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Review article

Review: Plant microRNAs in pathogen defense: A panacea or a piece of the puzzle?

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ABSTRACT

Plant microRNAs (miRNAs) control key agronomic traits that are associated with their conserved role(s) in development. However, despite a multitude of studies, the utility of miRNAs in plant-pathogen resistance remains less certain. Reviewing the literature identifies three general classes of miRNAs regarding plant pathogen defense. Firstly, a number of evolutionary dynamic 22 nucleotide miRNA families that repress large numbers of plant immunity genes, either directly, or through triggering the biogenesis of secondary siRNAs. However, understanding of their role in defense and of their manipulation to enhance pathogen resistance are still lacking. Secondly, highly conserved miRNAs that indirectly impact disease resistance through their targets that are primarily regulating development or hormone signaling. Any alteration of these miRNAs usually results in pleiotropic impacts, which may alter disease resistance in some plant species, and against some pathogens. Thirdly, are the comparatively diverse and evolutionary dynamic set of non-conserved miRNAs, some of which contribute to pathogen resistance, but whose narrow evolutionary presence will likely restrict their utility. Therefore, reflecting the diverse and evolving nature of plant-pathogen interactions, a complex interplay of plant miRNAs with pathogen responses exists. Any miRNA-based solution for pathogen resistance will likely be highly specific, rather than a general panacea.

1. Introduction

Small non-coding RNAs (sRNAs) and the post-transcriptional RNA interference (RNAi) mechanism were discovered via the study of plant-pathogen interactions (Waterhouse et al., 1998; Hamilton and Baulcombe, 1999). It was found that invading viral double-stranded RNA (dsRNA) is processed by plant DICER-LIKE RNase III endonuclease (DCL) complexes resulting in the production of 21–24 nucleotide (nt) sRNAs known as small interfering RNAs (siRNAs), that are then incorporated into ARGONAUTE (AGO) proteins, the key component of RNA-induced silencing complexes (RISCs). These siRNA loaded RISC complexes represent a basal immune housekeeping pathway, whose core function is genome stability through the protection from parasitic nucleic acids, be it exogenous viruses or endogenous transposons (Waterhouse et al., 2001; Carthew and Sontheimer, 2009). In plants, the utilization of this pathway through the transgenic expression of dsRNAs has successfully triggered immunity to a multitude of viruses in diverse species, highlighting its ubiquitous presence throughout the plant kingdom (Eamens et al., 2008).

From this basal RNAi pathway, it is believed that other sRNA pathways have arisen, including that of the extensively studied microRNA (miRNA) pathway. In contrast to siRNAs, miRNAs are derived from endogenous *MIRNA* (*MIR*) genes whose transcripts are known as primary-miRNAs that form imperfect dsRNA structures that are processed into miRNA:miRNA* duplexes (Wang et al., 2019). Subsequently, the mature miRNA which is typically 21–22 nts in length, is preferentially selected and loaded into an AGO protein to form the miRNA-induced silencing complex (miRISC) with the miRNA* strand preferentially degraded (Krol et al., 2010). Here, the miRNA guides the miRISC to target RNAs via high-complementary base-pairing where the miRISC then represses gene expression through a complex post-transcriptional gene silencing mechanism(s) that includes transcript cleavage and/or translational repression (Wang et al., 2019). Given the strong phenotypic impacts plant miRNAs can exert on many

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different fundamental plant processes, they are often referred to as "master regulators" of gene expression.

Over the last several decades, there have been a myriad of reports implicating a role for miRNAs in pathogen defense (for recent reviews see (Šečić et al., 2021; Islam et al., 2018)). The response of plant miRNAs to pathogen infections is complex, variable and versatile. Upon infection, the abundance of a variable suite of miRNAs alters, depending on which pathogen is infecting which plant species. This complex miRNA response then likely modifies regulatory networks that impact infection, or alternatively the miRNAs can move from the plant into the pathogens, impacting resistance (Zhang et al., 2016). Given all of this, miRNAs have been proposed to be critical players in plant-pathogen interactions with immense biotechnological potential to develop novel disease-resistance strategies for crops (Song et al., 2021). Given the size of the literature that has implicated plant miRNAs in pathogen defense, the aim of this review is not to summarize every possible role of a miRNA in pathogen defense that has been described, but a focus on which miRNAs appear most functionally relevant to pathogen resistance, the underlying mechanism(s) by which they work, and the potential they provide in developing new pathogen defense strategies. We will not cover the cross-kingdom mobility of miRNAs and their role in pathogen defense which has been extensively reviewed (Loreti and Perata, 2022).

2. Generalized principles of plant miRNAs

Plants contain a complex and fluid set of miRNAs in which their conservation varies dramatically. By far the most is known regarding a set of approximately two dozen miRNA families that are ancient and found in most lineages of land plants (Axtell and Meyers, 2018; Chávez Montes et al., 2014). Each of these conserved miRNA families predominantly regulate a single conserved target family making these miRNA-target interactions (MTIs) ancient (Axtell and Bartel, 2005; Wong and Millar, 2023; Jones-Rhoades, 2012). The sequences of these ancient miRNAs and the binding-sites within their conserved targets appear fixed, where in any given species, there are usually multiple miRNA family members that are targeting multiple members of a paralogous target family (Li et al., 2014). As there are multiple members in each family, there is the potential for the sequence of an individual family member to drift and acquire a new target. However, in plants there is very little evidence of miRNA neofunctionalization, arguing that acquiring a new conserved target family is rare (Wong and Millar, 2023). Many of these conserved target families correspond to regulatory genes, mainly transcription factors that appear fundamental to plant development, some of which work through hormone signaling (Liu et al., 2018). Other conserved families regulate nutrient response; miR395 - sulfate, miR398 - copper and miR399 - phosphate (Kumar et al., 2017). Either way, all these conserved MTIs appear ingrained, where once their functional role has evolved, that role has been strongly conserved. For example, miR165/166 controls organ polarity, miR156 controls phase transition and miR172 controls flowering time, and these roles appear conserved throughout terrestrial plants (Liu et al., 2018). This argues most of these conserved MTIs are under strong selective pressure to perform these fundamental roles in plant growth and development.

Curiously, the abundance (level of expression) of plant miRNAs are generally correlated with their conservation. An analysis of sRNA abundances of 99 different samples of different plant tissues and/or environmental treatments across diverse species found the more conserved the miRNA, the higher their abundance is likely to be (Chávez Montes et al., 2014). This is so much so that the several dozen conserved miRNA families can make up a total of 98% of entire miRNA population (miRNome) in a given species (Chávez Montes et al., 2014) (Fig. 1). This may in part reflect that most of these conserved miRNA families are composed of multiple family members that usually display some level of redundancy (Allen et al., 2007). Conversely, the vast majority of poorly conserved miRNAs have very low abundances, and usually are

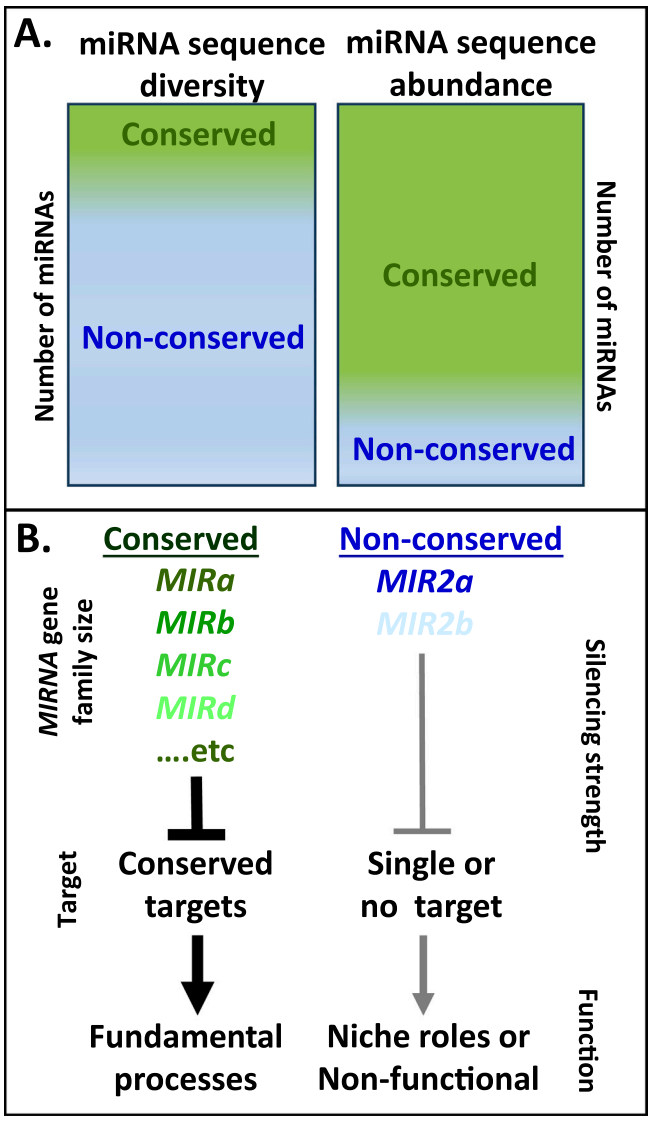

Fig. 1. Generalized principles of plant miRNAs. **A.** Most miRNAs in any given plant species are non-conserved, and so make up the bulk of the sequence diversity. However, non-conserved miRNAs are lowly expressed, whereas conserved miRNAs are highly abundant. **B.** This high abundance is in-part explain by conserved miRNAs being usually encoded by families of genes of identical, or near identical isoforms. By comparison, non-conserved miRNAs are predominantly represented by a single gene. The targets of conserved miRNAs are also conserved, and the silencing outcome of the interaction generally appears strong. By contrast, only a subset of non-conserved miRNAs have a known target, raising the possibility that the bulk of the non-conserved miRNAs are non-functional.

composed of a single family member, to which often there is no obvious corresponding target gene(s) (Axtell, 2008; Wong and Millar, 2022). From this, it has been hypothesized that the majority of young miRNAs are likely non-functional, being part of the myriad of sRNAs undergoing frequent birth and death from which very few functional MTIs emerge (Axtell, 2008; Fahlgren et al., 2007). Consistently, inhibiting the function of most of the conserved miRNAs in Arabidopsis resulted in a clear phenotypic alterations, whereas, the inhibition of a large set of non-conserved miRNAs failed to result in any discernible phenotypic impacts (Todesco et al., 2010).

Nevertheless, neither a failure to observe mutant phenotypes nor a low abundance does not demonstrate the miRNA is non-functional. For instance, many miRNAs are highly tissue specific accounting for their low abundance, and have been shown to have highly specialized roles

(Kutter et al., 2007). This is the case for many long non-coding RNAs, where they perform a function in a specific cell type, or a function that does not require the RNA to be at a high abundance (Mattick et al., 2023). However, as the only known role of plant miRNAs is to mediate post-transcriptional gene-silencing, in most instances they likely need to be in a relatively high miRNA:target ratio to confer a functional regulatory outcome (Li et al., 2014). Alternatively, the miRNA would need to act as a trigger for processes that amplify the silencing signal, such as the production of secondary siRNAs (Zhan and Meyers, 2023).

3. Plant pathogen defense systems

As mentioned above, miRNAs are often termed "master regulators" of plant growth and development, where they predominantly target key conserved regulatory genes that control genetic cascades and hormone responses. Most of these miRNAs have highly specific spatial and temporal expression domains, and upon alteration of their expression, can directly result in modification of key plant traits, making these miRNAs prime targets for crop improvement (Tang and Chu, 2017; Shriram et al., 2016). In contrast to these highly conserved regulatory mechanisms in plant growth and development, genes involved in pathogen defense are constantly evolving to counteract rapidly changing pathogens in a never-ending plant-pathogen arms race. Given this, any MTI involved in pathogen response are likely much more dynamic and would be less likely to be conserved.

Plant-pathogens interactions are complex, as are the plant defense systems and the genes involved. Plant defense encompasses the physical barriers of the plant cuticle and cell wall, and specialized chemicals, all of which protects the plant from the vast majority of pathogens (Malinovsky et al., 2014). However, if these initial barriers are breached, plants have a two-layered immune system that encompasses pathogen-associated molecular patterns (PAMPs)-triggered immunity (PTI), and effector-triggered immunity (ETI), both of which operate through receptor proteins that recognize pathogens (Jones and Dangl, 2006). Whereas PTI is triggered by strongly conserved cell surface molecules that are indispensable to the pathogen, ETI's receptor proteins correspond to plant resistance proteins (R proteins) that operate by physically recognizing highly variable virulence effectors that pathogens secrete to suppress PTI (Yuan et al., 2021). This interaction between R proteins and virulence effectors triggers an ETI response that results in strong immunity to the pathogen, often through a hypersensitive response (HR). If the pathogen can evade this system, a compatible interaction can arise, and disease can be established. Plant genes that enable this compatible interaction are termed susceptibility (S) genes, and modification of these can counteract infection (van Schie and Takken, 2014).

4. Knowns and unknowns of plant miRNAs in response to pathogens

Since the discovery of miRNAs in plants, there has been a multitude of studies investigating their role in pathogen defense. A PubMed search of "pathogen AND plant AND miRNA" retrieves over 900 publications (October 2023). A great many of these studies have carried out RNA profiling experiments that have shown the abundance of miRNAs and/or the RNA levels of their target genes, alter upon pathogen infection or differ between susceptible and resistant plant varieties [for examples see the reviews (Šečić et al., 2021; Islam et al., 2018). The potential here is that these miRNAs are regulating gene expression programs in response to pathogen infection and so are part of the plant's defense response, potentially being the difference in being susceptible or resistant to a pathogen. However, in the majority of these studies, it is unclear whether alterations to these miRNA levels can manifest in alterations to target gene expression levels that result in a physiological impact. An additional uncertainty is whether these changes to the miRNA levels are a direct response to the pathogen (cause), or a secondary effect stemming from the direct physiological consequences of pathogen infection (effect).

Moreover, given the diversity of sRNAs populations in plants, and their potential targets that are predicted by bioinformatics (Dai et al., 2018), the number of possible MTIs are generally so great that researchers can usually find predicted MTIs that are related to any biological process of interest, including that of pathogen response. Currently, only a subset of these potential pathogen responsive MTIs has been functionally tested via altering the expression of the miRNA or its target, and assaying whether this directly modifies pathogen resistance. In most of these instances there has only been a single study, restricting knowledge to a single plant species, single pathogen and in many instances a specific tissue. In cases were there have been multiple independent studies, there has usually been variability in plants species and pathogens tested. In many of these instances, there is variability in the impact of the miRNA, where it expression promotes disease resistance in some instances, but susceptibility in others. Consequently, for most plant miRNAs, there are only a very few instances of a clear, consistent trend of an increase/decrease in a miRNA/target abundance with disease resistance/susceptibility (Šečić et al., 2021; Islam et al., 2018). This likely in part reflects the diversity and complexity of plant-microbe interactions.

5. MiRNAs that directly regulate plant immune receptor genes

In plants, there are numerous genes that confer immunity (resistance) to pathogens. R proteins mostly correspond to a large class of genes encoding intracellular NOD-like receptors (NLRs), which itself encompasses a large class of genes encoding NUCLEOTIDE BINDING SITE-LEUCINE-RICH REPEAT (NBS-LRR) proteins (Barragan and Weigel, 2021). NLRs recognize specific pathogen effectors and then trigger downstream immune pathways to result in strong ETI-mediated pathogen resistance (Jones and Dangl, 2006). There can be greater than a 1000 *NLR* genes found within a plant genome, where they are being broadly expressed (Yue et al., 2012). However, the level of *NLR* expression is under strict regulation, as high expression can result in autoimmunity, leading to a strong growth penalty, even lethality (Cui et al., 2020).

It has been shown in numerous plant species that miRNAs target and repress the expression of these *NBS-LRR* genes, so in effect, negatively regulating ETI. Generally, these miRNAs are 22 nt in length and upon targeting of these *NBS-LRR* genes trigger further degradation of the *NBS-LRR* transcripts to produce secondary siRNAs known as either phased (phasiRNA) or trans-acting siRNAs (tasiRNAs), which then amplify and reinforce silencing (Fig. 2). Not only do they target the gene from which they originate, but they can also act in *trans*, potentially repressing hundreds of sequence related *NBS-LRR* genes, as these phasiRNA typically correspond to highly conserved regions (Zhai et al., 2011; Li et al., 2012; He et al., 2008; Shivaprasad et al., 2012; Xia et al., 2015). Given this, these miRNAs are often referred to as "master regulators", able to coordinate the expression of 100 s of *NBS-LRR* genes simultaneously (Zhai et al., 2011).

Multiple distinct miRNA families that target *NBS-LRR* genes have been found in species ranging from eudicots to gymnosperms (Fig. 2A), where for instance in Norway Spruce there are 19 miRNA families that can target over 750 *NBS-LRR* genes (Xia et al., 2015). This includes the miR482/2118 superfamily family that differ by a 2-nt shift (for review see (Zhang et al., 2022)). Compared to other conserved miRNAs, members of these families display far greater sequence diversity, but nevertheless, all target *NBS-LRR* genes, implying the miRNAs are co-evolving with these highly variable *NBS-LRR* genes (Shivaprasad et al., 2012). This is occurring to such an extent that different plant species have different miR482/2118 isoforms, and highly variable numbers of gene family members and expression levels (Shivaprasad et al., 2012). At one extreme, Arabidopsis has only a single miR482 representative (miR472) that is lowly expressed (Boccara et al., 2014),

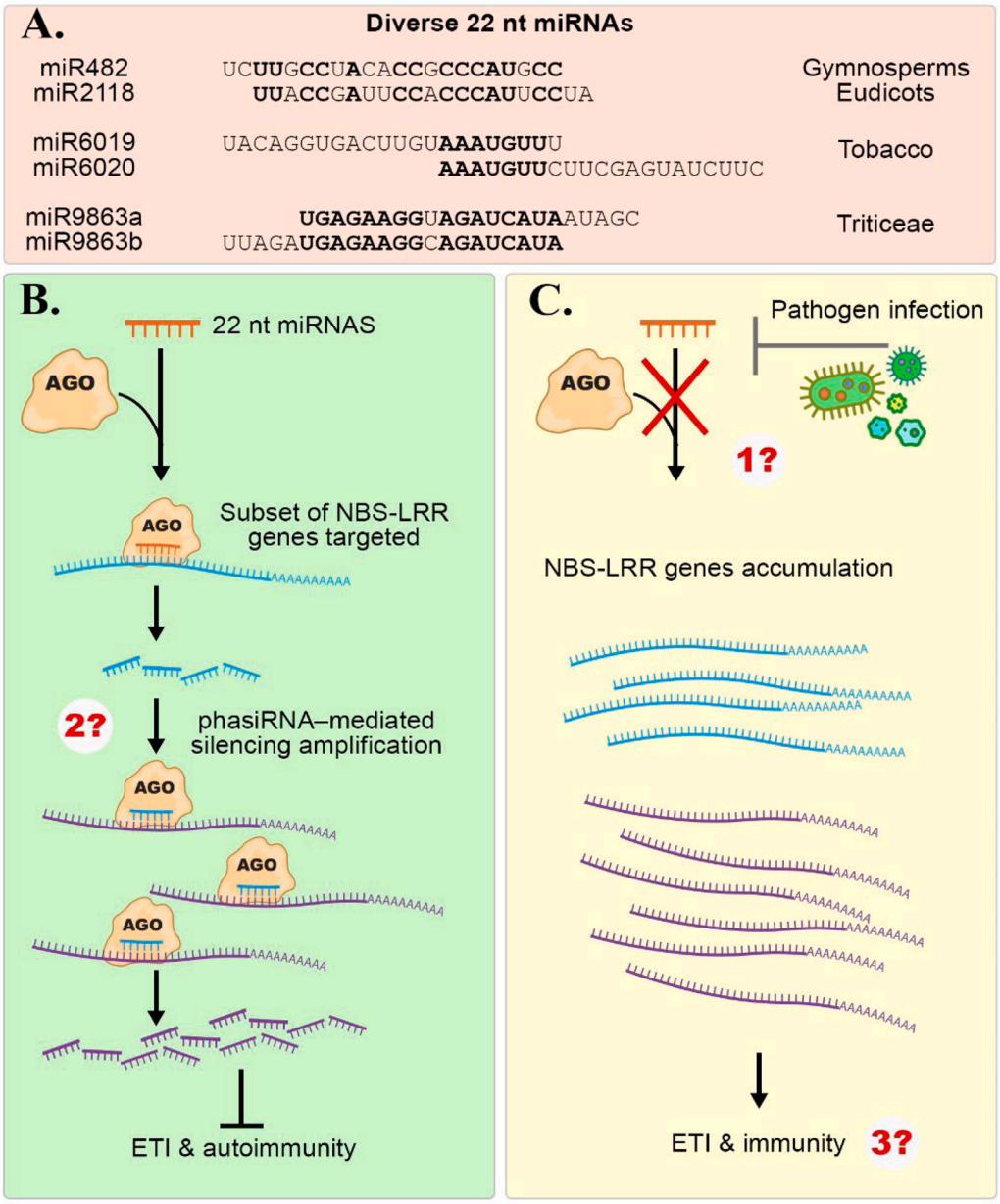

Fig. 2. Diverse 22 nt miRNAs trigger phasiRNA biogenesis to repress genes encoding plant immune receptors. (A) Diverse plant species have different 22 nt miRNA families of miRNAs which have appeared to have arisen independently in a possible convergent evolution manner. (B) These miRNA families repress a subset of genes encoding immune receptors, including that of *NBS-LRR* genes. This regulation triggers the biogenesis of phasiRNAs, which amplifies and expands silencing to additional homologous *NBS-LRR* genes. Therefore, these 22 nt miRNAs are considered "master regulators" of this large and diverse family of genes. It is thought that this regulation keeps *NBS-LRR* expression in check, which avoids autoimmunity and negative impacts on growth. (C) Hypothesis. During pathogen infection, the regulation of *NBS-LRR* genes is repressed, enabling induced expression of *NBS-LRR* genes for a strong ETI response and pathogen immunity. Currently, how these miRNAs respond to pathogen infection, and strategies to manipulate them for increased disease resistance are still work in progress. Outstanding questions. (1). Is miRNA repression of *NBS-LRR* genes repressed upon pathogen infection to enable a strong ETI response? If so, what are the mechanism(s) of repression? (2). Why is only a subset of the many *NBS-LRR* genes are repressed? Have different miRNAs evolved different specificities based on which pathogens are repressing these miRNA in 1.? (3). Can this pathway be manipulated to enhanced disease resistance?

an observation consistent with phasiRNAs being mostly absent in Arabidopsis (Zhai et al., 2011). On the other hand, in Medicago, five miRNAs (miR1507, miR2109, and miR2118a, b, and c) are able to target more than 100 *NBS-LRR* genes (Zhai et al., 2011). This is possible as most of these miRNAs are targeting highly conserved regions of the *NBS-LRR* genes, e.g., the region encoding the P loop region of the NBS domain, enabling the production of phasiRNAs that have high complementarity to suites of *NBS-LRR* family members. Given the number of miRNAs and *NBS-LRR* genes involved, *NBS-LRR* derived phasiRNAs often represent the largest proportion of all phasiRNAs in some plant species (Fei et al., 2013).

Compared to other conserved miRNA families that target regulatory genes involved in developmental processes, the miR482/2118 superfamily could be considered as displaying unusual characteristics. Firstly, in many species miR482/2118 homologs are arranged in genomic clusters, a feature unusual for plant miRNA genes (Zhang et al., 2022). Secondly, this family could be the best example of functional divergence in plants. In gymnosperms, miR482/2118 have a dual function, where they not only target *NBS-LRR* genes, but play a role in generating phasiRNAs in reproductive tissues from non-coding RNAs (Xia et al., 2015).

However, in eudicots, they appear to specifically target only the *NBS-LRR* genes, whereas in monocots, miR482/2118 isoforms do not target any *NBS-LRR* genes, but rather only target non-coding RNAs in reproductive tissues (Johnson et al., 2009; Zhai et al., 2015). This major functional diversification of miR482/2118 contrasts to other conserved miRNAs, highlighting how miRNAs that target genes involved in defense are evolving or diverging at a much higher rate than those miRNAs that target genes involved in other plant processes, such as development or hormone signaling. Thirdly, whereas most conserved miRNAs only appear to functionally target a few genes, miR482/2118 are likely functionally targeting 100 s of genes. However, given all these targets are *NBS-LRR* genes, they could be considered functionally related, and so in effect, they are only repressing a single activity, that of ETI. This coordinated control of expression of multiple genes simultaneously via a single regulatory mechanism would appear the strong selective advantage of this post-transcriptional regulatory mechanism (Zhai et al., 2011).

In monocots, in the absence of miR482/2118-mediated regulation of *NBS-LRR* genes, other non-related 22 nt miRNA families appear to be performing this function via a mechanism analogous to miR482/2118. In barley and wheat, miR9863a and miR9863b target *NBS-LRR* genes to trigger phasiRNAs that repress expression of many *NBS-LRR* genes (Fig. 2; (Liu et al., 2014)). In addition to targeting *NBS-LRR* genes, miRNAs also target other components of the immune response to generate analogous outcomes. For instance, in Arabidopsis miR825–5p represses *NBS-LRR* genes that contain a Toll/interleukin-1 domain (TNL) (López-Márquez et al., 2021), or completely distinct classes of R genes, with miR6022/23 targeting RLPs in tobacco (Li et al., 2012). Given these miRNA families appear unrelated (Fig. 2), this suggests these diverse 22 nt miRNAs have independently evolved and so may represent a dynamic, convergent evolution phenomenon. It emphasizes there is strong selective advantage for a repressive miRNA-mediated mechanism of genes directly involved in immunity (Fei et al., 2016).

Despite all that is known regarding these miRNA-*NBS-LRR* systems, evidence is still lacking that clearly defines what function in pathogen resistance this provides (Fei et al., 2016). The most obvious function is to suppress *NBS-LRR* expression to avoid autoimmunity and any associated yield penalty, and then upon pathogen infection, this miRNA silencing mechanism is transiently inhibited, enabling a strong and rapid ETI response to boost immunity (Zhai et al., 2011; Li et al., 2012; Fei et al., 2016; Yang et al., 2015; Zhu et al., 2014). Consistent with this, many of the miRNA-regulated *NBS-LRR* genes have been shown to confer resistance to pathogens (Shivaprasad et al., 2012; Ouyang et al., 2014), and over-expression of these miRNAs (e.g., miR482) results in enhanced susceptibility to pathogens, demonstrating they can directly influence resistance (Yang et al., 2015; Hong et al., 2019; Dey et al., 2022; Su et al., 2018). There are some observations that these miRNAs are inhibited upon pathogen infection, with mechanisms including the expression of silencing suppressors from bacterial pathogens that are able to inhibit miRNAs (Navarro et al., 2008), which have been hypothesized to inadvertently inhibit miRNAs such as the miR482/2118 superfamily upon infection (Fei et al., 2016). However, this remains to be determined, and is likely to be complex, with many outstanding questions to be answered, including the ability to manipulate these miRNAs to obtain enhanced disease resistance without a yield penalty.

Finally, there are other size classes of miRNAs that are regulating these *NLR* genes that are operating via different mechanisms [for review please see (Deng et al., 2018). This includes miR1876 that specifically regulates an *NBS-ARC* gene (*NBS8R*) that confers resistance to *Xanthomonas oryzae* in rice (Jiang et al., 2020). Interestingly, miR1876 is a 24 nt miRNA and it regulates *NBS8R* via DNA methylation, underscoring the complexity of MTI which occurs.

6. MiRNAs that are indirectly regulating plant defense

For the several dozen or so conserved miRNA families, it is clear their conserved canonical target genes are not directly involved in plant immunity, but rather are key in controlling other processes such as development, hormone signaling and nutritional homeostasis (Jones-Rhoades, 2012). Many have highly specific and narrow spatial and temporal expression patterns that are required to precisely execute these regulatory functions (Benkovics and Timmermans, 2014). Therefore, any alteration to the expression of these miRNAs in response to pathogens will likely impact multiple plant phenotypes, a mechanism potentially behind a subset of disease symptoms. For each of these conserved miRNA families, there have been numerous reports, encompassing many different species, implicating their role in resistance/-susceptibility to a large variety of pathogens (for reviews see (Šečić et al., 2021; Islam et al., 2018)). However, as would be expected from the ever-evolving nature of plant-pathogen interactions, very little generalizations can be made regarding the role of each of these miRNAs in pathogen defense from these numerous studies. Nevertheless, it is clear that many of these conserved MTIs can impact disease resistance. A selection of these studies is detailed in Table 1, and only include those studies that have obtained functional evidence for a role in disease resistance via genetically altering the miRNA or its target and correlating this with an altered disease resistance. However, as many of the target genes of conserved miRNAs control fundamental plant processes, altering expression of these conserved miRNA will have pleiotropic impacts on growth and development, and it is these impacts that likely have downstream effects on disease susceptibility. Therefore, the role of these miRNAs in pathogen resistance could generally be regarded as indirect.

miR156 This miRNA family targets a gene family encoding SQUAMOSA promoter binding protein/SBP-like (SBP/SPL) transcription factors that play fundamental roles in development, including juvenile-to-adult phase change and flowering-time (Poethig, 2013)(Fig. 3). Multiple studies have now found that manipulation of the miR156-*SPL* pathway can alter disease resistance (Table 1), where age-related resistance (ARR) to pathogens builds during the juvenile-to-adult phase transition (Hu et al., 2023b). In Arabidopsis, this ARR mechanism is in part controlled by specific *SPL* homologs that activate key defense signaling pathways (Hu et al., 2023b), with both reactive oxygen species (ROS) and salicylic acid (SA) signaling altering upon manipulation of miR156 levels (Yin et al., 2019). However, as would be expected, manipulating miR156 levels strongly impacts the plant phenotype, and in rice, inhibition of miR156 increases resistance to the bacterial pathogen *Xanthomonas oryzae*, but also reduces yield (Liu et al., 2019). However, expressing a *SPL* homolog (*Ideal Plant Architecture1*) under a pathogen-inducible promoter not only circumvented the problem of a yield penalty, but simultaneously enhanced disease resistance and yield. This demonstrated the conserved miR156-*SPL* pathway could be manipulated to result in favorable agronomic traits (Liu et al., 2019). However, it is currently unclear whether this approach would lead to decreased susceptibility to all pathogens, or whether this is specific to *Xanthomonas oryzae*.

miR393 is a conserved miRNA family that plays a clear role in pathogen defense via auxin signaling (Table 1; (Navarro et al., 2006)). It is modestly induced in a diversity of plants (Arabidopsis, tobacco, soybean and maize) when challenged with flagellin-derived peptides (bacterial PAMP peptide flg22; (Navarro et al., 2006)) or biotrophic and hemibiotrophic pathogens (Wong et al., 2014; Chand et al., 2017). The main gene targets of miR393 encode a family of F-box auxin hormone receptors known as Transport Inhibitor Response 1 (TIR1) and Auxin signaling F-Box (AFB) proteins (Navarro et al., 2006). MiR393 expression is generally positively correlated with disease resistance, with overexpression increasing resistance, and knocking down miR393 increasing susceptibility to a number of pathogens in a number of species (Table 1). However, miR393 overexpression can also result in increased susceptibility (Robert-Seilaniantz et al., 2011), underscoring the complexity of interactions to different plant pathogens.

miR168 is a conserved miRNA family that targets *AGO1*, resulting in

Table 1
Indirect regulation of plant defense by conserved miRNA families.

Species	miRNA	Target	Pathogen	Impact	Ref.
Rice	miR156	*SPL*	*Xanthomonas*	-ve	(Liu et al., 2019; Hui et al., 2023)
Arabidopsis	miR156	*SPL*	*Pseudomonas, Botrytis cinerea*	-ve	(Hu et al., 2023b; Sun et al., 2022)(Yin et al., 2019)
Tobacco	miR159	*GAMYB*	*Phytophthora*	-ve	(Zheng et al., 2020)
rice	miR160	*ARF*	*Magnaporthe oryzae*	+ve	(Li et al., 2013)
potato	miR160	*ARF*	*Phytophthora infestans*	both	(Natarajan et al., 2018)
Cotton	miR164	*NAC*	*Xanthomonas*	+ve	(Hu et al., 2020a)
Arabidopsis	miR164	*NAC*	*Alternaria, Pseudomonas*	+ve	(Lee et al., 2017)
Tomato	miR166	*HD-ZIP*	Tomato leaf curl New Delhi virus	+ve	(Prasad et al., 2022)
Maize	miR167	*ARF*	Maize chlorotic mottle virus	+ve	(Liu et al., 2022)
Arabidopsis	miR167	*ARF*	*Pseudomonas syringae* *Plasmodiophora brassicae*	+ve -ve	(Caruana et al., 2020) (Liao et al., 2023)
Rice	miR167	*ARF*	*Magnaporthe oryzae*	-ve	(Zhao et al., 2020)
Rice	miR168	*AGO1*	Rice stripe Tenuivirus, Rice dwarf Phytoreovirus	-ve	(Wu et al., 2015)
Rice	miR168	*AGO1*	*Magnaporthe oryzae*	-ve	(Wang et al., 2021)
Rice	miR169	*NF-YA*	*Xanthomonas*	-ve	(Yu et al., 2018)
Arabidopsis	miR169	*NF-YA*	*Ralstonia solanacearum*	-ve	(Hanemian et al., 2016)
Tomato	miR172	*AP2/ ERF*	*Phytophthora infestans*	+ve	(Luan et al., 2018)
Rice	miR319	*TCP*	*Magnaporthe oryzae*	-ve	(Zhang et al., 2018)
Brassica rapa	miR319	*TCP*	*Sclerotinia sclerotiorum*	-ve	(Dong et al., 2021)
Rice	miR319	*TCP*	Rice ragged stunt virus	-ve	(Zhang et al., 2016)
Apple	miR390		*Colletotrichum*	+ve	(Shi et al., 2022)
Rice	miR395	*APS, SULTR*	*Xanthomonas*	+ve	(Yang et al., 2022)
Arabidopsis	miR396	*GRF*	*Plectosphaerella, Botrytis, Fusarium,* Colletotrichum.	-ve	(Soto-Suárez et al., 2017)
Tomato	miR396	*GRF*	*Phytophthora, Botrytis*	-ve	(Chen et al., 2017)
Alfalfa	miR396	*GRF*	*Spodoptera litura*	-ve	(Yan et al., 2023)
Rice	miR398	*CSD, SODX*	*Magnaporthe oryzae*	+ve	(Li et al., 2013)
Arabidopsis	miR398	*COX, CSD*	*Pseudomonas,* flg22	-ve	(Li et al., 2010)

an auto-regulatory process that controls AGO1 homeostasis, and so indirectly regulates the majority of the miRNA pathway (Vaucheret et al., 2006). Underscoring its complexity, manipulating miR168 levels in rice via transgenic approaches had pleiotropic impacts, including that of yield (panicle number), flowering-time, and immunity to *Magnaporthe oryzae*, a fungus that causes rice blast disease, with each trait being modulated through different miRNAs (Wang et al., 2021). Despite this complexity, the inhibition of miR168 resulted in enhanced yield and immunity, the latter being controlled through the indirect changes to miR164-mediated silencing (Wang et al., 2021). Interestingly, in rice,

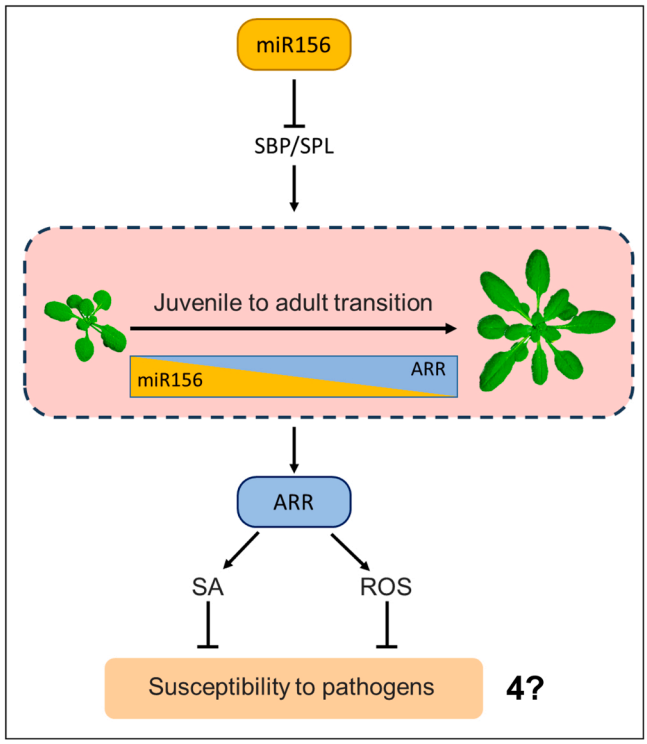

Fig. 3. An example of an indirect impact on disease resistance by a conserved miRNA. MiR156 controls the juvenile to adult transition. Age-Related Resistance (ARR) gives strong protection to the pathogen, *Xanthomonas oryzae*. Altering the miR156-*SPL* target interaction, alters ARR, that then impacts its susceptibility to the pathogen. Outstanding questions (4). Is enhanced disease resistance extended to pathogens other than *Xanthomonas oryzae* resulting in a broad-spectrum resistance?

there is a natural mechanism to modulate miR168 levels, where AGO18 sequesters miR168 that results in greater AGO1 expression (Wu et al., 2015). As AGO1 is directly involved in antiviral immunity, this is a mechanism that could be used to increase resistance to viruses.

miR164 targets a family of genes encoding NAC transcription factors and this regulation has been implicated in a wide variety of processes, fore mostly development, including organ boundary formation and other developmental processes (Sieber et al., 2007). Regarding a role in pathogen defense, overexpression of miR164 led to suppression of immunity in rice to blast fungus (Table 1; (Wang et al., 2018)). This and other data led the authors to propose miR164 is a universal negative regulator of plant immunity, acting across species and against different pathogens (Wang et al., 2018). However, the mechanism behind this is unknown, but a miR164-regulated *NAC* in Arabidopsis has been proposed to promote programmed cell death associated with the HR (Lee et al., 2017).

For many other miRNAs there are reports functionally implicating their role in pathogen response (Table 1). Of all the plant-pathogen systems, the rice - *Magnaporthe oryzae* system appears the most studied, likely reflecting the significance of this disease. In addition to the studies already mentioned above implicating miR164 and miR168, other studies have implicated the role of miR160 (Li et al., 2013), miR167 (Zhao et al., 2020), miR319 (Zhang et al., 2018) and miR398 (Li et al., 2013) in rice immunity to *Magnaporthe oryzae*. Such a large number of miRNA systems is consistent with the general role that miR168 appears to play in rice in response to this pathogen (Wang et al., 2021). However, miR160 and miR398 appear positive regulators of immunity, whereas miR167 and miR319 appear negative regulators of immunity. Clearly, the involvement of these miRNA systems in conferring resistance or susceptibility just to this pathogen, in just this species, appears complex and needs more research to unravel how best to

manipulate these miRNAs to result in increased, durable resistance.

This complexity likely arises as the impact of most of these conserved miRNAs are indirect, whether it is miR160 and miR167 that negatively regulate auxin signaling that leads to increased disease resistance (Fahlgren et al., 2007), or miR395 that regulates sulfate levels and its distribution in the plant that impacts pathogen viability (Yang et al., 2022). For many miRNA families, there is more limited evidence of their ability to impact pathogen interactions; families such as miR159, miR166, miR169, miR390, miR397, all of which have studies supporting a role in pathogen resistance (Table 1). However, more work is needed to determine whether these roles are consistent across species and against multiple pathogens, or whether their role varies from species to species and from pathogen to pathogen.

7. Non-conserved or lineage-specific miRNAs regulating defense

The majority of miRNAs in any given plant species can be considered non-conserved or lineage-specific miRNAs (Qin et al., 2014). Unlike conserved miRNAs, which are generally characterized by precise processing resulting in miRNAs of low sequence variation that are expressed in high abundance, non-conserved miRNAs are often processed with less precision and expressed at much lower levels (Vazquez et al., 2008). While some non-conserved miRNAs are transcribed from gene regions, most originate from intergenic sites similar to conserved miRNAs (Voinnet, 2009). However, unlike conserved miRNA families that correspond to multiple DNA loci, primary transcripts of non-conserved miRNAs are typically transcribed from fewer loci (many correspond to a single locus) and are processed by various DCLs rather than universally by DCL1 (Henderson et al., 2006). Given this sequence diversity of non-conserved miRNAs, and their frequent birth and death (Allen et al., 2004), they potentially represent a source of evolutionary dynamic regulators that could be recruited for pathogen defense. Indeed, certain non-conserved miRNAs are prominently expressed during pathogen invasions, implying their potential role in defense. Genetic analysis has identified a number of non-conserved miRNAs (Table 2), that play direct or indirect roles in plant defense responses.

miR846 is unique to Arabidopsis and is associated with the plant's defense mechanisms (Xie et al., 2018). Its expression level negatively correlates with plant resistance, which is evident in Arabidopsis where transgenic miR846 overexpression increases susceptibility to *Pseudomonas* infection, while knockdown enhances resistance. Predicted targets of miR846, such as *NBS-LRR* genes and jacalin lectin genes, undergo repression in miR846-overexpressing plants and up-regulation in miR846 knockdown plants. Furthermore, miR846 contributes to induced systemic resistance in Arabidopsis through jasmonic acid (JA)-dependent signaling, reinforcing its regulatory role in plant defense mechanisms (Xie et al., 2018).

miR773 is a non-conserved miRNA found in Arabidopsis that acts as a negative regulator of defense by targeting *METHYLTRANSFERASE 2* (*MET2*), a DNA methyltransferase (Salvador-Guirao et al., 2018). Inhibiting miR773 function via target mimics (*MIM773*) increases *MET2* expression that results in enhanced resistance to fungal pathogens. This defense response appears complex, involving ethylene, JA, and SA, with elevated callose deposition and ROS levels upon pathogen challenge (Salvador-Guirao et al., 2018). Conversely, Arabidopsis plants overexpressing miR773 displayed reduced callose deposition and increased susceptibility to *Pseudomonas* (Li et al., 2010), *Plectosphaerella* and *Fusarium* (Salvador-Guirao et al., 2018). Interestingly, although altering *MET2* expression would be predicted to have pleiotropic impacts, miR773-mediated regulation of *MET2* expression only appears to impact disease resistance. However, its utility for developing new strategies for disease resistance will depend on what other closely related species contain this miRNA.

miR444 is a monocot-specific miRNA which targets a family of genes encoding MADS box proteins. In rice, miR444 accumulates in response to Rice Stripe Virus (RSV) infection and overexpression of miR444 enhances rice's resistance to RSV. A potential mechanism is that the miR444 targets, OsMADS23, OsMADS27a, and OsMADS57, can form dimers that bind to CArG motifs of the *RNA-DEPENDENT RNA POLYMERASE1* (*RDR1*) promoter to repress its expression (Wang et al., 2016). Therefore, elevated expression of miR444 results in elevated *RDR1* expression, a recognized gene of antiviral defense (Li et al., 2010; Wu et al., 2009). However, miR444 has also been found to play a role in axillary bud outgrowth and tillering (Guo et al., 2013), as well as nitrate signaling (Yan et al., 2014). Although the latter has been proposed to potentially enhance rice's resistance by effectively managing nitrogen levels during virus infections (Wang et al., 2016), it is clear again that manipulation of miR444 is likely to have pleiotropic impacts on the plant that encompasses both viral RNA silencing and the regulation of host genes, some of which may or may not, impact its susceptibility to pathogens (Wang et al., 2016).

miR528 is another monocot specific miRNA that plays a role against RSV (Wu et al., 2017). This miRNA targets the *L-ascorbate oxidase* (*AO*) gene, which is involved in the production of ROS. Similar to miR168 as described above, during viral infection the AGO homolog AGO18 is induced and inhibits miR528 function by sequestering the miRNA. This enables *AO* to increase expression leading to increased ROS production, which plays a positive role in defense against RSV. Therefore, AGO18 is acting as a modulator of both conserved and non-conserved miRNA function which leads to increased viral resistance.

8. Other miRNA classes - miRNA*s in pathogen defense

The plant miRNome is complex, and there are other classes of

Table 2
Non-conserved or lineage-specific miRNAs regulating plant defense.

Species	miRNA	Target family	Pathogen	Impact	Ref.
Arabidopsis	miR773	*MET2*	*Plectosphaerrella cucumerina* *Fusarium oxysporum* *Colletototrichum higginianum*	-ve	(Salvador-Guirao et al., 2018) (Li et al., 2010)
Arabidopsis	miR163	*PXMT1 and FAMT*	*Pseudomonas syringae*	-ve	(Chow and Ng, 2017)
Arabidopsis	miR846	*JRL, NBS-LRR*	*Pseudomonas syringae*	-ve	(Xie et al., 2018)
Tomato	miR1916	*STR-2, UGT, MYB12*	*Phytophthora infestans* *Botrytis cinerea*	-ve	(Chen et al., 2019)
Rice	miR444	*OsMADS23 OsMADS27a OsMADS57*	*Rice stripe virus (RSV)*	+ve	(Wang et al., 2016)
Rice	miR444b.2	*ET, IAA, WRKYs, F-boxes*	*Rhizoctonia solani*	-ve	(Feng et al., 2023)
Rice	miR1871	*MFAP1*	*Magnaporthe oryzae*	-ve	(Li et al., 2022)
Rice	miR1873	*LOC_Os05g01790*	*Magnaporthe oryzae*	-ve	(Zhou et al., 2020)
Rice	miR528	*L-ascorbate oxidase*	*Rice stripe virus (RSV)*	-ve	(Wu et al., 2017)
Maize	unmiR4	*ZmGA2ox4*	*Fusarium verticillioides*	-ve	(Xu et al., 2022)
Cotton	miR477	*CBP60A*	*Verticillium dahlia*	-ve	(Hu et al., 2020b)
Cotton	miR530	*SAP6*	*Verticillium dahlia*	-ve	(Hu et al., 2023a)

miRNAs that would potentially also contribute to disease resistance. One such class is miRNA*s (or passenger strands) that are preferentially degraded during the process of miRNA loading into AGO, and so have been traditionally considered as being non-functional byproducts of miRNA biogenesis. However, there is emerging evidence suggesting that miRNA* strands can play significant and distinct roles, including that of plant immune responses (Liu et al., 2017). For instance, miR393b* in Arabidopsis is loaded into AGO2 which targets *MEMB12*, a gene encoding a SNARE protein that represses the exocytosis of antimicrobial PATHOGENESIS-RELATED proteins that confer resistance against bacterial pathogens (Zhang et al., 2011; Baldrich and San, 2016). This is intriguing given that miR393 also plays a role in pathogen defense in Arabidopsis, so the miR393/miR393* pair are functionally related but work via distinct targets and different AGO proteins (Zhang et al., 2011). However, there have been no subsequent reports of miR393* performing this role, so currently it is uncertain whether such functions occur in species other than Arabidopsis. Another example is the Arabidopsis miR825/miR825* pair, both of which are proposed to be regulating pathogen resistance, with miR825* being a 22-nt miRNA that targets an *NBS-LRR* gene that triggers phasiRNAs (Niu et al., 2016; Nie et al., 2019). However, miR825 * has been subsequently described as miR825–5p (López-Márquez et al., 2021), this being likely as in many of these non-conserved miRNAs, it is ambiguous which sRNA should be classified as the miRNA*. This highlight that although we have attempted to classify miRNAs into different groupings in this review, it must always be acknowledged that these groupings are human constructs that will have exceptions and should only be thought of as generalizations as a way to help summarize and understand complexity.

9. Conclusions and perspectives

As noted above, there has been extensive effort in understanding the role of miRNAs in plant pathogen defense and it is clear that many different miRNAs can impact plant-pathogen interactions. These miRNAs could be thought of as falling into three broad classes (Fig. 4).

Firstly, the 22 nt miR482/2111 superfamily and other functionally analogous miRNAs that target genes directly involved in plant immunity, such as the *NBS-LRR* families, thereby negatively regulating defense response. Despite this direct regulation of plant immunity, it is yet to be shown that these miRNAs can provide resistance to pathogens, including the extent and mechanism(s) by which these miRNAs respond to pathogens (López-Márquez et al., 2021). Currently, there are no clear examples of manipulating these miRNAs to increase disease resistance.

Secondly, the set of conserved miRNA families that are mostly 21-nt in length, all of which have some evidence that their expression responds to pathogen infection, although this is pathogen and plant species dependent, rather than a general conserved response. As the major target genes of these conserved miRNA families are not directly involved in defense, but rather primarily genes involved in developmental and/or hormonal responses, the impact of these miRNAs on disease susceptibility/resistance is indirect, and in many instances complex, as altering their expression generally has pleiotropic impacts. Although there are clear examples of their manipulation to increase resistance to a particular pathogen, in a particular plant species, given the diversity of plant-pathogen interactions, infection strategies and target tissues, currently it is not clear whether generalized resistance strategies can be engineered via manipulation of these miRNAs.

Thirdly, the set of non-conserved miRNAs represent a rapidly evolving, highly dynamic source of gene regulators with the greatest sequence diversity of miRNAs in any given species. Hence, they represent a source of potential regulators that could be recruited into the ever-present plant-pathogen arms race. However, given their narrow species range, this may limit their applicability across species in terms of developing novel resistance strategies, but understanding these systems may yield novel ideas and approaches.

There are promising reports of strategies to manipulate miRNAs for crop improvement regarding disease resistance. For example, altering conserved miRNAs expression via pathogen-inducible promoters limits altered miRNA expression both spatially and temporally to infected cells, avoiding widespread changes to miRNA expression and the pleiotropic impacts on phenotype associated with this. However, even in these instances, most studies have only looked at the outcome via testing of a single pathogen, so whether optimizing for resistance against one pathogen, affects the plants resistance to other pathogens, or to that of beneficial microorganisms remains to be determined. The complexity of plant-pathogen interaction becomes clearly apparent when looking at the rice - *Magnaporthe oryzae* interaction, where altering the expression of so many different miRNAs can impact this one particular interaction (Table 1 and 2). So, from all of this, and what should be expected regarding plant-pathogen interactions, that there is unlikely any miRNA that can be considered a silver bullet against plant pathogens, and although there are many promising strategies for regulating miRNAs to improve disease resistance, there still appears much to resolve before these strategies could be deployed into field grown crops.

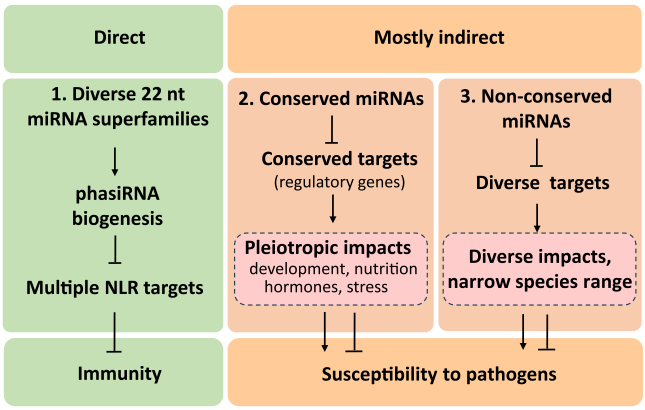

Fig. 4. An overview of the generalized classes of miRNAs involved in plant pathogen defense.

CRediT authorship contribution statement

Millar Anthony A: Writing – original draft, Writing – review & editing. **Asadi Mohsen:** Writing – original draft, Writing – review & editing.

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.

Data availability

No data was used for the research described in the article.

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