding to create a double-stranded precursor RNA (pre-miRNA) characterized by imperfect base pairing and a stem-loop configuration. The protein known as DAWDLE (DDL) plays a crucial role in stabilizing the transformation of primary microRNA (pri-miRNA) into structured stem-loop precursors of microRNA (pre-miRNA). The transition of pri-to-pre-miRNA is heavily dependent on two key proteins which are the double stranded RNA-binding protein HYPONASTIC LEAVES 1 and the

C2H2 zinc finger protein SERRATE (SE). They interact with DCL1 within specialized nuclear processing sites known as D-bodies or SmD3/SmB-bodies. (Voinnet et al., 2009)

The terminal region located at the 3′end of the processed double-stranded miRNAs, which consist of the mature miRNA strand and its complementary strand (referred to as miRNA/miRNA*), undergoes a biochemical modification known as methylation which is catalyzed by the enzyme HUA Enhancer 1 (HEN1) (Li et al., 2005; Yu B et al., 2005). The double stranded RNAs can move from the nucleus to the cytoplasm through the influence of HST (HASTY, the plant equivalent of exportin-5/Exp5) and various other unidentified elements. (Park MY et al., 2005) The miRNA* contained in the double-stranded miRNA molecule is subsequently broken down, resulting in the presence of the mature miRNA. This mature miRNA can inhibit gene expression by integrating into ARGONAUTE (AGO1), which interacts with various proteins to create the RNA induced silencing complex (RISC). The RISC complex is then able to either cleave messenger RNAs or inhibit their translation. (Baumberger et al., 2005) Recent research has demonstrated that the assembly of RISC in the nucleus can be facilitated by EXPO1, followed by its transport to the cytosol. Additionally, HST has been identified as a regulator of both pri-miRNA transcription and processing (Bologna et al., 2018; Cambiagno et al., 2021).

Studies have illustrated that mature miRNAs play a role in suppressing the translation of specific genes, controlling the function of plant genes through complementary base pairing with coding sequences, binding to 3′UTR and 5′UTR regions of target mRNA, or modulating gene expression by cleaving mRNA at the post-transcriptional stage. This inhibition caused by mature miRNAs leads to changes in the structure of plant organs, growth patterns, development processes, hormone release, signal transmission, and the capacity of plants to manage external stressors and environmental cues (Liu et al., 2009a; Yokotani et al., 2009; Naqvi et al., 2012).

Origin of miRNAs.

The emergence of MIRs encompasses two pivotal mechanisms: the generation of hairpin precursor sequences and the development of promoter functionality. The exploration of the initiation of MIR gene promoters from scratch is still relatively unexplored. Regarding the initiation of plant pre-MIRs from scratch, three hypotheses have been postulated, including inverted gene duplication, spontaneous evolutionary events, and transposon mobilization.

Inverted gene duplication.

Research carried out on a subset of juvenile MIR genes has put forth a hypothesis indicating that these genes may have originated from the reverse duplication of specific target genes. This hypothesis's validity is bolstered by the fact that the sequences surrounding the developed miRNAs in MIR genes resemble the regions adjacent to the miRNA-binding sites found in target genes (Allen E et al., 2004).

Inverted repeats have the ability to form hairpin structures, leading to the production of various small RNAs like siRNAs. As time passes, the hairpin structure goes through a selection process, keeping only a vital portion that is essential for the creation of an MIR gene, which is in charge of producing a specific type of small RNA, known as miRNA.

Numerous cases have been recorded where a significant homology in sequence exists between MIR genes and their target genes, further supporting the evolutionary model (Fahlgreen et al., 2007; He H et al., 2014; Xia R et al., 2015). The original proposal of inverted duplication of target genes suggests the presence of neutral evolution in sequences beyond those of the mature miRNAs and miRNA stars located in MIR genes (Allen E et al., 2004). However, this concept does not apply to certain recent miRNAs. For example, in the scenario of At miRNA824, selection has influenced not only the sequences of miRNA824 and miRNA824* in different ecotypes of Arabidopsis thaliana but also the fold-back structure of the pre-miRNA (Meaux J et al., 2008).

Spontaneous evolution.

Only half of the gene families belonging to the MIR category in Arabidopsis lyrata possess the ability to match up with protein-coding genes, leading to the creation of miRNAs that target genes similar to them (Fenselau de Felippes F et al., 2008). This intriguing observation defies a straightforward explanation based solely on the concept of target inverted duplication, hinting at the presence of other potential origins for MIR genes within plant species. One plausible theory regarding the genesis of miRNAs revolves around the existence of scattered hairpin regions across the plant genome, which could sporadically generate miRNA precursors following the acquisition of promoters that aid in transcription processes. An illustrative example of this is a putative pre-miRNA foldback entity known as mpss05 that has been detected in Arabidopsis thaliana. This foldback exhibits alignment with two separate regions believed to have originated from the duplication of a fragment of a chromosome. The intricate interplay between gene families and miRNA production in Arabidopsis lyrata underscores the complexity of regulatory mechanisms governing genetic expression. The existence of diverse sources for MIR genes highlights the rich tapestry of molecular evolution within plant genomes. Understanding the diverse origins and pathways leading to the formation of miRNAs provides valuable insights into the intricate web of genetic regulation in plant species. Exploring the multifaceted nature of miRNA biogenesis sheds light on the remarkable adaptability and versatility of plant genomes in responding to environmental cues and challenges. Studying the evolutionary pathways and mechanisms underlying the emergence of miRNAs enhances our appreciation of the sophisticated genetic networks that drive plant development and survival.

Miniature inverted repeat transposable elements.

The transposon model of transposons proposed that the ancestors of certain plant miRNAs have their roots in transposable elements. This particular model was formulated based on the observation that a segment of miRNA candidates from A. thaliana and rice were located

proximal to miniature inverted-repeat transposable elements (MITEs) (Piriyapongsa J et al., 2008). Nevertheless, there is a space for discussion on whether these candidates can be accurately categorized as genuine miRNAs. Several candidates, such as A. thaliana and rice miRNA416, rice miRNA420, miRNA445a, miRNA806b, miRNA806g, miRNA807b, miRNA807c, miRNA809h, miRNA811a-c, miRNA813, miRNA819a, miRNA819d, miRNA819g, miRNA819h, and miRNA819f, have come under scrutiny and a few have even been excluded from miR Base. Furthermore, it isfeasible that an existing MIR precursor might undergo a metamorphosis into a new one through processes like co-evolution or sudden bursts of changes in sequence diversity. To illustrate, MIR390 could potentially evolve into MIR4376, which in turn led to the emergence of MIR7122 (Xia R et al., 2013)

Despite three proposed models on the spontaneous emergence of plant pre-miRNAs, there remains a noticeable lack of detailed information on the initial evolutionary processes and concrete evidence to validate these models. Additionally, several unresolved matters persist, including investigations into the source and early evolutionary paths of miRNA gene promoters, the sequence of miRNA emergence and the acquisition of promoter activity, as well as the evolutionary mechanisms propelling the origin and advancement of miRNAs. The intricacy of unraveling the source and early evolutionary trajectories of plant miRNAs is exacerbated by the fact that most of these sequences boast a lengthy evolutionary timeline. The essential sequence data vital for the genesis of these miRNAs has gradually eroded over time. Consequently, comprehending the emergence of recently evolved miRNAs is pivotal for uncovering the origin of plant miRNAs, as the sequence traits acquired during their formation may be well-conserved in these new miRNAs (Lu et al., 2019).

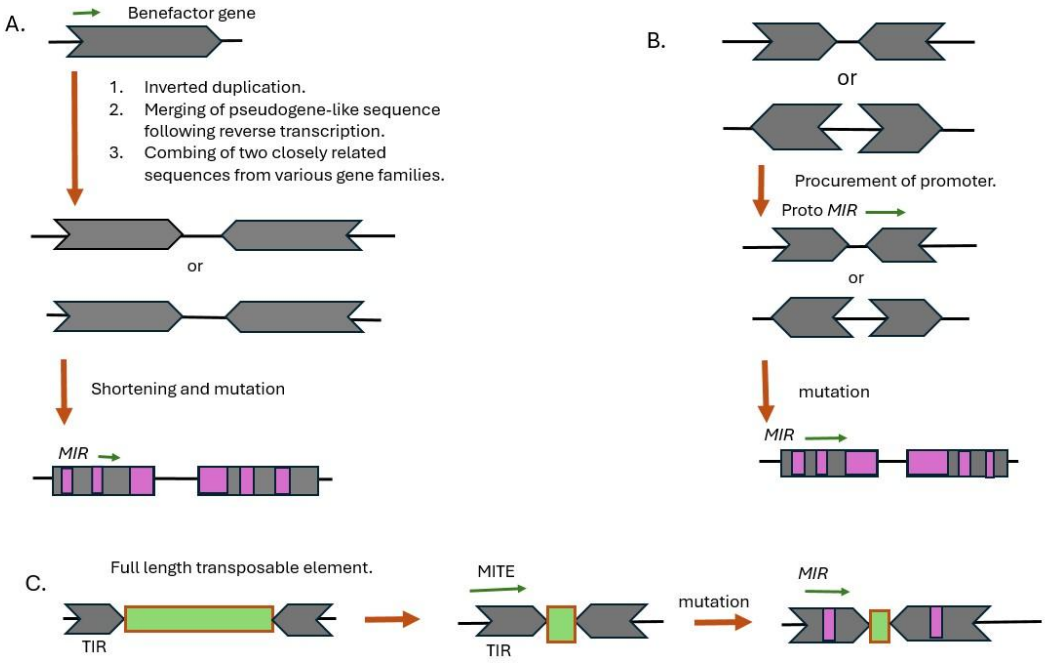

Fig: 1The inverted gene duplication, spontaneous evolution and transposon transposition models for *de*

novo origin and evolution of plant miRs. (A) The inverted gene duplication model. (B) The spontaneous evolution model. (C) The transposon transposition model.

Function of miRNAs in plant growth and development.

Root development.

The root, the underground part of land plants, plays a crucial role in their survival. Numerous microRNAs are essential participants in regulating root development and organization through their interactions with various transcription factors or genetic elements (Singh A et al ., 2016). The importance of miRNA160 lies in its crucial role in promoting root growth and branching through the negative modulation of its target genes ARF10, ARF16, and ARF17 (Wang JW et al ., 2005; Mallory AC et al ., 2005). miRNA164 controls the emergence and branching of lateral roots (LR) by regulating the transcription factor NAM/ATAF/CUC1 (NAC1) (Guo HS et al ., 2005). miRNA167 has been demonstrated to control the development of both primary roots (PR) and lateral roots (LR) by directly affecting IAA-Ala Resistant3 (IAR3) in conditions of elevated osmotic stress . Elevated levels of IAR3 in Arabidopsis in response to high osmotic conditions result in the inhibition of primary root development and enhanced lateral root formation, while the iar3 mutant displays reduced lateral root growth, suggesting that IAR3 serves as a facilitator for adjusting root growth in response to high osmotic stress (Kinoshita N et al ., 2012). miRNA167 regulates ARF6 and ARF8, both are positive regulators of adventitious root growth (Gutierrez L et al ., 2009). ARF17 functions as a suppressor of adventitious root formation, leading to an interplay between the miRNA-mediated pathway and the regulation of root growth in Arabidopsis. TRANSPORT INHIBITOR RESPONSE 1 (TIR1) and AUXIN SIGNALING F-BOX 2 (AFB2) has been known to be cleaved by miRNA393 and hence regulates LR growth (Meng, Y et al ., 2011; Chen et al ., 2009). miRNA390 facilitates the formation of a different type of small RNA called transacting small interfering RNA (ta-siRNA) by cutting TAS3 derived pri-RNA, resulting in the production of tasiR-ARF (ta-siRNA targeting ARF transcripts). tasiR-ARF then proceeds to cleave ARF2, ARF3, and ARF4 targets, subsequently controlling the auxin gradient and lateral root (LR) development (Yoon et al ., 2010). miRNA828 targets TAS4 mRNA resulting in the generation of ta-siRNA. The ta-siRNA derived from the TAS4 region acts on the MYB transcription factor, controlling the development of root hair patterns (Xia et al ., 2012). miRNA408 and miRNA528 are responsible for targeting transcripts of CUPREDOXIN, thereby controlling the processes of root cap formation, lateral root development, and root elongation (Liu et al ., 2008). miRNA165/166, along with its target genes, plays a crucial role in the differentiation of vasculature and the growth of roots (Carlsbecker A et al ., 2010).Studies have shown that root growth regulation by miRNA165/166 has been done through phytohormonal crosstalk (Singh A et al ., 2017). In the Arabidopsis root system, the SHORT-ROOT (SHR) protein undergoes movement from the stele to the endodermis, where it triggers the activation of SCARECROW (SCR) expression. Through the utilization of in situ

hybridization and miRNA sensor experiments, it has been demonstrated that SCR and SHR play a role in transcriptionally initiating the expression of MIR165a and MIR166b within the endodermis. Mature miRNA165/166 is observed to undergo radial movement from the endodermis in a bidirectional manner, leading to the degradation of transcripts of Class III HOMEODOMAIN-LEUCINE ZIPPER (HD–ZIP III) and consequently causing variations in the accumulation of target mRNA within the root vasculature (Carlsbecker A et al ., 2010).

In Arabidopsis, miRNA396 has been identified as a regulator of the stem cell niche (SCN) through its targeting of *GROWTH RESPONSE FACTORS (GRFs*), thereby influencing cell division (Bazin J et al ., 2013; Rodriguez RE et al ., 2015). Within the meristem niche, the activation of miRNA396 by PLT serves to reduce the expression of GRFs, thereby guaranteeing the effective functionality of PLT in delineating the meristem region within the root (Rodriguez RE et al ., 2015). In the past, it has also been mentioned that miRNA171 cleaves *HAIRY MERISTEM (HAM)* (Llave C et al ., 2002; Engstrom EM et al ., 2011).

At advanced phases of development, the development of both the main and side roots forms the structure of the root system. miRNAs play a role in this progression, specifically in regulating the signaling of the plant hormone auxin (Curaba J et al ., 2014; Wang JW et al ., 2005). Numerous auxin-related miRNAs play a crucial role in regulating root architecture by directly targeting genes from the ARF family. An example of this is miRNA160, which modulates ARF10, 16, and 17, leading to a decrease in root length while promoting the formation of more lateral roots when overexpressed. miRNA167 acts upon ARF6 and ARF8, which operate via the IAA-conjugating enzyme GRETCHEN HAGEN 3 (GH3) to regulate the development of lateral roots (Gutierrez L et al ., 2012; Tian CE et al ., 2004). Another microRNA, known as miRNA847, plays a role in controlling auxin-associated processes during the development of roots by targeting IAA28 (De Rybel B et al ., 2010; Wang JJ et al ., 2015). The upregulation of miRNA847 and the inactivation of IAA28 result in increased and accelerated growth of lateral roots. This phenomenon is in part facilitated by the suppressive influence of IAA28 on GATA23, a factor that determines the characteristics of lateral root progenitor cells (Wang JJ et al ., 2015).

Shoot apical meristem development.

The shoot apical meristem (SAM) performs two main functions: it generates leaves, stems, and floral organs, while also preserving a reservoir of pluripotent cells at its core. The SAM is divided into three distinct functional zones: the central zone (CZ), peripheral zone (PZ), and rib zone (RZ). The CZ consists of slowly dividing pluripotent stem cells, with the PZ surrounding it comprising rapidly dividing cells. Some progenies of the stem cells migrate from the CZ to the PZ, where they give rise to lateral organs. The organizing center (OC), situated beneath the CZ within the rib meristem, plays a crucial role in maintaining the stem cell population (Tian CE et al ., 2004). Stem cells located in the shoot apical meristem (SAM) give rise to a variety of functional cells in the aerial parts of plants. The precise regulation of these cells in terms of both space and time is fundamental in determining the fate of the cells and the development of plant organs (Mayer et al ., 1998; Singh MB et al ., 2006; Fahlgren N et al ., 2007). It has been undoubtedly proved that some miRNAs are participants in SAM development which includes

direct post-transcriptional regulation of key SAM related genes, which acts as mobile signal molecules for stem cell maintenance (Singh MB et al ., 2006; Fahlgren N et al ., 2007; Piriyapongsa J et al ., 2008; Xia R et al ., 2013).

The pathway known as *SHOOT MERISTEMLESS-WUSHEL-CLAVATA* (*STMWUS-CLV)* plays a crucial role in regulating the distinctiveness of meristematic cells within both the shoot apical meristem and the floral meristem. This pathway's impact extends to maintaining the unique characteristics of these cells at a controlled and restricted level within the floral meristem, highlighting its intricate involvement in the development and organization of meristematic tissues. The intricate interplay of *STMWUS-CLV* pathway components underscores the complexity and precision required for the proper functioning and maintenance of meristematic cells in different regions of the plant (Lu et al ., 2019). Various miRNAs play a role in targeting different elements of the STM–WUS–CLV pathway to complete the development and upkeep of SAM. For instance, miRNA394 is responsible for regulating the expression of WUS in the center of SAM. Initially produced in the L1 layer of SAM, miRNA394 moves towards the organizing center via plasmodesmata. This process enables the expression of WUS while also dampening the expression of *LEAF CURLING RESPONSIVENESS (LCR*) (Xia R et al ., 2013). The activity of miRNA394 could be influenced by both its appropriate level and other factors. The gradient of concentration has been observed from the L1 layer synthesis sites towards the organizing center. miRNA165 and miRNA166 stand out due to a slight difference in a single nucleotide, which plays a crucial part in maintaining SAM by regulating the expression of *CLASS III HOMEODOMAIN LEUCINE ZIPPER (HDZIP III)* proteins (Zhang Z et al ., 2012). The interaction between *AGO1* and *AGO10* controls the function of limited miRNA165/166 (Zhou Y et al ., 2015; Baumann K et al ., 2013). In one aspect, *AGO1* decreases the levels of *HD-ZIP III* by encouraging miR165/166 to induce the degradation of its mRNA. Conversely, *AGO10* supports the aggregation of *HD-ZIP III* by sequestering miRNA165/166 (Zhou Y et al ., 2015). *AGO1* is expressed throughout the entire apex, while miRNA165/166, which is expressed in the outer region, moves towards the central meristem region. *AGO10* separates miRNA165/166 due to its strong attraction, leading to an increase in the localized expression of *HD-ZIP III* (Zhou Y et al ., 2015). There is a positive feedback loop between the *REVOLUTA (REV)* (a transcription factor of *HD-ZIP III*) and *AGO10*, where *REV* provides positive feedback to *AGO10*. This loop is essential for maintaining the meristem (Knauer S et al ., 2013).

miRNA164 and its targets, *CUP-SHAPED COTYLEDON1 (CUC1)* and *CUC2*, are significantly involved in ensuring the correct development of organ boundaries during the initial stages of growth.*CUC1* and *CUC2* are responsible for encoding *NAM, ATAF*, and *CUC (NAC)* family transcription factors. These genes are active at organ boundaries, and when both are missing in the cuc1 cuc2 double mutant, there are pronounced boundary issues as the lateral organs fuse together (Gaillochet C et al ., 2015; Prigge MJ et al ., 2006).

Leaf development.

The plant leaf is crucial for carrying out photosynthesis, making it a key player in plant biomass and crop productivity. The development of a mature leaf requires a series of interconnected

processes. It begins with the creation of leaf primordia, which starts from an undifferentiated cell in the peripheral region of the shoot apical meristem (Zhu H et al ., 2011). Throughout plant establishment, boundary cells must delineate leaf primordia from the shoot apical meristem (SAM) and develop in accordance with leaf polarity. It has been shown that the regulatory factors *CUC1* and *CUC2*, along with their controller miRNA164, play a crucial role in influencing leaf development (Raman S et al ., 2008; Aida M et al ., 1997). Leaves emerge from the sides of the shoot apical meristem (SAM) and establish different axes such as proximo-distal, adaxial-abaxial, and medio-lateral before growing through cell division and expansion. Three pathways, including CLAVATA (CLV)-WUSCHEL (WUS), KNOTTED-LIKE HOMEOBOX (KNOX)-ASYMMETRIC LEAVES1 (AS1) in Arabidopsis, ROUGH SHEATH2 (RS2) in maize, and PHANTASTICA (PHAN) in snapdragon, collectively known as the AS1/RS2/PHAN (ARP) pathway, play roles in determining leaf polarity and SAM maintenance(Guo et al ., 2008; Tabata et al ., 2010; Reinhardt et al ., 2000; Fleishon et al ., 2011). In addition, *HD-ZIP III-KANADI* proteins work in a sequence along three axes to ensure the sturdy growth and development of leaves. The formation of leaves is controlled by inhibiting *Class I KNOX (KNOXI)* genes through two pathways. One pathway relies on plant hormones, where the location of leaf primordium initiation is determined by auxin transport and accumulation, while a low ratio of cytokinin (CK) to gibberellin (GA) supports SAM maintenance(Guo et al ., 2008; Choudhary et al ., 2021). The ARP genes-dependent pathway involves genes that code for MYELOBLASTOSIS (MYB)-domain TFs and are active in lateral organ founder cells. AS1 brings together a repressor complex containing the *LATERAL ORGAN BOUNDARIES* domain protein, AS2, which attaches to the promoter area of *KNOX* genes (Timmermans et al ., 1999).

The adaxial surface of a leaf is defined by the restricted activity of certain genes such as *PHABOLOSA (PHB)* and *PHAVOLUTA (PHV)* from the *HD-ZIPIII* family. miRNA165 or 166 plays a role in controlling the activity of these genes in the adaxial region by binding to their transcripts. Interestingly, miRNA165/166 is initially expressed in the abaxial region[Mallory AC et al ., 2004). Mutational analysis supports the idea, as shown by the phb-1 mutant of Arabidopsis and the RDL1 maize mutant, which exhibit a distinct defect in leaf polarity. This is due to abnormalities in the binding sites of the *PHB* and *RDL1* genes(Li L et al ., 2004; Kidner CA et al ., 2004). Moreover, to control the *HD-ZIPIII* transcripts, it is necessary for miRNA165/166 action to involve *AGO1*(Liu et al ., 2009c). *AGO1* mutant explained the necessity of AGO1 for PHB localization in the adaxial portion of leaves (Liu et al ., 2009c). Just like how *AGO1* is required, localization of *AGO10* is necessary on the adaxial side of leaves to restrict the acellular independent miRNA165/166 activity and to maintain the accumulation of *HD-ZIP III* mRNA in this region(Chitwood DH et al ., 2009). Regulation of miRNA165/166 expression is controlled by additional miRNAs and tasiRNA (Trans acting siRNA). The presence of tasiRNAs leads to the localization of *AUXIN RESPONSE FACTOR 3 (ARF3)* and *ARF4* in the abaxial region of leaves, where they inhibit translation. ARF3 and ARF4 collaborate in an auxin-dependent manner to enhance the transcription of miRNA165/166(Fahlgren N et al ., 2006; Nogueira FT et al ., 2007). *ARF3* and *ARF4* function in an auxin-dependent manner to increase the transcription of miRNA165/166 (Iwakawa H et al ., 2007). In the adaxial region, miRNA390 controls the expression of tasiRNA while AGO7 is specifically expressed in this area (Fahlgren

N et al ., 2006). This leads to an interaction between miRNA390, tasiRNA, and AGO7, which limits the activity of miRNA165/166 in the abaxial part of the leaf, allowing HDZIPIII to be expressed in the adaxial region.Additionally, the ASYMMETRICA LEAVES 1 (AS1) and AS2 transcription factors complex play a role in controlling the miRNA390 and ARF genes as part of an upstream mechanism (Machida C et al ., 2015; Miyashima S et al ., 2013). Likewise, the miRNA165/166 and miRNA390 are involved in coordinating other developmental processes like lateral root growth and root architecture(Marin E et al ., 2010a; Xia R et al ., 2017).

miRNAs play a role in the formation of leaf lamina. The relationship between auxin and *CUC2* is essential for creating serrations on leaves in Arabidopsis. *CUC2* is found in the depressed part of the leaf, influencing auxin to move towards the neighboring raised area to inhibit CUC2 expression (Nikovics K et al ., 2006). miRNA164 controls the expression of *CUC2*, with the mutation of the miRNA164 binding site leading to an even margin seen in mutant goblet tomatoes and Arabidopsis(Berger Y et al ., 2009; Blein T et al ., 2008). In the case of compound leaves, the collaboration between *CUC2* and miR164 is crucial, with *CUC2* being involved multiple times(Koyama T et al ., 2010). The transcription factors family *TEOSENTE BRANCHED 1*, *CYCLOIDEA AND PCF (TCP)*regulate the activity of miRNA164 and consequently influences the expression of *CUC*(Rubio-Somoza I et al ., 2014). In addition to its indirect impact on *TCP, TCP4* can directly impede the dimerization and transcription of *CUC2*. The SPL protein reduces the interaction between *TSP4* and *CUC2*. As *SPLs* become more mature, the rise in their levels results in a greater leaf complexity due to increased *CUC2* activity(Palatnik JF et al ., 2003). Furthermore, miRNA319 controls *TCP4*, as shown by the intense serrated leaf margins in miRNA319 mutant plants(Palatnik JF et al ., 2007; Ori N et al ., 2007). The LANCEOLATE mutant serves as a significant illustration with an abrupt miRNA319 binding site on the *TCP* gene. These mutants exhibit simple leaves and are incapable of producing the usual compound leaves(Ori N et al ., 2007). *GROWTH REGULATING FACTORs (GRFs)* are transcription factors that also play a role in controlling leaf shape by regulating cell elongation and division. Mutants of Arabidopsis with mutations in GRF1, GRF2, and GRF5 experience notable increases in leaf size, while mutants with loss of function have notably smaller leaves(Horiguchi G et al ., 2005; Kim JH et al ., 2003). In Arabidopsis, miRNA396 is required to be expressed in the distal part, limiting the GRF activity to the proximal area of young leaves. As leaves mature, increased miRNA396 production leads to decreased GRF levels, halting further growth of the leaf blade(Rodriguez RE et al ., 2010). The miRNA396-GRF pathway helps with both upward and downward growth in leaves, allowing for bidirectional growth. Typically, miRNA396 is found in the area where the leaf finishes growing, rather than in the region where it is actively growing (Gupta M et al ., 2015). Figure 2 shows the different miRNAs that plays a part in the leaf development.

Vascular development.

Plants generally use xylem and phloem to transport water, nutrients and carbohydrates throughout the plant system. This whole vascular bundle mainly consists of three main components: xylem, procambium/cambium, phloem. In case of model plant

Arabidposisthaliannathe HD-ZIP III gene family is strongly present in the vascular bundles of root stem and leaves. miRNA165 when overexpressed in *Arabidopsis thaliannareduces* the transcription level of majorly all members of the *HD-ZIP III* family, which helps in regulating the polar differentiation of vascular tissue as well as affecting plant morphogenesis(Zhong, R et al ., 1999; Kang et al ., 2002; Zhou et al ., 2007; Muraro et al ., 2014; Du et al ., 2015; Jia et al ., 2015). It has been noted that miRNA166 regulates the generation of phloem and xylem cells by controlling the *Homeobox 15 protein (ATHB15)* in *Arabidopsis thalianna.*In majority of plant species, it has also been stated that the target region of miRNA165/166 in class *HD-ZIP III* genes is highly preserved. Hence, this shows the importance of the mechanism in plant growth and evolution(Kim et al ., 2005; Floyd et al ., 2004).

Certain miRNAs have been known to relate to the synthesis of cell walls and development of fibres to the plant(Kim et al ., 2005). There have been studies reporting a novel miRNA (miRNA 857) which has been playing a critical role in formation of secondary walls in vascular tissues. This novel miRNA controls the expression of putative laccase, *LACCASE7* which is a member of the laccase gene family, which at the transcriptional level influences lignin content(Zhao et al ., 2015).

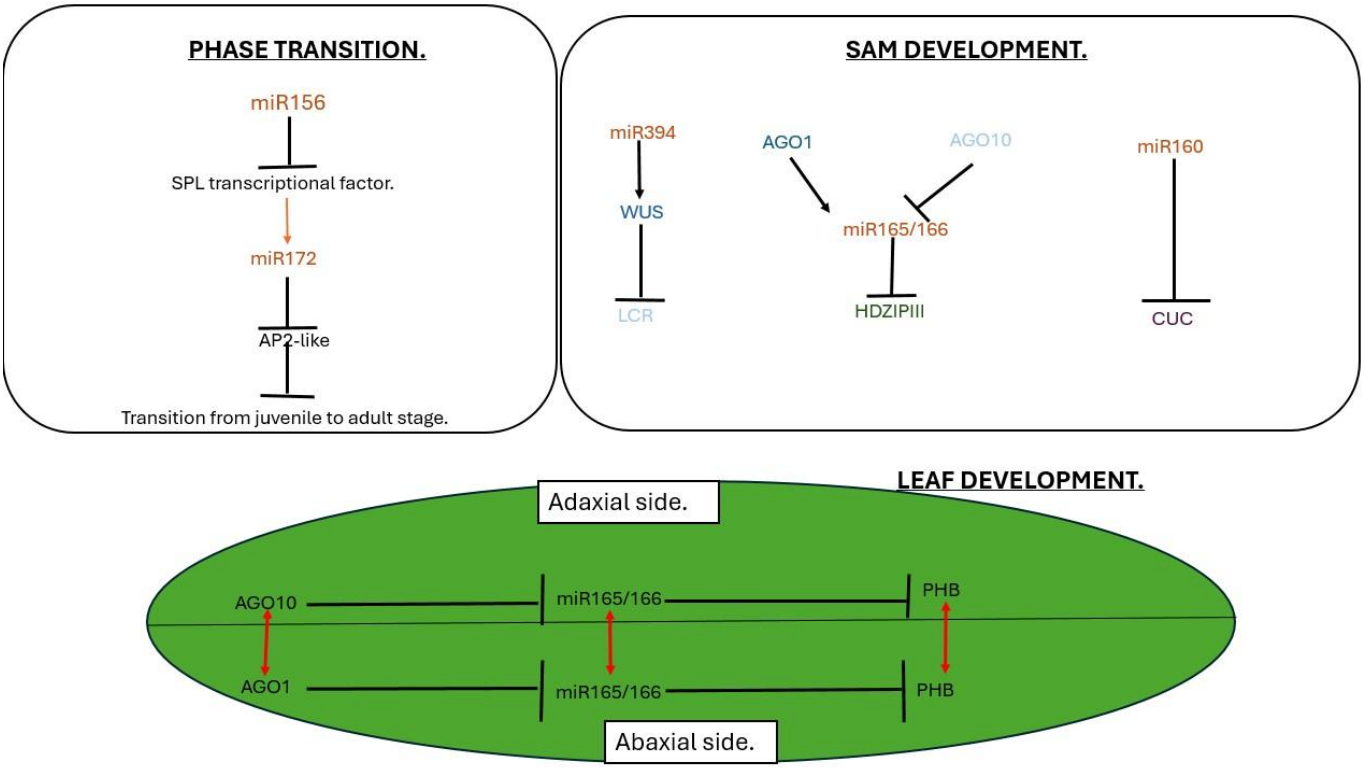

Fig 2: Schematic diagram representing the role of miRs in plant development.

Flowering phase development.

Flowering in plants plays a crucial role in their evolutionary process and the ability to reproduce. The transition from being a juvenile plant to reaching adulthood and then moving on to the reproductive stage is a significant journey that plants must undertake to ensure successful reproduction. Throughout this journey, plants regulate the expression of essential flowering-time

genes with precision, both at the transcriptional and post-transcriptional levels. miRNAs associated with flowering-time play a pivotal role as they can act as both positive and negative regulators in the plant's development, guiding it through the transition from vegetative growth to the reproductive phase. The impact of these miRNAs and their interactions with their target genes not only affect the flowering process but also engage in a complex interplay with other miRNA pathways. This intricate network of interactions involves biochemical signals and environmental cues, all working together to coordinate the timing of flowering in plants.

In *Arabidopsis thalianna,* the change from vegetative phase to reproductive phase is expedited by a group of transcription factors which are specific to the plant kingdom known as *SPL/SPB* proteins. During the juvenile development stage the expression of SPL/SPB proteins are repressed by miRNA156 and miRNA157. When the levels of miRNA156 and miRNA157 decrease there is an increase in the amount of *SPL/SPB* proteins, which triggers the shift from vegetative phase to reproductive phase as shown in Fig: 2 (Xu et al ., 2016a; He et al ., 2018; Fouracre et al ., 2021). The most important regulatory gene which overlooks the plant growth cycle is miRNA156. miRNA156 plays its role by targeting the *SPL (Squamosa Promoter binding protein- Like)* transcription factors (He et al ., 2018). Delayed flowering period in *Arabidopsis thalianna*was acheived by manipulating the expression levels of miRNA156, which lead to subsequent downregulation of *SPL3/5*. Whereas the downregulation of *SPL9* and *SPL15* resulted in laconic leaf plastochrons, lethargic growth and glut of leaves in *Arabidopsis thalianna*(Schwab et al ., 2005; Wu et al ., 2006; Xu et al ., 2016b; Zhang et al ., 2019). Studies have reported that the accurate negative modulation of miRNA156 on *SPL3* have a clear-cut impact on flowering phase transition mechanism on *Arabidopsis thalianna* by inflicting the expression of *FT* gene in leaves, which results in delayed flowering(Kim et al ., 2012). Further studies have elucidated that the decrease in miRNA156 is not unforeseen on the absolute age of the plants but is tangled with the physiological age of the plants(Cheng et al ., 2021b).

miRNA172 is like miRNA156 in the aspect that they both regulate flowering time as well as development of floral organs through the degeneration and reticence of target mRNA (Jung et al ., 2007). miRNA172 plays a central role in coordinating the transition of plant development from juvinile stage to reproductive stage by inflecting *AP2 like* genes which contains S*M-LIKE 2*, *SCHNARCHZAPFEN* and *TARGET OF EARLY ACTIVATION TAGGED 1/2/3*. miRNA172 exerts influence on various other aspects of the plant physiology such as flowering time, flower organ morphogenesis as well as overall plant development with the regulation of *AP2* transcription factors(Aukerman et al ., 2003). Notably, the overexpression of miRNA172 in A. thaliana is linked to the acceleration of flowering onset, whereas overexpression of *AP2* genes leads to a delay in the flowering process.

During certain stages of plant development which are under miRNA regulation, it has been observed that there exist a convoluted interplay between miRNA156 and miRNA172. miRNA156 acts to stifle the expression of the *SPL* family whereas, certain SPLs have been observed to augment the expression of miRNA172. Previously studies have mentioned that the miRNA156-SPL-miRNA172 pathway which is present in *Arabidopsis thalianna* plays a key role in the regulation of the change from juvenile stage to adult stage of plants.This pathway can be

dichotomized into two definite modules, the leaf and apical meristem modules.Both modules are characterized with exclusive combinations of *SPL* and miRNA172 encoding gene modules. In case of leaves, the *SPL9*-miRNA172b/c modules oversee the flowering time by inflecting the expression of *FT* gene whereas, in case of apical meristem the *SPL15*-miRNA172d module promote flowering by triggering the expression of *MADS-box* genes. Moreover, the expression of miRNA172 gene is conditional to regulation by ambient temperature and photoperiod(Lian et al ., 2021).

Other miRNAs such as miRNA159 and miRNA319 also play important roles in the convoluted process of flowering development in plants. miRNA159 targets *MYB* transcription factors whereas, miRNA319 targets *TCP (TCP family transcription factor)*transcription factors. Diverse floral developmental disorders such as delayed flowering can be caused by the overexpression of miRNA159 and miRNA319(Palatnik et al ., 2007). Expression of *MYB33* and *MYB65* is regulated by miRNA159. An impairment in miRNA159 can result in a myriad of pleotropic defects which includes stunted growth, curled leaves, abnormalities in sepals, petals and anthers, these have been observed in *Arabidopsis thalianna*(Achard et al ., 2004; Millar et al ., 2005; Tsuji et al ., 2006; Yu et al ., 2012). Moreover, miRNA159 also prevents excessive activation of miRNA156 thereby inflecting the phase transition of *Arabidopsis thalianna,* during its vegetative developmental stage(Guo et al ., 2017). *MYB33* which is the target gene of miRNA159 also plays a critical role in enhancing the transcription of *ABA INSENSITIVE 5 (ABI5)* by directly binding with its promoter site. *ABI5* participates in regulating the change from juvenile to adult stage in *Arabidopsis thalianna*by influencing gene expression in miRNA156-*SPL* pathway (Guo et al ., 2021).

Within the context of A. thaliana, miRNA164 is involved in the regulation of petal numbers and the differentiation of floral organ marginal cells and apical meristem cells by enhancing the accumulation of *CUC* transcription factors at the boundary. Notably, ectopic expression of miRNA164 leads to sepal fusion and a reduction in the number of petals, underscoring its association with flower meristem activity and the precise division of the meristem region(Laufs et al ., 2004; Jung et al ., 2009).

Furthermore, miRNA165/166 contributes significantly to the regulation of flower morphogenesis. The expression patterns of the miRNA166/165 gene vary across different floral organs, with miRNA166a predominantly expressed in stamens, miRNA166b highly expressed in ovules and stigma, and miRNA166d and miRNA165a exhibiting high expression levels in ovules. Conversely, miRNA166g displays a broad expression pattern in the stigma, stamen, and receptacle but not in the ovule(Jung et al ., 2007). In terms of meristem activity control, miRNA165/166 is closely intertwined with meristem formation in floral organs. In Arabidopsis mutants characterized by overexpression of miRNA165/166, severe structural damage is evident in the flowers. For instance, overproduction of miRNA166 in *mum enhancer 1* and *jabba* mutants results in a diminutive pistil population and a reduced number of carpels(Zhang et al ., 2007). The dramatic increase in expression of miRNA396 can result in the bending of stigma in flowers. In A. thaliana, an excessive amount of miRNA167 results in floral defects such as short filaments, anthers unable to release pollen properly, and non-germinating pollen grains(Ru et al .,

2006). The target genes of miRNA167, *ARF6,* and *ARF8,* are crucial for regulating pistil and stamen populations. miRNA167 also influences the fertility of male and female flowers in *A. thaliana* (Wu et al ., 2006).

Besides from controlling reproductive organs in *Arabidopsis thalianna*miRs are also known to regulate these organs in other plant species too. Tomato miRNA156b plays a vital role in managing flower and fruit shapes by controlling meristem activity and early fruit development stages. Additionally, in tomatoes, the overexpression of A. thaliana miRNA167a leads to the downregulation of *ARF6* and *ARF8,* causing severe disorders in floral organ development and female gamete fertility(Liu et al ., 2014b). In Petunia and Antirrhinum species, researchers discovered that miRNA169 can partially substitute *AP2* by regulating the transcription factor *NF-YA*, hence impacting flower organ development (Chen et al ., 2004; Cartolano et al ., 2007; Zhao et al ., 2009; Waheed et al ., 2020).

miRNAs also oversee flower and seed production in monocots. In rice, it has been observed that the overexpression of miRNA172 can result in spikelet deletion, malformation in floral organ development, and reduced fertility(Zhu et al ., 2009). OsmiRNA397, expressed at high levels in young rice panicles and grains, enhances grain yield by downregulating its target gene *OsLAC*. Increasing OsmiRNA397 levels can boost grain size and enhance panicle branching(Zhang et al ., 2013). In maize,the critical role of miRNA-targeting *SBP-box* transcription factor tasselsheath4 in maize bract development and meristem boundary establishment in inflorescences(Chuck et al ., 2010).

Conclusion.

MicroRNAs (miRNAs) are crucial components in plant development, playing a key role in regulating various developmental processes such as root development, shoot meristem development, vascular development, flowering development, and phase transition. These small RNA molecules are responsible for precise cleavage of target mRNAs and the production of secondary siRNAs, which together coordinate complex gene regulatory networks that control plant growth and how plants respond to different environmental stimuli. The wide array of functions performed by miRNAs highlights their importance as fundamental regulators in determining plant morphology and physiology. Despite the substantial progress made, there are still gaps in our knowledge regarding the exact mechanisms through which miRNAs carry out their regulatory functions, especially within intricate developmental pathways and in response to environmental signals. It is imperative for future research efforts to concentrate on uncovering the specific targets and regulatory networks influenced by miRNAs in various plant species and across different environmental settings. By doing so, we can enhance our understanding of plant development and potentially leverage miRNAs for enhancing strategies aimed at improving crops.

Author Contributions.

AMP wrote the initial draft, collected the data and prepared the figures and table. VM edited the manuscript, helped in designing the manuscript. All the authors have approved the final draft of the manuscript.

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Conflict of Interest.

The authors declare no conflict of interest.

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