

Role of non-coding RNAs in plant immunity

Li Song¹, Yu Fang¹, Lin Chen¹, Jing Wang^{1,*} and Xuewei Chen^{1,*}

¹State Key Laboratory of Crop Gene Exploration and Utilization in Southwest China, Rice Research Institute, Sichuan Agricultural University at Wenjiang, Chengdu, Sichuan 611130, China

*Correspondence: Jing Wang (jingwang406@sicau.edu.cn), Xuewei Chen (xwchen88@163.com)

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ABSTRACT

Crops are exposed to attacks by various pathogens that cause substantial yield losses and severely threaten food security. To cope with pathogenic infection, crops have elaborated strategies to enhance resistance against pathogens. In addition to the role of protein-coding genes as key regulators in plant immunity, accumulating evidence has demonstrated the importance of non-coding RNAs (ncRNAs) in the plant immune response. Here, we summarize the roles and molecular mechanisms of endogenous ncRNAs, especially microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs), in plant immunity. We discuss the coordination between miRNAs and small interfering RNAs (siRNAs), between lncRNAs and miRNAs or siRNAs, and between circRNAs and miRNAs in the regulation of plant immune responses. We also address the role of cross-kingdom mobile small RNAs in plant–pathogen interactions. These insights improve our understanding of the mechanisms by which ncRNAs regulate plant immunity and can promote the development of better approaches for breeding disease-resistant crops.

Key words: non-coding RNAs, miRNA, lncRNA, circRNA, plant immunity

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INTRODUCTION

Plants are sessile organisms that are constantly attacked by various pathogens, including bacteria, fungi, and viruses. In the face of these biotic stresses, plants have evolved two layers of immune response: pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI) and effector-triggered immunity (ETI) (Chisholm et al., 2006; Jones and Dangl, 2006; Peng et al., 2018). PAMPs on the cell surface are recognized by plant membrane-located pattern recognition receptors (PRRs) to activate the basal immune response (Jones et al., 2016). ETI is mediated by resistance (R) proteins, commonly intracellular nucleotide-binding/leucine-rich-repeat receptors (NLRs), that specifically recognize their cognate microbial effectors directly or indirectly to induce a robust resistance response (Bialas et al., 2018). Emerging evidence has shown that PTI and ETI share largely overlapping signaling networks and downstream responses (Tsuda et al., 2009; Dodds and Rathjen, 2010; Qi et al., 2011). The concept of three-layer plant immunity has become commonly accepted and involves a recognition layer, a signal-integration layer, and a defense-action layer (Wang et al., 2019). The recognition layer includes PRRs that recognize apoplastic effectors and intracellular receptors that recognize intracellular effectors or host proteins. The signal-integration layer accepts signals from the recognition layer and transmits a set of signals to the defense-action layer. The defense-action layer consists of diverse responses,

including the deposition of callose, the production of reactive oxygen species (ROS), and the induction of *pathogenesis-related (PR)* genes (Wang et al., 2019).

Previous studies have focused on the function of protein-coding genes in biotic stress-response signal transduction. Recent advances in high-throughput gene sequencing technology and large-scale transcriptomic analyses have revealed that a large proportion of the eukaryotic genome is transcribed into RNAs that do not encode proteins. These transcripts are called non-coding RNAs (ncRNAs). Based on their length, ncRNAs are mainly classified into small ncRNAs (sRNAs) (18–30 nt), medium-sized ncRNAs (31–200 nt), and long ncRNAs (lncRNAs) (>200 nt) (Wang et al., 2017a). Plants have two main classes of sRNAs, microRNAs (miRNAs) and small interfering RNAs (siRNAs), which are distinguished by their modes of biogenesis and mechanisms of action. miRNAs are usually 21–24 nt long and are generated from RNAs with imperfectly base-paired hairpin structures. siRNAs are generated from perfectly complementary long double-stranded RNAs (dsRNAs) and may require RNA-dependent RNA polymerases (RDRs) (Borges and Martienssen, 2015). Also, circular RNAs (circRNAs) are a novel type of ncRNA that arises when pre-

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mRNA is spliced in a reversed order and the 3' and 5' ends are covalently closed (Patop et al., 2019).

Many studies have revealed that ncRNAs play critical roles in plant development, including meristem organization, leaf development, and flowering (Knauer et al., 2013; Csorba et al., 2014; Kidner and Martienssen, 2004; Yang et al., 2019a). Emerging evidence has also shown that ncRNAs are responsive to different environmental stimuli and are implicated in the modulation of gene expression against abiotic and biotic stresses (Hou et al., 2019a; Jabnour et al., 2013; Li et al., 2018; Kinoshita et al., 2012; Song et al., 2019; Zhao et al., 2018). In this review, we summarize current advances in the regulatory roles of ncRNAs in plant immunity against biotic stress, and we discuss their implications for future studies.

ncRNAs THAT TARGET REGULATORS OF IMMUNE PERCEPTION AND TRANSDUCTION

Membrane-located PRRs and cytoplasmic NLRs are two types of immune receptors important to plant immune response (Wang et al., 2019). The membrane-located PRRs comprise mainly receptor-like kinases (RLKs) and receptor-like proteins (RLPs), both of which are usually involved in PTI (Macho and Zipfel, 2014). NLRs are another type of plant immune receptor that is usually involved in ETI (Cui et al., 2015). PRRs and NLRs are regulated at the transcriptional, post-transcriptional, and post-translational levels. The downstream signaling components of these receptors include kinases, transcription factors, and other types of proteins. A number of plant ncRNAs directly target the expression of signaling components to regulate immune response (Figure 1; Table 1).

R proteins are responsible for the recognition of effector proteins secreted by pathogens to initiate stronger ETI (Zhou and Zhang, 2020). Several miRNAs have been shown to guide the cleavage of *R* genes, serving to tightly control *R* gene expression to fine-tune the immune response in *Arabidopsis*, *Leguminosae*, *Solanaceae*, and other species. Most of these miRNAs are 22 nt in length and trigger the production of phased siRNAs (phasiRNAs) from their NLR targets (Fei et al., 2013). For example, in *Arabidopsis*, miR472 (a variant of the miR482 family) targets a typical NLR gene (*RPS5*) and promotes its phasiRNA biogenesis to repress ETI-based resistance (Boccaro et al., 2014). In *Medicago truncatula*, miR2118a, miR1507, and miR2109 target the NLR genes *Medtr4g023400*, *Medtr5g071220*, and *Medtr4g014580*, respectively, to trigger widespread phasiRNAs (Zhai et al., 2011). In tobacco, miR6019 and miR6020 guide cleavage of transcripts of the TIR-NB-LRR immune receptor gene *N*, which confers resistance against tobacco mosaic virus (Li et al., 2012; Deng et al., 2018b). In barley, some members of the miR9863 family target a subset of NLR *Mla* alleles to confer race-specific disease resistance against the powdery mildew fungus (Liu et al., 2014). Discoveries in different plant species indicate that several miRNAs target multiple NLR motifs, such as TIR1, kinase-2, and P-loop motifs (Fei et al., 2013). For example, the miR482/2118 superfamily triggers the production of phasiRNAs by targeting the conserved P-loop-encoding sequence in NLR

genes (Shivaprasad et al., 2012; de Vries et al., 2019). These findings suggest that there is a high level of redundancy in the miRNA-mediated suppression of NLR genes.

Some miRNAs silence NLR genes by mRNA cleavage rather than by triggering phasiRNA production to further suppress NLR genes. For example, in soybean, miR1510 targets the NLR gene *16G135500* for mRNA cleavage and negatively regulates plant resistance against *Phytophthora sojae* (Cui et al., 2017b). In apple, Md-miRln11 directly targets the NLR gene *Md-NBS* for mRNA cleavage and compromises plant resistance against apple leaf spot disease (Ma et al., 2014a). These facts suggest that diverse plant species may use a broadly conserved immunity mechanism in which miRNAs directly target NLR genes to regulate the immune response.

Some miRNAs and siRNAs directly target regulators for signal transduction to modulate immunity. In *Arabidopsis*, miR172b enhances the transcription of the immune receptor gene *FLS2* by targeting TOE1 and TOE2, both of which bind directly to the *FLS2* promoter to inhibit its activity (Zou et al., 2018). miR863-3P participates in mRNA cleavage and degradation of two atypical receptor-like pseudokinase genes (*ARLPK1* and *ARLPK2*) that are negative regulators of plant immunity during the early stages of *Pseudomonas syringae* pv. *tomato* (*Pst*) infection in *Arabidopsis* (Niu et al., 2016). The natural antisense transcript-associated siRNA natsiRNAATGB2 silences a gene encoding a pentatricopeptide repeat protein that functions as a negative regulator of RPS2-mediated ETI during infection by *Pst*, which carries the *avrRpt2* effector gene (Katiyar-Agarwal et al., 2006). In tomato, circRNA45 and circRNA47 may act as positive regulators of immunity against *P. infestans* by regulating the expression of miR477-3P and *SpRLK* (Hong et al., 2020). These ncRNAs are elaborate regulators of immune signal transduction to modulate plant immunity.

Many miRNAs and siRNAs target transcription factors to regulate the transcription of defense-related genes. In *Arabidopsis*, miR396 expression decreases during *Plectosphaerella cucumerina* infection, allowing its *GROWTH-REGULATING FACTOR* (*GRF*) transcription factor targets to trigger the reprogramming of gene expression in the host (Soto-Suarez et al., 2017). In rice, miR169 targets *NF-YA* transcription factors to negatively regulate plant immunity against *Magnaporthe oryzae* (Li et al., 2017). miR164a expression is suppressed by *M. oryzae* infection, derepressing its targeted transcription factor *OsNAC60*, which subsequently increases ROS production, callose accumulation, and the expression of defense-related genes to enhance rice immunity (Wang et al., 2018). miR156 negatively regulates rice resistance against bacterial blight by targeting the squamosa promoter-binding protein-like transcription factors *IPA1* and *SPL7* (Liu et al., 2019). The transposable element-encoded siRNA TE-siR815 is generated from the intron of *WRKY45-1* and represses *ST1*, which encodes a leucine-rich repeat receptor kinase-type protein, to attenuate WRKY45-mediated rice resistance against *Xanthomonas oryzae* pv. *oryzae* (Xoo) (Zhang et al., 2016b). These ncRNAs mediate transcriptional reprogramming upon

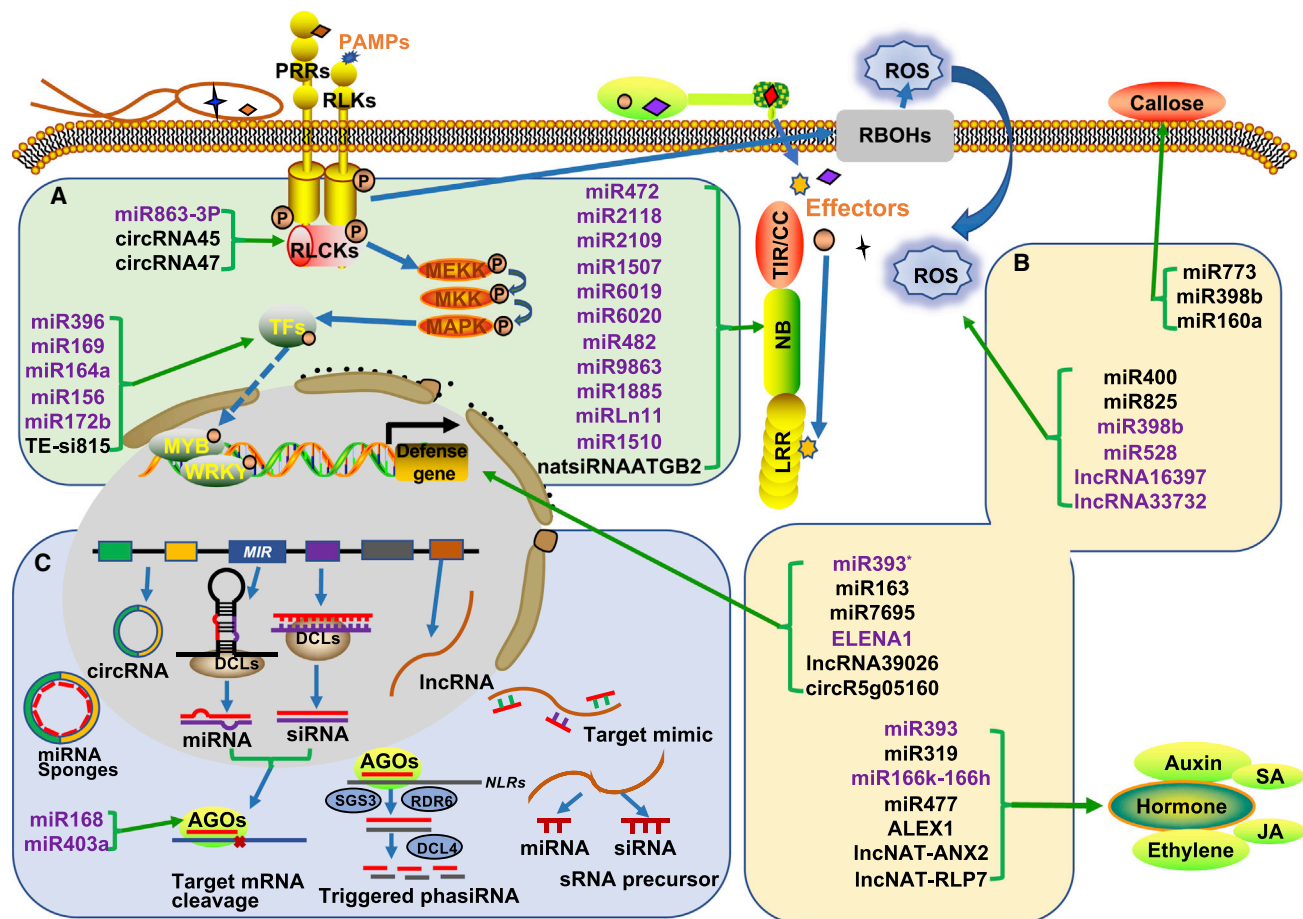


Figure 1. ncRNAs involved in plant immunity and their underlying regulation.

(A) ncRNAs that regulate immune signaling components. Some ncRNAs target immune receptor PRRs and NLRs such as *FLS2* and *RPS5*, which mediate pathogen perception. Other ncRNAs regulate RLCKs and TFs such as *SpRLK* and *WRKY45*, which are involved in immune signal transduction.

(B) ncRNAs that directly or indirectly modulate various biological processes of PTI or ETI response, including ROS accumulation, callose deposition, defense-related gene expression, and plant hormone regulation, to regulate plant immunity.

(C) Coordinated function among ncRNAs in immunity. miRNAs targeting NLR genes can trigger the production of phasiRNAs. lncRNAs mainly serve as target mimics and miRNA/siRNA precursors. circRNAs may act as decoys for miRNAs to upregulate the expression of mRNAs targeted by miRNAs. Abbreviations: PAMPs, pathogen-associated molecular patterns; PRRs, pattern recognition receptors; RLKs, receptor-like kinases; RLCKs, receptor-like cytosolic kinases; TFs, transcription factors; P, phosphorylation; ROS, reactive oxygen species; DCL, DICER-LIKE; AGO, ARGONAUTE; SGS3, SUPPRESSOR OF GENE SILENCING 3; RDR6, RNA-DEPENDENT RNA POLYMERASE 6; phasiRNA, phased secondary small interfering RNA. ncRNAs marked in purple directly regulate immune signaling components and downstream responses, whereas those marked in black have indirect or unknown mechanisms of regulation. Red lines represent miRNAs and siRNAs.

pathogen infection by directly targeting transcription factors to regulate diverse immune responses.

number of ncRNAs play critical roles in PTI or ETI responses by regulating various biological processes (Figure 1 and Table 2).

ncRNAs THAT REGULATE THE PRODUCTION OF DEFENSE MARKERS, HORMONE BIOSYNTHESIS AND SIGNALING, OR RNA-MEDIATED SILENCING

Plant immune response is a complex biological process. Immune signaling typically includes the production of ROS, activation of the MAPK cascade, reprogramming of gene expression (for example, *PR* genes), accumulation of secondary metabolites, and regulation of plant hormone biosynthesis and signaling. A

Many ncRNAs are involved in the regulation of ROS production. In *Arabidopsis*, for example, miR400 guides the cleavage of two pentatricopeptide repeat (*PPR*) genes, resulting in greater ROS accumulation and impaired disease resistance against *Pst* and *Botrytis cinerea* (Park et al., 2014). Compared with wild-type plants, *Arabidopsis* transgenic plants with attenuated miR825 and miR825* levels show higher ROS production and therefore exhibit enhanced resistance against *B. cinerea* (Nie et al., 2019). In rice, miR398b overexpression reduces the transcript levels of genes encoding superoxide dismutases (*CSD1*, *CSD2*, *SODX*, and *CCSD*), leading to elevated ROS production and enhanced plant resistance against *M. oryzae* (Li et al., 2014, 2019). miR528 negatively regulates viral resistance in rice by

Function	ncRNAs	Target	Plant species	Reference
Trigger phasiRNA production	miR472	<i>RPS5</i>	<i>Arabidopsis</i>	Boccaro et al. (2014)
	miR2118/miR2109/miR1507	<i>Medtr4g023400/ Medtr4g014580/ Medtr5g071220</i>	<i>Medicago truncatula</i>	Zhai et al. (2011)
	miR6019/miR6020	<i>N</i> gene	tobacco	Li et al. (2012); Deng et al. (2018b)
	miR482	<i>FRG3 LRR1/LRR2 EU713768</i>	tomato tomato tobacco	Shivaprasad et al., (2012); Ji et al. (2018); de Vries et al. (2018)
	miR9863	<i>MLA1</i>	barley	Liu et al. (2014)
Regulate immune receptor	miR1885	<i>BraTNL1</i>	<i>Brassica rapa</i>	He et al. (2008); Cui et al. (2020b)
	miRLn11	<i>Md-NBS</i>	apple	Ma et al. (2014a)
	miR1510	<i>Glyma.16G135500</i>	soybean	Cui et al. (2017b)
	natsiRNAATGB2	<i>PPRL</i>	<i>Arabidopsis</i>	Katiyar-Agarwal et al. (2006)
	miR172b	<i>TOE1/TOE2</i>	<i>Arabidopsis</i>	Zou et al. (2018)
	lncRNA23468	miR482b	tomato	Jiang et al. (2019)
	lncRNA15492	miR482a	tomato	Jiang et al. (2020)
Regulate receptor-like kinase	miR863-3P	<i>ARLPK1/ARLPK2</i>	<i>Arabidopsis</i>	Niu et al. (2016)
	circRNA45 circRNA47	miR477-3P	tomato	Hong et al. (2020)
Transcription factor	miR396	<i>GRFs</i>	<i>Arabidopsis</i>	Soto-Suarez et al., 2017
	miR169	<i>NF-YAs</i>	rice	Li et al. (2017)
	miR164a	<i>NAC60</i>	rice	Wang et al. (2018a)
	miR156	<i>IPA1</i>	rice	Liu et al. (2019)
	TE-siR815	<i>ST1</i>	rice	Zhang et al. (2016b)
	lncRNA42705 lncRNA08711	mi159	tomato	Cui et al. (2020a)

Table1. ncRNAs that target plant immune signaling components.

Abbreviations: *RPS5*, *RESISTANT TO P. SYRINGAE 5*; *LRR1/2*, LEUCINE RICH REPEAT 1/2; *MLA1*, MILDEW RESISTANCE LOCUS A1; *TNL1*, TIR-NBS-LRR1; *NBS*, NUCLEOTIDE-BINDING SITE; *PPRL*, PENTATRICOPEPTIDE REPEAT-LIKE; *TOE1/2*, TARGET OF EAT1; *ARLPK1/2*, ATYPICAL RECEPTOR-LIKE PSEUDOKINASE 1/2; *GRFs*, GROWTH-REGULATING FACTORS; *NF-YAs*, NUCLEAR FACTOR Y-As; *NAC60*, NAM/ATAF/CUC 60; *IPA1*, IDEAL PLANT ARCHITECTURE1; *ST1*; siR815 TARGET 1.

cleaving *L-ascorbate oxidase* (*AO*) mRNAs, thereby reducing ROS accumulation (Wu et al., 2017; Yao et al., 2019). In addition, the tomato lncRNA16397 induces *GRX* expression to reduce ROS accumulation and cell membrane damage, leading to enhanced resistance against *P. infestans* (Cui et al., 2017a). In tomato, lncRNA33732 is activated by *WRKY1* and induces *RBOH* expression to increase ROS accumulation during early defense against *P. infestans* attack (Cui et al., 2019). These examples suggest that ncRNAs regulate ROS accumulation by directly targeting the cleavage of genes that encode synthetase or scavenger enzymes of ROS to modulate plant immunity.

Induction of *PR* gene expression is observed in many disease-resistant plants. *Arabidopsis* miR393*, the complementary strand of miR393 within the miRNA/miRNA* duplex, contributes to immunity against *Pst* (*avrRpt2*) by targeting the protein trafficking gene *Membrin 12* (*MEMB12*) to promote the secretion of PR1 proteins (Zhang et al., 2011). In the basal defense of *Arabidopsis* against *Pst*, miR163 acts as a negative regulator by

targeting *PXMT1* and *FAMT* to inhibit the expression of defense genes, including *PR1* and *NPR1* (Chow and Ng, 2017). Also, an *elf18*-responsive lncRNA (*ELENA1*) induces *PR1* expression by directly interacting with mediator subunit 19a (*MED19a*) to enrich *MED19a* on the *PR1* promoter in *Arabidopsis* (Seo et al., 2017). Furthermore, *ELENA1* dissociates the *FIB2/MED19a* complex and releases *FIB2* from the *PR1* promoter to enhance *PR1* expression, thereby increasing plant resistance against *Pst* (Seo et al., 2019). In rice, *osa-miR7695* targets an iron transporter gene that encodes natural resistance-associated macrophage protein 6 (*OsNramp6*) and enhances the expression levels of defense-related genes, including *PR* genes and diterpenoid biosynthetic genes (Campo et al., 2013; Sanchez-Sanuy et al., 2019). In tomato, lncRNA39026 induces the expression of *PR* genes such as *PR1* and *PR2* to increase plant resistance against *P. infestans* (Hou et al., 2020). In addition, the overexpression of a circRNA (circR5g05160) in rice enhances plant resistance against *M. oryzae* by upregulating defense-related genes, including *PR10b*, *PBZ1*, *HSP90*, and *SGT1* (Fan et al., 2020). Thus, many ncRNAs regulate the expression of *PR*

Function	ncRNAs	Target	Plant species	References
ROS accumulation	miR400	<i>PPR1/PPR2</i>	<i>Arabidopsis</i>	Park et al. (2014)
	miR825	<i>At5g38850/At3g04220</i>	<i>Arabidopsis</i>	Nie et al. (2019)
	miR398b	<i>CSD1/CSD2/SODX</i>	<i>Arabidopsis</i> /rice	Li et al. (2014); Li et al. (2019)
	miR528	<i>AO</i>	rice	Wu et al. (2017); Yao et al. (2019)
	lncRNA16397	<i>SIGRX21/SIGRX22</i>	tomato	Cui et al. (2017a)
	lncRNA33732	<i>RBOH</i>	tomato	Cui et al. (2019)
PR gene expression	miR393*	<i>MEMB12</i>	<i>Arabidopsis</i>	Zhang et al. (2011)
	miR163	<i>PXMT1/FAMT</i>	<i>Arabidopsis</i>	Chow and Ng (2017)
	miR7695	<i>Nramp6</i>	rice	Campo et al. (2013); Sanchez-Sanuy et al. (2019)
	<i>ELENA1</i>	<i>PR1</i>	<i>Arabidopsis</i>	Seo et al. (2017); Seo et al. (2019)
	lncRNA39026	miR168a	tomato	Hou et al. (2020)
	circR5g05160		rice	Fan et al. (2020)
Callose deposition	miR773	<i>MET2</i>	<i>Arabidopsis</i>	Salvador-Guirao et al. (2018a)
	miR160a	<i>ARF16</i>	rice	Li et al. (2010)
Hormone	miR393	<i>TIR1/AFB2/AFB3</i>	<i>Arabidopsis</i>	Navarro et al. (2006)
	miR319	<i>TCP21</i>	rice	Zhang et al. (2016a); Zhang et al. (2018b)
	miR166k-166h	<i>EIN2</i>	rice	Salvador-Guirao et al. (2018b)
	miR477	<i>CPB60A</i>	cotton	Hu et al. (2020)
	<i>ALEX1</i>		rice	Yu et al. (2020)
	<i>GhIncNAT-ANX2</i> <i>GhIncNAT-RLP7</i>	<i>LOX1/LOX2</i>	cotton	Zhang et al. (2018a)
miRNA biosynthesis pathway	miR863-3P	<i>SERRATE</i>	<i>Arabidopsis</i>	Niu et al. (2016)
	miR168	<i>AGO1</i>	rice	Wu et al. (2015)
	miR444	<i>MADS23/27a/57</i>	rice	Wang et al. (2016a)
	miR403a	<i>AGO2</i>	tobacco	Diao et al. (2019)

Table 2. ncRNAs that affect other aspects of the immune response.

Abbreviations: PPR1/2, PENTATRICOPEPTIDE REPEAT 1/2; CSD1/2, COPPER/ZINC SUPEROXIDE DISMUTASE 1/2; SODX, SUPEROXIDE DISMUTASE; AO, L-ASCORBATE OXIDASE; GRX21/22, GLUTAREDOXIN 21/22; RBOH, RESPIRATORY BURST OXIDASE HOMOLOG; MEMB12, MEMBRIN 12; FAMT, FARNESOIC ACID METHYLTRANSFERASE; Nramp6, natural resistance-associated macrophage protein 6; PR1, PATHOGENESIS-RELATED 1; MET2, METHYLTRANSFERASE 2; ARF16, AUXIN RESPONSE FACTOR 16; TIR1, TRANSPORT INHIBITOR RESPONSE 1; AFB2/3, AUXIN SIGNALING F-BOX PROTEINS 2/3; TCP21, TEOSINTE BRANCHED 1, CYCLOIDEA, PROLIFERATING CELL NUCLEAR ANTIGEN BINDING FACTOR 21; EIN2, ETHYLENE INSENSITIVE 2; CPB60A, CALMODULIN BINDING PROTEIN 60A; LOX1/2, LIPOXYGENASE 1/2; AGO1/2, ARGONAUTE 1/2; ELENA1, ELF18-INDUCED LONG NONCODING RNA; ALEX1, AN LEAF EXPRESSED AND XOO-INDUCED LNCRNA1; ANX2, ANXUR2; RLP7, RECEPTOR-LIKE PROTEIN 7.

genes indirectly. However, the underlying mechanism is largely unknown.

Callose deposition is a typical PTI response against pathogen infection. In *Arabidopsis*, the flg22 PAMP can decrease miR773 accumulation and therefore derepress its target gene *methyltransferase 2 (MET2)*, resulting in increased callose deposition and enhanced disease resistance against *P. cucumerina*, *Fusarium oxysporum*, and *Colletotrichum higginsianum* (Salvador-Guirao et al., 2018a). *Arabidopsis* miR398b can reduce callose deposition and compromise disease resistance against *Pst* (Li et al., 2010). Conversely, miR160a increases PAMP-induced callose deposition and enhances plant immunity (Li et al., 2010). Regulation of callose deposition by the above miRNAs is an indirect result. Hence, future studies will be

necessary to clarify how these miRNAs mediate callose deposition.

Some ncRNAs regulate plant immunity by altering the biosynthesis or signaling of plant hormones, including auxin, ethylene, jasmonic acid (JA), and salicylic acid (SA). In *Arabidopsis*, miRNA393 is induced by flg22 to downregulate the mRNA levels of F-box auxin receptor genes, including *TIR1*, *AFB2*, and *AFB3*, thereby repressing auxin signaling and restricting bacterial growth (Navarro et al., 2006). In rice, miR166k-166h positively regulates rice immunity during *M. oryzae* and *Fusarium fujikuroi* infection by controlling the expression of *EIN2*, which encodes a critical regulator of ethylene signaling (Salvador-Guirao et al., 2018b). Rice miR319 negatively regulates plant immunity by targeting *TCP21*, which encodes a transcription factor that

promotes the expression of *LOX2*, *LOX5*, *COI1*, and *COI2* to affect JA biosynthesis and signaling (Zhang et al., 2016a, 2018b). Furthermore, overexpression of the lncRNA *ALEX1* in rice upregulates the expression of JA-responsive genes such as *JAZ8* and *MYC2* and then increases the endogenous levels of JA to enhance resistance against *Xoo* (Yu et al., 2020). In cotton, miR477 positively regulates plant resistance against *Verticillium dahliae* by targeting *GhCPB60A*, which downregulates *GhICS1* expression to suppress SA biosynthesis (Hu et al., 2020). Decreased expression of *GhIncNAT-ANX2* and *GhIncNAT-RLP7* in cotton increases the expression of *LOX1* and *LOX2*, which are involved in the regulation of the JA pathway, enhancing resistance against *V. dahliae* and *B. cinerea* (Zhang et al., 2018a). The ncRNA-mediated regulation of plant immunity by fine-tuning multiple plant hormone pathways allows plants to adapt dynamically and flexibly to diverse environments.

The biosynthetic pathways of miRNAs and siRNAs and the components of the RNA-induced silencing complex (RISC) also modulate plant immune response. In *Arabidopsis*, miR863-3P inhibits the expression of *SERRATE*, which is essential for the processing of primary miRNA transcripts to miRNAs, thereby suppressing immune response by inhibiting the translation of mRNA (Niu et al., 2016). In rice, stable transgenic expression of *Argonaute 18* (*AGO18*), a key component of the RNA-silencing machinery, elevates the level of *AGO1* by sequestering miR168, and therefore confers broad-spectrum virus resistance (Wu et al., 2015). In rice, miR444 upregulates *OsRDR1* expression, which is required for the amplification of single-stranded RNAs into dsRNAs, by silencing the MADS-box protein transcriptional repressors of *OsRDR1*, leading to enhanced virus resistance (Wang et al., 2014, 2016a). In tobacco, miR403a attenuates tobacco mosaic virus resistance by regulating the expression of its target gene *AGO2*, which enables virus-derived siRNAs to load into the RISC and directs the degradation of the viral RNAs (Diao et al., 2019). Disruption of miRNA biosynthesis and RISC function have a broad impact on diverse aspects of plant immune responses.

COORDINATED FUNCTION AMONG miRNAs, siRNAs, lncRNAs, AND circRNAs IN PLANT IMMUNITY

Recent studies have demonstrated that a number of ncRNAs alter their expression levels under biotic and abiotic stresses. These ncRNAs, including miRNAs, siRNAs, lncRNAs, and circRNAs, usually interact with each other and coregulate the expression of target genes to modulate plant immunity (Figure 1). The complex interaction among miRNAs, siRNAs, lncRNAs, and circRNAs can coordinate various immune responses in a synergistic or antagonistic manner.

miRNAs and siRNAs

miRNAs and siRNAs are generated by ribonuclease III-like enzyme Dicer or Dicer-like (DCL) proteins and are incorporated into AGO proteins to induce gene silencing by binding to target mRNAs in a sequence-complementary manner (Wu et al., 2009). miRNAs can guide the cleavage of their target mRNAs and trigger the production of secondary siRNAs from their

target genes in a phased pattern through the coordinated action of RDR6, Suppressor of Gene Silencing 3, Silencing Defective 5, DCL4, and AGO1 (Peragine et al., 2004; Allen et al., 2005; Hernandez-Pinzon et al., 2007; Song et al., 2012a, 2012b). These secondary siRNAs include mainly *trans*-acting siRNAs (tasiRNAs) and phasiRNAs, which have a dramatic impact on gene regulation mediated by miRNAs. tasiRNAs act in *trans* to suppress the expression of genes that are distinct from their original miRNA targets (Vazquez et al., 2004). phasiRNAs are generated from protein-coding genes called *PHAS* genes and usually promote the cleavage of their target genes in *cis*. Notably, a set of miRNAs, especially those 22 nt in length that target NLR genes, can trigger the production of phasiRNAs from their target mRNAs. These phasiRNAs further target NLR genes for cleavage to suppress NLR gene function (Fei et al., 2013). These miRNAs are highly conserved in different species, and most of them belong to the miR482/2118 superfamily (Canto-Pastor et al., 2019). This miRNA-NLR-siRNA regulatory mode is an effective way for plants to prevent the autoimmunity and growth inhibition caused by unregulated *R gene* expression in the absence of pathogens (Deng et al., 2018a). phasiRNAs derived from conserved regions of the NLR genes increase the number of genes targeted by a single miRNA, thus enhancing its silencing effect on NLR genes (Fei et al., 2013). In addition, some miRNAs can target more than one gene to trigger different secondary siRNAs. For instance, in *Brassica rapa*, the NLR gene *BraTNL1* and the *trans*-acting silencing gene *BraTIR1* are both directly targeted by miR1885. phasiRNAs derived from *BraTNL1* further target *BraTNL1* to regulate plant resistance against TuMV. However, tasiRNAs derived from *BraTIR1* target *BraCP24* to modulate floral transition (Cui et al., 2020b). Therefore, these 22-nt miRNAs establish regulatory cascades in which mRNAs are targeted by miRNAs and secondary siRNAs.

lncRNAs and miRNAs or siRNAs

Several lines of evidence have shown that some lncRNAs serve as precursors for miRNAs and siRNAs and assist in target gene cleavage. In wheat, three powdery mildew-responsive lncRNAs (*TalncRNA5*, *TapmlncRNA19*, and *TapmlncRNA8*) act as precursors for miRNAs (Xin et al., 2011). Likewise, 16 powdery mildew-responsive lncRNAs act as siRNA precursors, and most of them produce more than one siRNA family. In *Brassica napus*, 41 lncRNAs that are responsive to *Sclerotinia sclerotiorum* infection have been identified as precursors for miRNAs, including miR156 and miR169, which play important roles in plant immunity (Joshi et al., 2016). Recently, in mulberry, the novel lncRNA *MuLnc1* was found to be cleaved by mul-miR3954 to produce secondary siRNAs, including si161579. It has been demonstrated that si161579 can silence the calmodulin-like protein gene *CML27* (*MuCML27*) in mulberry. *MuCML27*-overexpressing *Arabidopsis* plants exhibit enhanced resistance against *B. cinerea* and *Pst*. Thus, the miR3954-*MuLnc1*-siRNAs-mRNAs module provides novel insights into the mulberry defense response (Gai et al., 2018). In addition, it has been reported that lncRNAs containing long-stem structures can be an endogenous source for the generation of DCL1-dependent siRNAs (Ma et al., 2014b). Therefore, to investigate the function of lncRNAs as precursors for miRNAs and siRNAs involved in plant immunity, we must consider the secondary structures of the lncRNAs and the corresponding expression

patterns of their cognate miRNAs and siRNAs. It is worth noting that one lncRNA can produce more than one miRNA and/or one siRNA, thus expanding and strengthening the regulation of their target genes.

In addition, several lncRNAs compete with endogenous RNAs (ceRNAs) to sequester miRNAs in a type of target mimicry. In tomato, slylnc0195 and slylnc1077 act as decoys for miR166 and miR399, respectively, to regulate plant resistance against tomato yellow leaf curl virus (TYLCV) (Wang et al., 2015). Similarly, lncRNA39026 in tomato acts as an endogenous target mimic for miR168a to positively modulate defense response to *P. infestans* infection through the regulation of *SIAG O 1* expression (Hou et al., 2020). Also, lncRNA42705 and lncRNA08711 increase the mRNA levels of *MYB* genes by acting as decoys for miR159, thereby enhancing resistance against *P. infestans* (Cui et al., 2020a). Overexpression of lncRNA23468, which contains conserved endogenous target mimic sites for miR482b, decreases miR482b expression in tomato, increasing expression of the target NLR gene *Solyc02g036270.2* and enhancing resistance against *P. infestans* (Jiang et al., 2019). The half-life of miRNA is usually very long, making it difficult to rapidly reduce the abundance of miRNA when plants are under pathogen attack. Thus, plants use lncRNAs as endogenous target mimics to repress miRNA activity, which may be faster than inhibiting miRNA biogenesis and enhancing miRNA turnover.

Conversely, an miRNA or siRNA may directly target an lncRNA to attenuate its presence through cleavage. Recently, it has been reported that tomato SI-lncRNA15492 interacts with SI-miR482a to regulate host immunity against *P. infestans*: SI-lncRNA15492 inhibits the production of mature SI-miR482a through an SI-miR482a precursor contained in the antisense sequence of SI-lncRNA15492. In turn, SI-miR482a suppresses SI-lncRNA15492 expression through direct cleavage. It has been noted that SI-miR482a targets the NLR gene *SI-NBS-LRR1* to negatively regulate plant resistance in tomato. Therefore, SI-lncRNA15492 and SI-miR482a mutually inhibit each other to maintain an appropriate *SI-NBS-LRR1* level during regulation of the tomato immune response to *P. infestans* (Jiang et al., 2020). This interaction between a miRNA and an lncRNA to regulate an NLR gene reveals a novel mechanism for the regulation of plant immunity. In addition, a TYLCV-derived siRNA induces silencing of the tomato lncRNA *SILNR1*, which contributes to TYLCV resistance, through the direct cleavage of *SILNR1* (Yang et al., 2019b). The interaction between viral siRNAs and host lncRNAs provides integrative regulation of the arms race between pathogens and hosts.

circRNAs and miRNAs

Although a few cases in animals have shown that circRNAs act as miRNA sponges, the same function for plant circRNAs requires further empirical validation. Bioinformatic analysis has shown that the majority of circRNAs do not possess multiple binding sites for miRNAs and thus may not function as miRNA sponges (Guo et al., 2014). Genome-wide analysis of circRNAs in *Arabidopsis* and rice has revealed that only a small portion of circRNAs (5.0% in *Arabidopsis* and 6.6% in rice) are potential target mimics of miRNAs (Ye et al., 2015). As one example, circRNA

Os08circ16564 was predicted to be a target mimic of miR172. However, RT-PCR results showed that the miR172 levels in Os08circ16564-overexpressing plants were not significantly different from those in wild-type plants, indicating that Os08-circ16564 may not function as a sponge for miR172 (Lu et al., 2015). This result also suggests that serving as miRNA sponges may not be the major mode of circRNA function in plants. However, bioinformatic analysis predicted that 24 circRNAs in tomato and 6 circRNAs in wheat may act as miRNA sponges (Zuo et al., 2016; Wang et al., 2017b). This prediction is largely dependent on linear sequence matching using bioinformatic tools. However, the secondary structures of circRNAs may hide a portion of potential miRNA binding sites, a fact that is often overlooked when predicting potential miRNA binding sites for circRNAs in plants. This may explain why Os08circ16564 overexpression did not affect miR172 levels. In addition, to act as miRNA sponges, each circRNA must have a sufficient number of miRNA binding sites or be present at a sufficiently high level (Ebert and Sharp 2010). Nevertheless, although the mammalian circRNAs ciRS-7 and CDR1 possess high-density miRNA binding sites (Hansen et al., 2013; Memczak et al., 2013), no plant circRNAs contain such a high density of miRNA binding sites. On the other hand, a recent study showed that circRNA45 and circRNA47 levels were induced upon *P. infestans* infection, and these circRNAs may act as sponges for miR477-3P to regulate its target gene *SpRLK* in tomato (Hong et al., 2020). Therefore, whether plant circRNAs function to directly inhibit miRNAs requires further investigation. One benefit of circRNAs acting as miRNA sponges may be that one circRNA can target a number of miRNAs simultaneously. When needed, many miRNAs can be quickly released from the circRNA and miRNA interaction complex to modulate plant immunity rapidly and efficiently.

ROLES OF PATHOGEN EFFECTORS AND MOBILE ncRNAs IN THE INTERACTION BETWEEN PATHOGENS AND HOST PLANTS.

In addition to host-derived ncRNAs that regulate the biosynthesis and signaling of ncRNAs involved in plant immunity, effectors secreted by distinct pathogens also hijack the RNA-silencing machinery to interfere with plant immunity and achieve successful infection (Figure 2). This type of effector is called an RNA-silencing suppressor, and such suppressors are expressed by pathogenic viruses, bacteria, fungi, and oomycetes (Spanu, 2015; de Vries et al., 2019). For example, the virus P19 protein of tobamoviruses prevents post-transcriptional gene silencing by specifically binding to double-stranded siRNAs in tobacco (Silhavy et al., 2002). In bacteria, the HopT1-1 effector of *Pst* interferes with AGO1 to suppress RNA silencing and cause disease in *Arabidopsis* (Navarro et al., 2008). In fungi, the PgtSR1 effector proteins from the wheat stem rust pathogen *Puccinia graminis* f. sp. *tritici* (Pgt) were the first identified RNA-silencing suppressors from fungi. They compromise wheat immunity by altering the abundance of small RNAs involved in defense processes, including miR164, miR398, and miR169 (Yin et al., 2019). In oomycetes, PSR1 and PSR2 from *P. sojae* suppress RNA silencing in plants by inhibiting the biogenesis of small RNAs such as miR393 and ASRP255 to promote infection

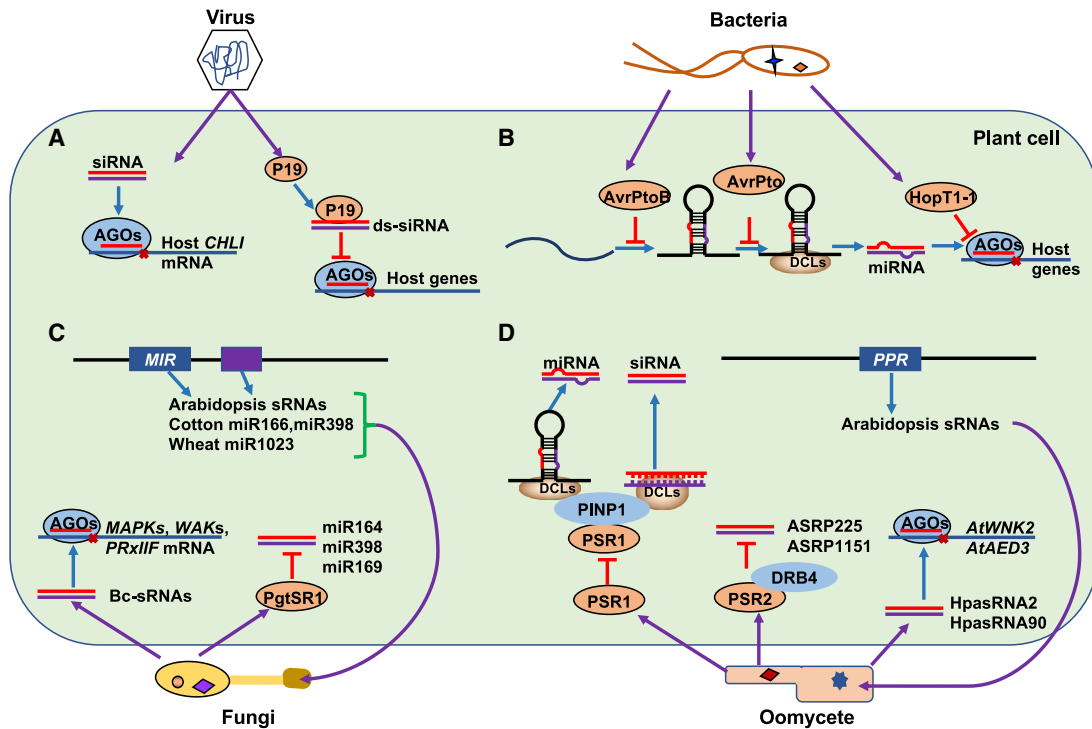


Figure 2. Effectors and mobile small RNAs in the interactions between pathogens and host plants.

(A) Role of sRNAs in plant–virus interaction. Virus-derived siRNAs directly target a chlorophyll biosynthetic gene in the plant. The virus also encodes proteins, such as P19, to suppress RNA silencing by interfering with DCL function, the binding of virus-derived siRNAs, and the prevention of RISC assembly.

(B) Role of sRNAs in plant–bacteria interaction. Bacterial effectors translocate into host plant cells and inhibit the regulation of plant sRNA. The effector AvrPtoB represses the accumulation of miR393 at the transcriptional level, whereas AvrPto reduces the processing of miR393. HopT1-1 suppresses AGO1 function to inhibit RNA silencing.

(C) Role of sRNAs in plant–fungi interaction. Fungal sRNAs, Bc-sRNAs, translocate into host cells and utilize plant RNA-silencing components to reduce the expression of host immune genes such as MAPKs and WAKs. The fungal effector PgtSR1 regulates the abundance of a set of miRNAs involved in plant immunity. Plants also send several small RNAs into fungi to modulate their growth and virulence.

(D) Role of sRNAs in plant–oomycete interaction. The PSR1 and PSR2 effectors of oomycetes are secreted into plant cells and alter the host RNA-silencing machinery to decrease host immunity. Oomycetes also send small RNAs to silence host genes such as *AtWnk2* and *AtAed3*. Host plants export many small RNAs into oomycetes to change pathogen virulence. Abbreviations: PSR1/2, *Phytophthora* suppressors of RNA silencing 1/2; DRB4, dsRNA-binding protein 4; PINP1, PSR1-interacting protein 1; DCL, DICER-LIKE; AGO, ARGONAUTE; PPR, pentatricopeptide repeat; *AtWnk2*, *Arabidopsis* WITH NO LYSINE (K) KINASE 2; *AtAed3*, APOPLASTIC, ENHANCED DISEASE SUSCEPTIBILITY1-DEPENDENT 3; WAKs, cell wall-associated kinases; red lines represent miRNAs and siRNAs.

(Qiao et al. 2013, 2015). These results demonstrate that pathogens use a conserved strategy to inhibit plant defense responses by suppressing RNA silencing in the host.

Notably, regulation by ncRNAs is not restricted to the individual organism in which they are generated. Many mobile miRNAs and siRNAs can translocate between hosts and pathogens, silencing genes in the interacting organism by a mechanism termed cross-kingdom RNAi (Huang et al., 2019) (Figure 2). However, lncRNAs and circRNAs involved in plant immunity have not yet been found to move between pathogens and plants.

Small RNAs derived from pathogens mediate cross-kingdom RNAi in plant hosts and represent a novel class of pathogen effectors that inhibit host immunity for successful infection (Kwon et al., 2020). For example, cucumber mosaic virus Y-satellite RNA-derived siRNAs directly target the chlorophyll biosynthetic gene *CHLI* in tobacco to cause yellowing symptoms (Smith et al., 2011). In fungi, some small RNAs from *Botrytis cinerea*,

such as Bc-sR3.1, Bc-sR3.2, Bc-sR5, and Bc-sR37, are delivered into host cells and silence *Arabidopsis* and tomato genes involved in immunity, including MAPKs, cell-wall-associated kinases, and other defense proteins (Weiberg et al., 2013; Wang et al., 2017c). A group of small RNAs from *V. dahliae* also move into plant cells to silence genes involved in immunity by associating with AGO1 (Wang et al., 2016b). In oomycetes, HpasRNA2 and HpasRNA90, two small RNAs from *Hyaloperonospora arabidopsidis*, are translocated into *Arabidopsis* cells and associate with AGO1 to silence the plant defense genes *AtWnk2* and *AtAed3*, respectively (Dunker et al., 2020). This phenomenon has been discovered in several cases of plant–pathogen interactions, indicating that pathogen-induced gene silencing is widespread and complex.

Plant hosts also transport small RNAs into pathogens to suppress the expression of virulence-related genes, thereby contributing to plant defense response (Zhu et al., 2019). *Arabidopsis* cells secrete exosome-like extracellular vesicles to deliver small

RNAs into the fungal pathogen *B. cinerea* to induce the silencing of fungal genes involved in pathogenicity (Cai et al., 2018). The wheat miRNA1023 inhibits a *Fusarium graminearum* alpha/beta hydrolase gene that plays an important role in fungal infection (Jiao and Peng, 2018). Similarly, cotton plants export miR166 and miR159 to the *V. dahliae* hyphae to separately target two *V. dahliae* genes that encode a Ca²⁺-dependent cysteine protease (Cip-1) and an isotrichodermin C-15 hydroxylase (HiC-15), leading to enhanced disease resistance (Zhang et al., 2016c). Interestingly, in the interaction between *Phytophthora* and *Arabidopsis*, *Phytophthora* infection induces a set of secondary siRNAs generated from a plant PPR gene cluster, and these siRNAs potentially silence target genes in *Phytophthora* to confer resistance. As a counter defense mechanism, the PSR2 effector interferes with secondary siRNA production by associating with dsRNA-binding protein 4, which is involved in secondary siRNA biogenesis (Hou et al., 2019b). These results demonstrate that cross-kingdom RNAi is bidirectional during plant–pathogen interactions.

CONCLUDING REMARKS AND PERSPECTIVES

An increasing number of plant ncRNAs involved in plant immunity have been identified. However, mechanistic details of immunity regulation by these plant ncRNAs are very limited. Accumulating findings highlight important roles for ncRNAs in the regulation of diverse aspects of plant immunity, including pathogen perception, signal transduction, and downstream immune responses. Furthermore, these ncRNAs play multiple roles in plant immunity through the use of different strategies, including modulation of gene expression, interaction with proteins, and interplay with other ncRNAs. An ncRNA can target more than one gene, and a single ncRNA may thus show pleiotropic effects not only on plant immunity but also on other biological processes, including plant development and response to abiotic stresses. For instance, the *Brassica* miRNA miR1885 regulates both plant growth and immunity by repressing the expression of the NLR gene *BraTNL1* and the photosynthesis-related gene *BraCP24*, suggesting that miR1885 and its target genes are ideal breeding targets for disease resistance and high yield (Cui et al., 2020b). Conversely, one target gene may be regulated by multiple ncRNAs simultaneously, underscoring the diversity and complexity of plant ncRNA modes of action. Taking advantage of this, in the case of growth attenuation caused by *R* genes, the introduction of regulatory miRNAs may help to achieve a balance between resistance and crop development.

Although the potential models for plants are similar to those for mammals, it remains to be determined whether ncRNA modes of action are conserved between plants and mammals and whether plant ncRNAs exhibit novel mechanisms. Recent studies have shown that mobile ncRNAs translocate between plants and pathogens to mediate cross-kingdom regulation of plant immunity and pathogen virulence (Weiberg et al., 2013; Wang et al., 2016b; Zhang et al., 2016c; Cai et al., 2018; Huang et al., 2019). It is important to characterize the targets of these mobile ncRNAs and their molecular regulation. The diverse subcellular localizations of ncRNAs may be related to their specific roles in plant cells, and determining the subcellular localization of

individual ncRNAs is important for understanding their functions. In addition, as ncRNAs may encode peptides, it will be interesting to determine whether these potential peptides play roles in plant immunity and to uncover their underlying mechanisms. We believe that future studies on ncRNA will provide additional insight into plant immunity and offer effective approaches for the improvement of plant disease resistance, thereby ensuring global food security.

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