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Guodong Ren
University of Nebraska-Lincoln, gren2@unl.edu

Bin Yu
University of Nebraska - Lincoln, byu3@unl.edu

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Post-transcriptional control of miRNA abundance in Arabidopsis

Guodong Ren, Bin Yu*

Center for Plant Science Innovation & School of Biological Sciences; University of Nebraska; Lincoln, NE USA

*. Correspondence to: Bin Yu, Email: byu3@unl.edu

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Abstract

MicroRNAs (miRNAs) are a class of small non-coding RNAs (small RNAs) that are 20–24nt in length and predominantly repress gene expression at post-transcriptional levels. They regulate many biological processes including development, metabolism and physiology. Numerous studies have revealed that the steady-state levels of miRNA are under sophisticated control to ensure their proper function. In this review, we summarize recent advances on regulation of miRNA processing and stability in plants.

Plants use multiple mechanisms to refine gene expression in order to maintain their normal development and physiology. miRNAs are repressors of gene expression in plants. They associate with and guide the Agronaute

(AGO) protein to cleave and/or inhibit translation of mRNAs containing their complementary sequences. Since first isolated in 2002,[1-3] hundreds of plant miRNAs have been identified. Some miRNAs are highly conserved among different plant species.[4] These miRNAs regulate the expression of hundreds of genes, most of which are transcription factors involved in various biological processes such as development, metabolism and plant responses to biotic and abiotic stresses.[5,6]

miRNAs are derived from primary transcripts called pri-miRNAs, which are encoded by miRNA genes. Many miRNA genes are located in intergenic regions while a few reside in the introns of host genes. Like mRNAs, pri-miRNAs are mainly transcribed by RNA polymerase II, which are followed by 5′ capping, 3′ polyadenylation and/or splicing.[7,8] A characteristic feature of pri-miRNAs is the presence of imperfect stem-loop structure with long flanking arms (also termed hairpin structure), which can be recognized by RNase III family enzymes.[9] The framework of plant miRNA biogenesis has been established in model plant Arabidopsis thaliana (Fig. 1A). In Arabidopsis, RNase III enzyme DICER-LIKE 1 (DCL1) releases miRNA duplex from pri-miRNAs. The miRNA duplex contains a miRNA strand and a passenger strand called miRNA*.[10] DCL4, a homolog of DCL1, is responsible for the generation of some miRNAs as well.[11] After production, miRNAs are loaded into AGO1 to form an active RNA-induced silencing complex (RISC), while the miRNA* is degraded.[12-14] RISC formation is an ATP-dependent process and requires CYCLOPHILIN 40 (CYP40) and HEAT SHOCK PROTEIN 90 (HSP90)[15-17] (Fig. 1A). Studies have established that miRNA levels depend on the combination effect of biogenesis, RISC loading and degradation. Due to space limitation, we focus

on the regulatory mechanisms on pri-miRNA processing and miRNA turn over in this mini review.

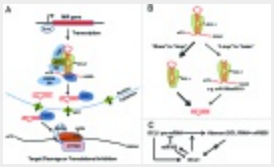

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Figure 1. The miRNA pathway in Arabidopsis. A. miRNA biogenesis. MIR genes are transcribed by Pol II. Like mRNAs, primary transcripts of miRNAs (pri-miRNAs) are 5′ capped and 3′ polyadenylated. The DCL1 complex recognizes hairpin structure of pri-miRNA and catalyzes sequential cleavage to release miRNA/miRNA* duplex. The duplex is then exported to the cytoplasm by HASTY (HST) and loaded into an AGO1 complex to form a functional RISC complex. HEN1 prevents small RNA degradation by the addition of a methyl group to the last nucleotide of miRNA/miRNA* duplex. B. Two ways of pri-miRNA processing in plants. Most pri-miRNAs use a conical "base" to "loop" processing pathway. Instead, a few pri-miRNAs containing unusual long stem structure may employ a nonconical "loop" to "base" processing pathway. C. Autoregulation and feedback regulation of DCL1. DCL1 is required for miR162 maturation, which in turn guides *DCL1* mRNA cleavage to repress *DCL1* expression. In addition, DCL1 acts on its own pre-mRNA to produce miR838, resulting in aberrant *DCL1* RNA that fails to produce functional DCL1.

Regulation of Pri-miRNA Processing

DCL1 forms a complex with the dsRNA-binding protein HYPONASTIC LEAVES1 (HYL1) and zinc-finger protein SERRATE (SE) to process pri-miRNAs.[18-20] HYL1 and SE are required for efficient and accurate processing of pri-miRNAs.[21-25] A majority of pri-miRNAs are first cleaved by the DCL1 complex to release the stem-loop precursors (pre-miRNAs), which are further processed by DCL1 to generate the miRNA duplexes (Fig. 1B).[26,27] This conventional "base" to "loop" processing is similar to those in animals.[28] Studies on several miRNAs reveal that a double strand to single strand transition at 14–17 nt proximal to the mature miRNA:miRNA* duplex is essential for the accurate processing.[26,27,29,30] This stem segment

is believed to be the docking site for DCL1 to execute a first cut, and then a second cut is made by measuring 21nt from the first cut. However, pri-miR159 and pri-miR319 are not processed from "base" to "loop"[31,32] (Fig. 1B). Their processing starts with a cut just below the terminal loop, which is followed by three additional cleavages.[31,32] This variation may be caused by their long upper stem structure.[32] In Arabidopsis, like pri-miR159 and pri-miR319, 17 additional pri-miRNAs contain long stem loop structure and generate two or more miRNAs from the same precursor.[33] It is possible that these precursors may also utilize this non-conical mechanism.

Analysis of pri-miRNA levels using dcl1, hyl1 and se mutants implicates tissue- and precursor-specific patterning of pri-miRNA processing,[34] indicating that the activity of DCL1 complex is regulated.[34] The core component, DCL1 itself is under stringent feedback regulation by one of its product, miR162[35] (Fig. 1C). In addition, DCL1 can act on its own pre-mRNA to release pre-miR838, which produces nonfunctional DCL1 pre-mRNA and therefore, regulates the levels of DCL1[11] (Fig. 1C). The Short Interspaced Elements-Derived RNAs (SINE RNAs) have been shown to control the HYL1 activity.[36] Because SINE RNAs are structurally similar to pri-miRNAs, they will compete with pri-miRNAs for HYL1 and therefore modulate the processing of pri-miRNAs through tissue- or developmental stage-specific expression.[36]

The activity of DCL1 is also controlled by factors other than HYL1 and SE. Gel filtration analysis revealed that the DCL1 complex is about 660kDa in size, suggestive of the existence of additional components.[13] Indeed, the

RNA-binding proteins DAWDLE (DDL) and TOUGH (TGH) are identified as DCL1 interacting proteins[37,38] (Fig. 1A). DDL is a forkhead-associated domain-containing protein and is required for the accumulation of miRNAs.[38] DDL interacts with DCL1 and binds pri-miRNA162b in vitro, supporting its role in facilitating pri-miRNA processing. However, DDL seems to have additional roles in the miRNA pathway, because pri-miRNA levels are reduced in ddl while they are increased in dcl1. However, DDL does not affect the transcription of MIR genes, suggesting that DDL may stabilize pri-miRNAs. TGH contains a G-patch and a SWAP domain in its N-terminus, which are often found in RNA binding and/or processing related proteins.[39] TGH binds both pri-miRNAs and pre-miRNAs and interacts with DCL1, HYL1 and SE.[37] Mutation of TGH impairs DCL1 activities in vitro and reduces the accumulation of miRNAs.[37] In addition, tgh-1 reduces the amount of pri-miRNAs in the DCL1 complex.[37] These facts suggest that TGH may promote DCL1 activity and facilitate the recruitment of pri-miRNAs to the DCL1 complex. Unlike SE and HYL1, TGH may not contribute to the DCL1 processing accuracy as revealed by small RNA deep sequencing analysis.[37] 5′ capping and 3′ adenylation of pri-miRNA may play important roles for miRNA processing. Disruption of either 5′ capping or 3′ adenylation in cdkf;1 or cdkd123 mutant, respectively, leads to the less accumulation of mature miRNAs.[40] In addition, two cap-binding proteins, CBP20/80 have been shown to participate in pri-miRNA processing.[41,42]

miRNA Stability Control

After generation, miRNAs are 2’-O-methylated at 3′ terminal ribose by an

RNA methyltransferase named HUA ENHANCER 1 (HEN1).[43] HEN1 methylates 21–24 nt RNA duplexes with 2 nt overhangs but not single-stranded RNAs (ssRNAs) in vitro.[43,44] Crystal structure analyses of HEN1 reveal that the coordinated action of multiple RNA binding domains and the methyltransferase domain measures the length of the RNA duplex and determines the substrate specificity.[45] In hen1 mutant, miRNAs and small interfering RNAs (siRNAs, another class of endogenous non-coding small RNAs represses gene expression) are reduced in abundance and become heterogeneous in size.[46] Furthermore, siRNAs compete with miRNAs for HEN1 mediated methylation since depletion of siRNAs in weak alleles of hen1 increases overall methylated miRNAs levels.[47] The heterogeneity is caused by trimming and tailing activities at 3′ ends of the unmethylated small RNAs, while the 5′ ends are not affected by hen1 mutation.[46] Uridine is preferentially used for the addition of untemplated nucleotides and thus the tailing process is sometimes referred to as uridylation.[46] These results demonstrate that methylation protects miRNAs and siRNAs from 3′ degradation and uridylation.[46] Recently, both forward and reverse genetics identified HEN1 SUPRESSOR1 (HESO1) as an enzyme uridylating miRNAs in hen1.[48,49] The facts that miRNA abundance is increased in heso1 hen1 and decreased in hen1 overexpressing HESO1 demonstrate that uridylation promotes degradation. The degradation should be highly processive as no degradation intermediates is detected in vivo. It's worth noting that additional enzyme(s) responsible for miRNA uridylation must exist since miRNA U-tail is not abolished in hen1 heso1. However, T-DNA mutants of all other nine putative terminal nucleotidyl transferases failed to rescue hen1–8 phenotype, indicating that they may only play a minor role and their

function in miRNA uridylation may be only detectable in the absence of HESO1. One effective way to test this is to introduce one or more of these mutations into hen1heso1. Also, a role of HESO1 in HEN1 competent background is unknown. It is possible that HESO1 acts on some small RNAs to regulate their stability and/or function. In addition, HESO1 may have RNA substrates other than small RNAs. In support of these, MUT68, also encodes a terminal nucleotidyl transferase, has dual roles in adenylating 5′ fragment of target RNA generated by AGO cleavage and uridylating unmethylated miRNAs in green algae Chlamydomonas reinhardtii.[50,51]

In hen1, the 3′-to-5′ truncated miRNAs are also observed. Their abundance is increased in hen1 heso1 relative to hen1. This result suggests that the 3′-to-5′ trimming activity most likely competes with U-tailing activity for unmethylated small RNAs. The enzymes responsible for 3′-to-5′ trimming in hen1 are currently unknown. A potential candidate is the small RNA-degrading nuclease (SDN), which degrades small RNAs from 3′-to-5′ in vitro.[52] Arabidopsis encodes a total of four SDN family proteins. Simultaneously knock-down of several SDN genes causes elevated miRNA levels and pleiotropic phenotypes, demonstrating that SDN has a role in miRNA turnover.[52] Another potential candidate for 3′-to-5′ trimming of miRNAs is homolog protein of Nibbler. Nibbler catalyzes 3′-to-5′ trimming of miRNAs in animals.[53,54]

Future Perspective

The core question in pri-miRNA processing is how DCL1 recognizes and processes pri-miRNAs precisely and efficiently. Analyses of the detailed function of DCL1 complex components will help us address this. A

characteristic feature of DCL1 complex components is their ability of RNA binding. High-throughput sequencing of RNAs isolated by cross-linking immunoprecipitation (HITS-CLIP)[55] is a powerful tool for the whole genome identification of binding sites by these proteins. Recent studies have also uncovered diverse miRNAs modifications and their roles in stability control. A key challenge in the identification of enzymes in miRNA decay is that multiple enzymes often function in parallel and/or redundantly. In addition, some of the decay enzymes may be essential for multiple RNA degradation and knockout mutants may be non-viable, which makes them difficult to be discovered. In conclusion, the knowledge on the regulation of miRNA abundance will undoubtedly increase our ability to manipulate RNA silence and gene regulation for both agronomic and therapeutic purposes.

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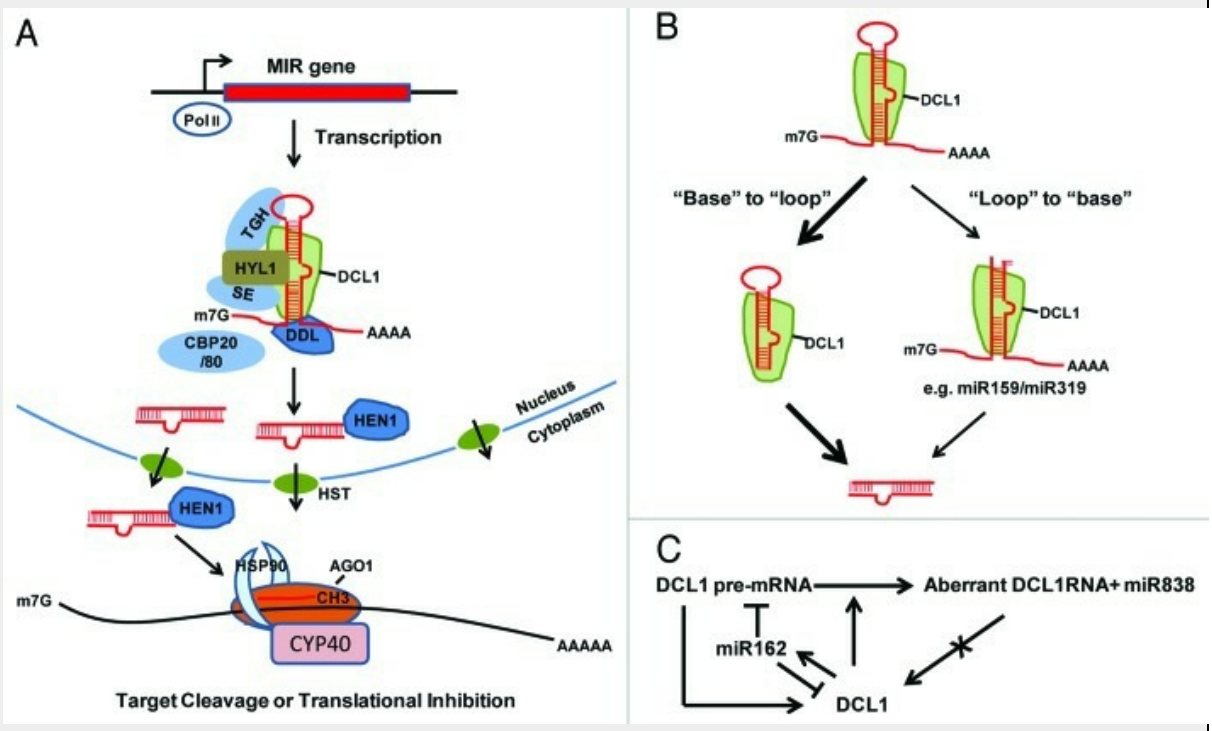

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