Interplay between miRNAs and IncRNAs: Mode of action and biological roles in plant development and stress adaptation

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Abstract
Plants employ sophisticated mechanisms to control developmental processes and to cope with environmental changes at transcriptional and post-transcriptional levels. MicroRNAs (miRNAs) and long noncoding RNAs (IncRNAs), two classes of endogenous noncoding RNAs, are key regulators of gene expression in plants. Recent studies have identified the interplay between miRNAs and IncRNAs as a novel regulatory layer of gene expression in plants. On one hand, miRNAs target IncRNAs for the production of phased small interfering RNAs (phasiRNAs). On the other hand, IncRNAs serve as origin of miRNAs or regulate the accumulation or activity of miRNAs at transcription and post-transcriptional levels. These IncRNA-miRNA interplays are crucial for plant development, physiology and responses to biotic and abiotic stresses. In this review, we summarize recent advances in the biological roles, interaction mechanisms and computational prediction methods of the interplay between miRNAs and IncRNAs in plants.

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1. Introduction

The expression of genes is often spatiotemporally controlled at transcriptional and post-transcriptional levels. Transcription factors and proteins that remodel and modify chromatin play crucial roles in regulating gene transcription [1,2]. During transcription, pre-mRNAs are subjected to processing such as capping, splicing and adenylation, which provide additional regulations of gene expression. After transcription, the levels and activities of RNAs can be further controlled through RNA modifications, non-coding RNAs (ncRNAs) and various protein factors [3-6]. In eukaryotes, over 90% RNA transcripts do not encode proteins, which are called ncRNAs [7,8]. Some of these ncRNAs are basal components of molecular machineries such as ribosome and spliceosome, while others are important riboregulators of gene expression named regulatory ncRNAs [6,9,10]. Based on the length, the regulatory ncRNAs are classified into long ncRNAs (lncRNAs, greater than 200 nt) and short ncRNAs, including microRNAs (miRNAs), small interfering RNAs (siRNAs) and piwi-interacting RNAs (piRNAs). These regulatory RNAs modulate a variety of biological processes from cell differentiation, organ size and shape determination, to immunity at transcriptional and/or post-transcriptional levels [9,11-13]. Interestingly, the emerging evidence has documented the complex interplay between lncRNAs and short ncRNAs on gene regulation in plants and other eukaryotes [14-16].

To date, thousands of ncRNAs have been identified in plants, such as Arabidopsis [17], rice [18], maize [19], wheat [20], soybean [21], tomato [22], brassica [23], and sorghum [24]. As the two important types of ncRNAs, miRNAs and lncRNAs play critical roles in plant growth, development, biotic and abiotic stress responses such as floret development [25,26], male sterility [27,28], flower time [29,30], grain yield [31,32], fruit ripening [33], leaf morphogenesis [34], trichome formation [35,36], stem elongation [37,38], cell wall biosynthesis [39,40], tillering [41], root architecture [42], nodule formation [43,44] and responses to fungal infection [45], bacterial infection [46], virus infection [47], nematode infection [48], drought [49], cold [50], heat [51], submergence [52,53], salt [54,55], light [56] and nutrient stresses [57-61] (Fig. 1). However, the functional significance and action mechanisms of these regulatory RNAs remain to be deciphered, especially in crops with large and complex genomes. In this mini-review, we will summarize the current advances in the biological functions and action modes of miRNAs and IncRNAs with a focus on their interplays in plants.

2. Biological roles and molecular mechanisms of miRNAs

miRNAs are short (20–24 nucleotides in length) ncRNAs. From interval of 2002 to 2020, 20,388 miRNAs have been annotated in 88 phylogenetically representative plant species [62]. Studies on some miRNAs show that miRNAs regulate almost every biological process of plants from the developmental transition to responses to biotic and abiotic stresses [12,63-66] (Fig. 1). We briefly summarize plant miRNA biogenesis, action and related regulatory mechanisms here, since these aspects of miRNAs have been nicely reviewed [67-71] (Fig. 2). In plants, miRNAs mainly inhibit gene expression at the post-transcriptional level through directly targeting mRNA transcripts for cleavage or translational repression [72].

![Fig. 1. The biological roles of IncRNAs, miRNAs and their interplay in plant growth and development, biotic and abiotic stress. (a) The representative IncRNAs (green), miRNAs (red) and their interactions (blue) regulate plant growth and development such as floret development [25,26], male sterility [27,28], flower time [29,30], grain yield [31,32], fruit ripening [33], leaf morphogenesis [34], trichome formation [35,36], stem elongation [37,38], cell wall biosynthesis [39,40], tillering [41], root architecture [42], and nodule formation [43,44]. (b) The representative IncRNAs (green), miRNAs (red) and their interactions (blue) are involved in biotic and abiotic stress responses such as fungal infection [45], bacterial infection [46], virus infection [47], nematode infection [48], drought [49], cold [50], heat [51], submergence [52,53], salt [54,55], light [56], and nutrient stresses [57-61]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)](2568)
MiRNA biogenesis starts with transcription of primary miRNA transcripts (pri-miRNAs) from miRNA-encoding genes (MIRs) mainly by the DNA-dependent RNA polymerase II (Pol II) [72]. Pri-miRNAs harbor an imperfect stem-loop where the mature miRNAs are embedded. Following transcription, pri-miRNAs are processed into the miRNA/miRNA* duplex in nucleus mainly by the RNase III enzyme, DICER-LIKE1 (DCL1) [73]. Then the miRNA/miRNA* duplex is methylated by HUA ENHANCER 1 (HEN1) to improve its stability and then transported out of nucleus into cytoplasm [74-76]. MiRNA is incorporated into the ARGONAUTE 1 (AGO1) protein complex to form the miRNA-mediated silencing complex (miRISC) for repressing gene expression [77,78]. To ensure the efficiency and accuracy of miRNA biogenesis, a plethora of factors such as chromatin modifiers [79,80], transcriptional factors [81,82], RNA-associated proteins [83-85], and protein kinases [86] are employed to regulate the MIR transcription, pri-miRNA processing, RNA stability, and siRNA actions.

3. Biological roles and molecular mechanisms of lncRNAs

LncRNAs are a large family of non-coding RNAs with the length of more than 200nt. In plants, similar to mRNAs, Pol II-dependent lncRNA maturation requires capping, splicing and addition of a ploy-A tail, while Pol IV/V-dependent ones do not [87,88] (Fig. 2). LncRNAs are divided into three groups, long intergenic ncRNAs (no overlapping with protein-coding genes), long intronic ncRNAs (synthesized from intronic region), and natural antisense transcripts (NATs, synthesized from the opposite strand of the associated genes) according to their positions relative to protein-encoding genes in genomes [89]. In the past decades, great efforts have been made toward the systematic identification and characterization of lncRNAs. For instance, using a reproducibility-based bioinformatics strategy, 6480 lncRNAs were identified from 200 transcriptome data sets in Arabidopsis [17]. Wang et al. identified 37,238 NATs, which are associated with 70% annotated mRNAs,

Fig. 2. The action models of plant lncRNAs, miRNAs and their interplay in diverse biological processes. (a) LncRNAs interact with histone modification complex to regulate histone modification [30,159]. (b) LncRNAs are involved in DNA (de)methylation to regulate gene transcription [27,160]. (c) LncRNAs regulate gene transcription by directly binding to proteins required for promoter activity of target genes [101,102]. (d) LncRNAs interact with alternative splicing factor such as RNA-binding protein to modulate alternative splicing (AS) patterns [97]. (e) LncRNAs mediate protein relocation from nucleus to cytoplasm [161]. (f) miRNAs cleave PHAS transcripts to generate phasiRNAs [28,33]. (g) LncRNAs are cleaved by miRNAs leading to lncRNA degradation [109]. (h) MiRNAs cleave mRNAs to impact gene transcription [44,55]. (i) LncRNAs act as eTMs to inhibit miRNA effect on target mRNAs [42,59].
from Arabidopsis [90]. In cotton, 9240 IncRNAs from 21 tissues were identified by integrating multi-strategy RNA-seq data with a pipeline named plant full-length (PULL) [91]. Using the uniform annotation pipeline, 1,246,372 IncRNAs from 80 plant species have been collected according to 13,834 RNA-Seq datasets in Plant Long noncoding RNA Database (PLnCDb) V2.0 [92]. Many IncRNAs identified by the prediction tools (see below) have been found to play important roles in plant growth and development. For example, in Arabidopsis, based on the prediction of a pipeline integrating Swiss-Prot database and CPC software [93,94], the IncRNA MAS, transcribed from MADS AFFECTING FLOWERING4 (MAF4) locus, was found to be induced by cold and required for activating MAF4 transcription by interacting with WDR5A during vernalization [95]. Arabidopsis IncRNA T5120 obtained by the prediction of CPC and CNIc is activated by NLP7, the master nitrate regulatory transcription factor, and promotes plant growth through regulating nitrate assimilation [57].

Although a large number of IncRNAs have been identified, their biological roles and related molecular mechanisms only start to emerge in plants due to the low expression level compared with mRNAs or miRNAs. Studies show that IncRNAs regulate gene expression in both nucleus and cytoplasm via diversified action modes. In the nucleus, IncRNAs modulate gene expression through affecting chromatin remodeling, epigenetic modifications and alternative splicing [96-98] (Fig. 2). For instance, long intronic ncRNA COLDAIR (COLD ASSISTED INTRONIC NONCODING RNA) controls the transcription of FLOWERING LOCUS C (FLC), which is a key repressor for flowering time [30]. The nuclear-localized COLDAIR is transcribed from a locus within the FLC gene. It physically interacts with a component of polycomb repressive complex 2 (PRC2), and recruit PRC2 to the FLC locus for epigenetic repression during vernalization [30]. Interestingly, the antisense strand of FLC locus encodes another IncRNA named COOLAIR, which interacts with the RNA-binding protein FLOWERING CONTROL LOCUS A (FCA) to represses FLC transcription, accompanied with increased H3K27me3 and decreased H3K36me3 levels in cold condition [99,100]. The COLDAIR-FLC and COOLAIR-FLC modules represent one of the important roles of IncRNAs in the link of environmental signal and plant development. LncRNA ELF18-INDUCED LONG-NONCODING RNA (ELEN1) is induced by the pathogen-associated molecular pattern (PAMP) [101]. ELEN1 directly interacts with the Mediator subunit 19a (MED19a) and promotes its enrichment on PATHOGENESIS-RELATED GENE 1 (PR1) promoter to increase the resistance to bacterial pathogen Pseudomonas syringae pv. tomato DC3000 [102,103]. In the cytoplasm, IncRNAs can inhibit protein translation or act as miRNA mimics to inhibit miRNA activity (Fig. 2). MIKIKI is a root-specific retrotransposon IncRNA in rice [42]. MIKIKI binds and acts as miR171 decoy to inhibit its cleavage on SCARECROW-Like (SCL) mRNAs, leading to the increased cell elongation in root [42].

Despite of their biological importance, IncRNA biogenesis and related regulation mechanisms are still less known. Like the majority of miR genes, IncRNAs are mostly transcribed by RNA Pol II, but sometimes by Pol III or the plant-specific RNA Pol IV/V [104,105]. In tomato, 187 IncRNAs are directly targeted by MADS-box transcription factor RIPENING INHIBITOR (RIN), which is a key factor required for tomato fruit ripening [106], suggesting the importance of transcription regulation in IncRNA biogenesis. In addition, cyclin-dependent kinase C (CDKC2), a component of positive transcription elongation factor b (P-TEFb), is also involved in IncRNA biogenesis [107]. CDKC2 can promote COOLAIR transcription by enhancing RNA Pol II Ser2 phosphorylation, thereby regulating flowering time in Arabidopsis [107]. Interestingly, the biogenesis of IncRNA and miRNA shares some key components in plants. SERRATE, CBP20 and CBP80, which are key components of miRNA biogenesis, act as regulators of IncRNA biogenesis and intron splicing of some intron-containing IncRNAs [17]. However, DCL1, HYL1 and AGO1 are not required for lncRNA accumulation [17].

4. The interplay between miRNAs and IncRNAs

Recent studies have identified the interplay between miRNAs and IncRNAs. Besides serving as targets or origins of miRNAs, some IncRNAs are able to regulate the biogenesis and function of miRNAs (Fig. 2). The interactions between miRNAs and IncRNAs play important roles in regulating various biological process including development, nutrient absorption, biotic and abiotic stresses [108,109](Fig. 1).

4.1. IncRNAs are targets of miRNAs to generate phasiRNAs

LncRNA transcripts can be targeted by miRNAs to generate phased small interfering RNAs (phasiRNAs) [92] (Fig. 2). In phasiRNA biogenesis, RNAs including IncRNAs are first typically cleaved by 22 nt miRNAs. Then the RNA-DEPENDENT RNA POLYMERASES (RDR6) recruited by AGO1-RISC or AGO7-RISC converts the 3′ fragment into double-stranded RNAs (dsRNAs), which are further processed by a Dicer protein to generate duplexes of phasiRNAs [110-112]. The resulting phasiRNAs are loaded into AGO proteins and then direct AGOs to find their target transcripts [113]. In plants, ~15 years ago, a subset of IncRNAs that generate a class of phasiRNAs named trans-acting siRNAs (tasiRNAs) were first identified in Arabidopsis [110-112]. These IncRNAs are targeted by miRNAs including miR173, and miR390, respectively, to produce tasiRNAs [110-112]. Recently, some IncRNAs from reproductive organ were shown to produce reproductive phasiRNAs [114-117]. The targets for these phasiRNAs are largely unknown. However, they may regulate reproductive development, given their enrichment in reproductive tissues.

4.2. LncRNAs regulate pri-miRNA processing

Natural antisense transcripts (NATs) belong to a class of coding or ncRNAs that are divided into two clades, cis-NATs and trans-NATs, according to their derived region in genome [90]. cis-NATs are transcribed from the opposite DNA strands at the same genomic locus, while trans-NATs originated from separate genomic loci [118]. Recent studies have revealed the role of cis-NAT in regulating pri-miRNA processing. cis-NAT398b and cis-NAT398c locate on the complementary strands to MIR398b and MIR398c, respectively [119]. Although the RNAs transcribed from these two loci encode proteins, Core-2/I-branching beta-1,6-N-acetylglucosaminyltransferase and high-affinity nitrate transporter 2.7, they act as IncRNAs in the nucleus to impair the stability and processing of pri-miR398b/c without impacting their transcription [119]. Interestingly, pri-miR398b/c, but not the mature miR398b/c, directly activates NAT398b/c transcription in an unknown mechanism. By this feedback regulatory loop, plant fine-tunes thermostolerance [119], implying the complexity of miRNA-lncRNA interplay. cis-NATs are widely present in plants and often affect the expression level of the associated sense genes. Bioinformatic analysis has identified 22 cis-NATs that show reverse-complementary to MIR genes in Brassica [119], implying that the NAT-miRNA regulatory mechanism may be widely present.

Besides cis-NATs, some ncRNAs form dsRNA structures similar to that of pri-miRNAs to hijack the DCL1 complex, and thereby inhibit miRNA biogenesis. For instance, the transcripts derived from the short-interspersed elements (SINEs) can form a structure similar to pri-miRNAs, which in turn decay HYL1 from pri-miRNA processing [120]. Another example is intron lariat RNAs, the byproducts derived from pre-miRNA splicing, which binds the
DCL1 complex and prevents pri-miRNA processing as the molecular sponge in Arabidopsis [121]. In addition, IncRNAs may impair microprocessor recognition and processing activity by forming IncRNA-miRNA precursor dimer. Actually, in human cells, some IncRNAs have been found to directly bind to miRNA precursors and block their processing to miRNAs by DICER complex [122,123]. However, this kind of miRNA processing-related IncRNAs has not been reported in plants to date.

4.3. lncRNAs act as target mimics of miRNAs

Target mimicry is one of the most important mechanisms of miRNA-lncRNA interplay, by which IncRNAs harboring endogenous target mimic (eTM) sites sequester miRNAs by sequence complementarity to inhibit their effects on target mRNA. Target mimicry is also described as miRNA decoy, miRNA sponge or competing endogenous RNA (ceRNA) in animals [124]. Arabidopsis IPS1 (INDUCED BY PHOSPHATE STARVATION 1) is the first identified IncRNA which pairs with miR399 [59]. Both IPS1 and miR399 are induced by Phosphate (Pi) deficiency. In contrast to the cleavage effect of target mRNA by miRNA, miR399-IPS1 pairing contains a bulge which prevents miR399-mediated IPS1 cleavage, and simultaneously cripples miR399-mediated PHO2 degradation [59]. In maize, a novel IncRNA target of miR399, PLINCR1, is also required for low Pi tolerance [125], suggesting the IncRNA-miR399-PHO2 regulatory module may be a widely mechanism in plant response to Pi deficiency.

Moreover, IncRNA39026 binds miR168a and inhibits its function, which in turn improves tomato resistance to Phytophthora infestans [126]. These results suggest that IncRNAs may modulate various biological processes via hijacking miRNAs. Wu et al. developed a computational method and identified 36 and 189 potential miRNA targets in Arabidopsis and rice, respectively [34]. Since then, additional IncRNAs that potentially decoy miRNAs have been identified in maize [127], cassava [128], tomato [47,129,130], and melon [131]. However, the functional significance of these IncRNA-miRNA interactions still needs to be further analyzed.

4.4. LncRNAs inhibit miRNA expression

Some nuclear-localized lncRNAs regulate gene transcription through mediating chromatin modification. They serve as a bridge between transcription factors and chromatin [30,132,133]. Recent evidences show that the transcription of MIRs can also be regulated by IncRNAs in plants. Tomato Sl-miR482a functions as a negative regulator in immunity against Phytophthora infestans [127] by repressing the expression of NBS-LRR genes [109]. Interestingly, Sl-INC1RNA15492 locates in the reverse strand of Sl-MIR482a and inhibits its transcription [109].

5. Methods to predict the interaction between IncRNAs and miRNAs

Despite the importance of the interplay between IncRNAs and miRNAs, a large portion of IncRNA-miRNA interactions remains to be identified. We summarize the available tools used to identify plant IncRNA-miRNA interactions here.

The prediction of IncRNA-miRNA interactions begins with the identification of miRNAs and IncRNAs. The miRNAs can be identified from the database such as miRBase [134], PmiREN [62], pmiMiRKB [135] and PMRD [136], while IncRNAs can be obtained from the IncRNA database such as NONCODE [137], IncRNaDb [138], GreeNC [139], PNRD [140], and PIncDB [92]. Once miRNAs and/or IncRNAs are identified, their interactions can be predicted with additional bioinformatic tools, such as TargetFinder [141], TAPIR [142], psRobot [143], spongeScan [144], and PetMbaase [145]. Among these tools, TargetFinder, TAPIR and PmiPred require users to supply miRNA and potential target sequences. After sequence loading, these tools use various methods to find miRNA-target interactions. TargetFinder utilizes a FASTA local sequence alignment program to identify miRNA targets [142]. The RNAhybrid algorithm finds the alignment between miRNA and IncRNA sequences that has the minimum free energy, which allows to predict less perfect match targets including IncRNA eTM s [142]. Indeed, using TAPIR, two IncRNA eTMs were identified to act at JA/MeJA biosynthesis in Oolong Tea [146], while 40 IncRNA eTMs of 15 miRNAs were predicted to be involved in early somatic embryogenesis in Dimocarpus longan. In addition to the tools requiring user-prepared libraries, other ones perform prediction via the database-stored libraries. For instance, SpongeScan predicts miRNA response elements (MREs) within IncRNA eTMs, based on sequence complementary with preloaded miRNA library [144]. By cross-species conservation filter, Tarhunter identifies eTMs in 13 plant species [149]. Another tool called psRobot discovers small RNAs with stem-loop precursors (e.g. miRNA) and their target transcripts via a Smith-Waterman algorithm up to 26 plant species [143]. A set of IncRNA eTMs identified by psRobot have been shown to function in responses to tomato yellow leaf curl virus [47]. Based on the predefined scoring schema, PsRNATarget analyzes the complementary match between miRNAs and their target RNAs by evaluating target site accessibility [150]. Using PsRNATarget, Lnc_973 and Lnc_253 have been found to serve as eTMs of ghr-miR399 and ghr-156e in cotton, respectively, to regulate salt stress response [151]. Using PsRobot and PsRNATarget, twelve IncRNAs were predicted to function as eTMs involved in S neb821-induced tomato resistance to M. incognita [48].

Precision and recall rate are two important parameters to evaluate accuracy and sensitivity of the prediction results [152]. A comparison of prediction tools found that Targetfinder has a better efficiency in predicting miRNA targets in Arabidopsis, while PsRNATarget and TAPIR-hybrid perform well in non-Arabidopsis species [152]. The combination of different tools enhances the precision, but may reduce the sensitivity of prediction reducing the numbers of positive predictions [152,153]. For the precise and sensitive prediction, the algorithm of tools, multiple source of sequence and the co-expression miRNAs need to be taken into consideration [154]. Taken together, with the above tools and database, more IncRNA-miRNA interactions will be identified, which shall provide insight into the cross-talk among ncRNAs in various biological process.

6. Future perspectives

miRNAs and IncRNAs play essential roles in regulating various biological processes. The interplay between miRNAs and IncRNAs not only provides additional layers of gene expression, but also contributes to the complexity of biological systems. Technologies based on eTMs such as target MIMICS and short tandem target MIMICS have also been developed to study gene function and to improve agricultural traits such as grain yield and quality, resistance to environmental stresses [59,155-158]. However, studies on the interplay between miRNAs and IncRNAs are still in the
infant stage. Identification of the potential miRNA-lncRNA interaction in various plant species and in various physiological and developmental conditions is still a huge task. Moreover, among identified miRNA-lncRNA interactions, only a few have been analyzed in terms of biological significance. The detailed functional mechanisms for these interactions are still unclear. It will also be interesting to know if these miRNA-lncRNA interactions, related functions and mechanisms are conserved among different plant species. In addition, how various interplays between miRNAs and lncRNAs themselves are modulated at physiological and/or spatiotemporal levels and integrated into gene regulatory networks are still largely unknown. Despite of these challenges, studies on the interplay between miRNAs and lncRNAs will be a rich source for exciting new discoveries, lead to a better understanding of gene regulation network and provide intellectual basis for improving important agricultural traits.

CRediT authorship contribution statement

Xiangxiang Meng: Writing - original draft, Writing - review & editing. Aixia Li: Writing - original draft, Writing - review & editing. Bin Yu: Conceptualization, Supervision, Writing - original draft, Writing - review & editing. Shengjun Li: Conceptualization, Supervision, Writing - original draft, Writing - review & editing. Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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