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Review Article

Receptor-mediated nonhost resistance in plants

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Nonhost resistance (NHR) is a plant immune response that prevents many microorganisms in the plant's environment from pathogenicity against the plant. Since successful pathogens have adapted to overcome the immune systems of their host, the durable nature of NHR has potential in the management of plant disease. At present, there is genetic and molecular evidence that the underlying molecular mechanisms of NHR are similar to the plant immune responses that occur in host plants following infection by adapted pathogens. We consider that the molecular basis of NHR is multilayered, conferred by physicochemical barriers and defense responses that are induced following molecular recognition events. Moreover, the relative contribution of each component may depend on evolutionary distances between host and nonhost plants of given pathogen species. This mini-review has focused on the current knowledge of plant NHR, especially the recognition of non-adapted pathogens by nonhost plants at the cellular level. Recent gains in understanding the roles of plasma membrane-localized pattern-recognition receptors (PRRs) and the cytoplasmic nucleotide-binding leucine-rich repeat receptors (NLRs) associated with these processes, as well as the genes involved, are summarized. Finally, we provide a theoretical perspective on the durability of receptor-mediated NHR and its practical potential as an innovative strategy for crop protection against pathogens.

What is nonhost resistance?

In their natural environment, plants coexist with numerous microorganisms. Most relationships between plants and microbes are benign or even mutually beneficial. For any species of plant, only a few of the microbes it encounters are pathogenic to it [1]. Plants have evolved a multilayered defense system to fend off invading pathogens, and only microbe species or strains that have adapted to successfully bypass or incapacitate those defense systems are able to infect plants. This defense of plants against most microbes is considered nonhost resistance (NHR).

NHR can be simply defined as a plant immune response against non-adapted pathogens. The relationship between pathogen and host has been referred to as a co-evolutionary arms race, in which the adapted pathogen must continuously evolve to overcome host defense systems, which are, in turn, also evolving. In this scenario, it is clear that host resistance is not necessarily durable [2]. This specialization of pathogenicity and host defense is inefficient as the machinery by which plants provide resistance to a wide range of potential pathogens. Thus, lack of adaptation is assumed to be an essential concept of the durable nature of NHR [3].

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Molecular components of NHR

Recently, numerous studies on the interactions between nonhost plants and non-adapted pathogens have been performed by inoculating various nonhost plants with non-adapted pathogens. The cytologic, genetic, and molecule-based evidence has led to the suggestion that nonhost plant responses to non-adapted pathogens and host response to pathogens share pre- and post-invasion components [4,5].

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Physicochemical barriers

In many studies, non-adapted pathogens failed to penetrate the plant epidermis. Apparently, the pathogens could not overcome the physicochemical barriers on the plant surfaces. Consequently, there was no macroscopic evidence of infection [6]. Failure to invade host tissue was in some instances due to the composition of the cell wall or the waxy cuticle on the epidermis.

Evidence for the importance of physicochemical barriers comes from genetic studies. The *irg1/palm1* mutant of the legume *Medicago truncatula* does not synthesize epicuticular wax, and could be colonized by non-adapted rust pathogens [7]. The *P450 CYP96B22* gene of barley is believed to be related to the synthesis of epicuticular wax, and silencing the gene enabled isolates of the non-adapted fungal pathogen *Magnaporthe oryzae* to infect nonhost barley [8]. It is also interesting to note that the germination rates of spores of the fungus *Melampsora larici-populina* in cuticle extracts derived from host and nonhost plants were markedly reduced in nonhost extracts compared with host extracts [9]. From these results, we suggest that the composition of plant cuticles not only functions as a physical barrier to non-adapted pathogens but also acts as an inductive signal for initiating infection by adapted pathogens.

Plant secondary metabolites with antimicrobial activity may also be determinants of plant host status. *Phytophthora infestans* is the oomycetes pathogen that causes late blight of potato and tomato but is not a pathogen of pepper and tobacco. The *P. infestans* was more susceptible to the sesquiterpene phytoalexin capsidiol produced by pepper and tobacco compared with the *Phytophthora capsici*, a species adapted to be pathogenic to tobacco and pepper [10,11]. Similarly, avenacin is an antimicrobial agent present in the roots of many oats. *Gaeumannomyces graminis* pv. *avenae*, a pathogen of oats, produces avenacinase, an enzyme that can degrade avenacin [12]. *G. graminis* pv. *tritici*, in contrast, cannot infect oats that accumulate avenacin [12]. Glucosinolate compounds are suggested to be a component of NHR in Brassicaceae. *Arabidopsis* plants deficient in PEN2, a glycosyl hydrolase, can be infected by the grass pathogen *Blumeria graminis* f. sp. *hordei*, a non-adapted pathogen of *Arabidopsis* plants [13]. Also in *Arabidopsis*, mutants that were deficient in a tryptophan-derived antimicrobial compound were colonized by the non-adapted pathogen *P. infestans* [14,15].

We conclude, from the studies discussed above, that physicochemical barriers contribute to NHR. Especially, while adapted pathogens are able to suppress or bypass these barriers of host plants, non-adapted pathogens cannot overcome them.

Receptor-mediated recognition

In addition to physicochemical barriers, plants have evolved surveillance systems composed of plasma membrane-localized pattern-recognition receptors (PRRs) and cytoplasmic nucleotide-binding leucine-rich repeat receptors (NLRs) that recognize nonself-derived molecules [16]. PRRs generally recognize pathogen-associated molecular patterns (PAMPs), such as bacterial flagellin and fungal chitin, and induce PAMP-triggered immunity (PTI). NLRs directly or indirectly recognize pathogen effectors, which are secreted into plant cells by pathogens to modulate the plant immune system and induce effector-triggered immunity (ETI). Both defense responses lead to oxidative burst, transcriptional reprogramming, and biosynthesis of defense-related compounds through intracellular signaling to limit invading pathogens [17]. While the repertoire of downstream signaling is broadly shared in both processes, responses in ETI are known to be more prolonged and robust [18] and often culminate in highly localized hypersensitive response (HR) cell death, which restricts pathogen growth in invading tissues.

PTI

PAMPs are generally (but not always) conserved in microbial pathogens. Thus, plants can recognize the PAMPs of non-adapted pathogens. For example, when *Arabidopsis* was inoculated with the non-adapted *Pseudomonas syringae* pv. *phaseolicola*, PTI-like transcriptional changes similar to flg22 treatment were induced [19]. Genetic analysis of this response revealed that the flg22 receptor FLS2 is involved in this type of NHR [20]. In addition, studies with loss-of-function mutants have been interpreted to support the involvement of multiple PTI-related components, specifically nonhost 1 (NHO1) [21], PEN2 [22,23], BRI1-associated receptor kinase (BAK1) [24], and the PRR receptor HvLEMK1 [25], in NHR. More examples and references have been well documented in earlier reviews [26].

Not only the PAMPs of non-adapted pathogens are recognized by their nonhost plants, but several lines of evidence are consistent with the contention that non-adapted pathogens are less capable of suppressing the defense mechanisms of nonhost plants than adapted pathogens. One example is the *Arabidopsis* flg22-induced downstream defense component NHO1. It is suppressed by the adapted bacterium *Pseudomonas syringae* pv. *tomato* (*Pst*), but not by the non-adapted pathovar *tabaci* [27]. Considering that no less than nine effectors of *Pst* (HopS1, HopAI1, HopAF1,

HopT1-1, HopT1-2, HopAA1-1, HopF2, HopC1, and AvrPto, which are not conserved in *P. syringae* pv. *tabaci* except for HopT1-1) are involved in suppressing flg22-induced NHO1 expression [28], effector-mediated suppression would be the crucial strategy of adapted pathogen, *Pst*, to overcome PTI, while non-adapted pathogens, pv. *tabaci*, is less-likely to be specialized to suppress PTI of nonhost. Similarly, when the *Arabidopsis* EF-Tu receptor (EFR), which recognizes the bacterial elongation factor Tu, was transferred into *Nicotiana benthamiana* and tomato, the transgenic plants acquired broad-spectrum disease resistance. This resistance extended to *Ralstonia solanacearum*, a bacterial pathogen of Solanaceae plants but not adapted to *Arabidopsis* [29]. More recently, it was noted that the orthologous PRRs, Rphq2 and Rph22, which are derived from cultivated and wild barley, respectively, modified host status against leaf rust caused by *Puccinia hordei*. Cultivated barley is resistant to *P. hordei-bulbosi*, while wild barley is resistant to *P. hordei.* Barley accessions were generated that were extremely susceptible to both the leaf rust pathogens. The two PRRs were cloned, and each was singly transferred into susceptible accession. Transgenic plants with Rphq2 were more resistant to *P. hordei-bulbosi* compared with *P. hordei*, while transgenic plants that received Rph22 exhibited the reverse reaction. Both lines were resistant to the wheat pathogen *Puccinia triticina*, which is non-adapted to both cultivated and wild barley [30]. These results imply that non-adapted pathogens are less capable of overcoming nonhost-derived PRRs.

Although PRR-mediated PAMP recognition is a highly conserved process in plants, small differences between host and nonhost plants may contribute to durable NHR. Thus, the identification of PRR orthologs from various plant species and further characterization of the differences between hosts and nonhosts PRRs could be a promising strategy for understanding the durable nature of PRR-mediated NHR. In addition, recent studies suggesting PAMPs could be also variable between the species, especially flg22 [31]. Thus, identification of PRR homologs in various plant species could be also prominent strategy for broad-spectrum resistance, as the $FLS2^{XL}$ derived from wild grape (*Vitis riparia*) recognizes $flg22^{Atum}$ of *Agrobacterium tumefaciens* which is not recognized by FLS of *Arabidopsis* [32].

ETI

While PAMPs are relatively conserved in pathogenic microorganisms, effectors have lineage-specific sequence diversity and are prone to mutation [33]. Based on a number of studies, it seems that NLR-mediated effector recognition is also associated with NHR. For example, in several pioneering works, HR-like cell death phenotypes were acquired by inoculating nonhost plants with non-adapted pathogens [34–37]; these phenotypes are hallmarks of ETI. Results from studies with loss-of-function mutants, specifically loss of ETI signaling components such as enhanced disease susceptibility 1 (EDS1), phytoalexin-deficient 4 (PAD4), senescence-associated gene 101 (SAG101) [13], WRKY [38], and SGT1 [39], have also provided evidence that NLRs are components of NHR.

Numerous effectors of non-adapted pathogens elicit HR cell death and defense responses in nonhost plants. For examples, the *P. capsici* effector PcAvr3a1 triggers HR in nonhost *Nicotiana tabacum* [37] and multiple RxLR effectors of *P. infestans* trigger HR-like cell death in nonhost chili pepper [40]. In the latter, it was noted that the HR phenotypes were inherited by Mendelian genetics. The *Xanthomonas campestris* effector XopQ triggers EDS1-dependent HR in nonhost *Nicotiana* spp. [41] and multiple *Hyaloperonospora arabidopsidis* effectors inhibit bacterial growth when transferred into nonhost turnip plants through the bacterial type-three secretion system [42]. Based on these examples, ETI could be a component of NHR, and some instances, recognition of multiple non-adapted pathogen effectors contributes to NHR. This proposal requires a caution, however, as there are examples of single effector deletions, such as HopAS1, HopQ1 of *Pseudomonas syringae* [43,44], or PWT3 of rice blast [45], enabling host 'jumps' in which the pathogens infect previous nonhost plants. The quantitative nature of NHR (a number of genes) might depend on which plant and pathogen species are considered. In other words, it may be context dependent [5,46].

Several plant NLRs that correspond to HR-inducing effectors from non-adapted pathogens have been identified in nonhost plants. Some of these NLRs have been transferred into host species and, indeed, conferred resistance to non-adapted pathogens. Several examples are summarized below (Table 1). Silencing a homolog of the I_2 gene family in *N. tabacum* resulted in loss of ability to recognize *P. capsici* effector PcAvr3a, and subsequently compromised the resistance to the *P. capsici* [47]. An NLR from maize, Rxo1, conferred resistance to the bacterial streak pathogen *Xanthomonas oryzae* pv. *oryzicola* (*Xoc*) upon its transfer into rice plants [48,49]. Similarly, an NLR from *Arabidopsis*, WRR4, conferred resistance to the pathogen that causes white rust when transferred into oilseed brassica crops [50,51]. When the *CcRPP1* gene from pigeon pea, which encodes an NLR, was transferred into soybean, the plant acquired resistance to the soybean rust pathogen *Phakopsora pachyrhizi* (*Pp*) [52]. In barley, the NLR resistance to *Pseudomonas syringae* (Rps)7 were transferred into experimentally generated susceptible barley (SusPtrit) and conferred resistance to the wheat stripe rust pathogen *Puccinia striiformis* [53]. An exciting prospect is apparent

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Table 1 Examples of receptors that contribute to NHR

Receptors	Nonhost	Pathogen	Description	References
NLRs				
Rxo1	*Zea mays (Maize)*	*Xanthomonas oryzae* pv. *oryzicola*	Resistance in rice	[48,49]
WRR4	*Arabidopsis thaliana*	*Albugo candida*	Resistance in *Brassica napus* and *Brassica juncea*	[50,51,55]
CcRPP1	*Cajanus cajan* (pigeon pea)	*Phakopsora pachyrhizi*	Resistance in soybean	[52]
Rps7	*Hordeum vulgare* (barley)	*Puccinia striiformis*	Resistance in susceptible barley (SusPtrit*)	[53]
Pm3	*Triticum aestivum*	*Blumeria graminis* f. sp. *tritici*, *secalis*, *dactylidis*	Resistance in SusPtrit barley and tolerant to suppression of Svrpm3 homologs from non-adapted pathogens	[65]
Rpi-amr1	*Solanum americanum*	*Phytophthora parasitica, Phytophthora cactorum*	Induce HR against Avr-amr1 homologs of non-adapted pathogens	[57]
Rpi-amr3	*Solanum americanum*	*Phytophthora parasitica, Phytophthora palmivora*	Resistance in *Nicotiana benthamiana*	[56]
PBR1	*Hordeum vulgare*	*Pseudomonas syringae* pv. *phaseolicola*	Recognize AvrPphB and trigger HR	[59]
RPS2/MR5	*Arabidopsis thaliana/Malus domestica*	*Pseudomonas syringae, Erwinia amylovora*	Recognize both *PsAvrRpt2* and *EaAvrRpt2* and trigger HR	[60]
Ntl2	*Nicotiana tabacum*	*Phytophthora capsici*	*l2*-silenced plants exhibited compromised resistance to *Pc* and HR against *PcAvr3a1*	[47]
PRRs				
FLS2	*Arabidopsis thaliana*	*Pseudomonas syrngae* pv. *tabaci*	Suppressed by adapted pathogen, *P. syringae* pv. tomato, but tolerant to non-adapted *P. syringae* pv. *tabici*	[20,27,28]
EFR	*Arabidopsis thaliana*	*Ralstonia solanacearum*	Resistance in tomato and *Nicotiana benthamiana*	[29]
Rph22	*Hordeum bulbosum*	*Puccinia hordei, Puccinia tritici*	Resistance in Golden SusPtrit barley	[30]
Rphq2	*Hordeum vulgare*	*Puccinia hordei-bulbosi, Puccinia tritici*	Resistance in Golden SusPtrit barley	[30]
HvLEMK1	*Hordeum vulgare*	*Blumera graminis* f. sp. *tritici*	*HvLEMK1*-silenced barley exhibited compromised resistance against non-adapted pathogen, and transient expression of *HvLEMK1* in both wheat and barley conferred quantitative resistance to *Bgt*	[25]

here. Resistance in wild rice to *Xoc*, or resistance to *Pp* in soybean has not been identified. The possibility of identifying NLRs from nonhost plants effective in host–pathogen interactions could represent a novel genetic resource for managing plant disease.

Physicochemical barriers of plants are generally polygenic trait in nature, and transfer of these traits between plants may prove problematic. Conversely, transferring immune receptors (PRRs or NLRs) from nonhost to host plants using biotechnological approaches, may prove more tenable. It is also an untapped genetic resource. Thus, further characterization and understanding of receptor-mediated NHR could provide promising strategies for developing durable resistant crops.

We conclude that, while only one or a few genes determine host status in some cases, NHR is generally conferred by coordination of multiple defense mechanisms. These vary from physicochemical barriers to receptor-mediated induced responses [4]. The molecular evolutionary concept could provide a plausible explanation for the context dependency of NHR. The phylogenetic distances between the host and nonhost plants may determine the quantitative nature and relative contribution of each component to NHR against pathogens [54]. Moreover, the lack of adaptation in pathogens to defense machinery of nonhost plants makes NHR effective.

A molecular evolutionary concept of receptor-mediated NHR: recognition and durability

As previously discussed, nonhost PRRs recognize conserved PAMPs of non-adapted pathogens. It has also been demonstrated that nonhost PRRs are more tolerant to suppression by non-adapted pathogens than are host PRRs [30], which may explain the durability of PRR-mediated NHR. We assumed that NLR-mediated NHR would be similar. Therefore, we consider two questions here. First, 'How do NLRs recognize the effectors of non-adapted pathogens, which are more diversified than PAMPs?' Our second question is 'Do NLRs from nonhosts confer durable resistance

against immune suppression by host-adapted pathogens?' These two questions can be partly answered from the results of recent studies on recognition and durability.

How do plants maintain receptors recognizing non-adapted pathogens?

Accumulating evidence suggest that effectors, similar to PAMPs, are conserved in closely related species of pathogens and multiple NLRs recognize homologous effectors of both non-adapted and adapted pathogens. For example, the *Arabidopsis* WRR4A and WRR4B NLRs recognize CCG effectors derived from both adapted and non-adapted races of *Albugo candida* [55]. Another example is the NLR resistance to *Phytophyhora infestans* (Rpi)-amr1 derived from *Solanum americanum* could recognize *P. infestans* Avramr1 as well as its homologs from *Phytophthora parasitica*, and *Phytophthora cactorum* [56,57]. Furthermore, Rpi-amr3 of *S. americanum* recognizes not only *P. infestans* Avramr3 but also Avramr3 orthologs from various *Phytophthora* spp. and confers resistance against *P. parasitica* and *P. palmivora* in the *N. benthamiana* system [58]. It may be NLRs that evolved to recognize adapted pathogen effectors also could recognize non-adapted pathogen effectors because those effectors are conserved in closely related adapted and non-adapted pathogens.

On the other hand, several NLRs reported to recognize the effectors of non-adapted pathogen, which infect evolutionarily distant host, through the homologous host targets. *Arabidopsis* RPS5 indirectly recognizes the *Pseudomonas syringae* effector AvrPphB, which cleaves the *Arabidopsis* host target AtPBS1. Likewise, an NLR from barley, PBR1, also recognizes AvrPphB via PBS1 orthologs of barley [59]. Moreover, *Arabidopsis* RPS2 indirectly recognizes both AvrRpt2 homologs of *Erwinia amylovora* and *Pseudomonas syringae*, which are non-adapted and adapted pathogens of *Arabidopsis*, respectively, via AtRIN4. Similarly, MR5, an NLR derived from wild apple, recognized both AvrPphB homologs through MdRIN4 [60]. Notably, MR5/RPS2 and PBR1/RPS5 exhibit no sequence homology between the functionally homologous (those recognize same or similar effectors) NLRs, but the effector targets exhibit sequence homology between AtRIN4/MdRIN4 and AtPBS1/HvPBS1. These results indicate that the ability to recognize these two effectors evolved separately in each plant.

In summary, it appears that plants can recognize effectors from both adapted and non-adapted pathogens through similar NLRs because the effectors are conserved in closely related pathogens. Furthermore, even considering distantly related pathogen species, some effectors could share similar virulence strategies or host targets. Thus, plants could recognize both effectors using NLRs that surveil homologous host targets (Figure 1A,B). Therefore, if the phylogenetic distance between nonhost and host plants to a given pathogen go closer, the possibility (or a number) of cross recognition of non-adapted pathogen effectors by nonhost NLRs may be increased. This proposal is similar to the molecular evolutionary concept advanced with regard to ETI in NHR [54]. In this context, we expect NLRs of nonhost plants that are homologous to previously known host resistance genes to be promising candidates for conferring NHR.

In addition, though without the sequence similarity between effectors, recent studies also suggest that conserved 3D structural features of effectors is crucial for recognition by NLRs, such as AVR1-CO39 and AVR-Pia [61,62]. Considering sequences of effectors are often not conserved even between the closely related species, recognizing conserved structurally similar effectors could be another mechanism of recognizing non-adapted pathogens.

Could immune receptors from nonhost plants be more durable?

About the PTI-mediated NHR, the following scenario is proposed. Orthologous PRRs derived from nonhost recognize the same or similar PAMPs as host PRRs, while PRRs from nonhost plants are more tolerant to suppression by non-adapted pathogens and contribute to the durability of NHR [30]. This scenario is reasonable, considering that pathogens are specialized to suppress host immune system rather than that of nonhost. In this context, pathogen machinery that is most likely to act as a suppressor of immune response would be an effector. Indeed, effector-mediated suppression of PTI/ETI is a well-known phenomenon [2,63].

We next consider the question: If homologous NLRs derived from both host and nonhost plants that recognize the same or similar effectors, would the homologous NLRs derived from nonhost plants be more tolerant to suppression by non-adapted pathogens? A suitable example for this hypothesis is the NLRs in the Poaceae family, specifically Pm3, which is a NLR family of wheat. Its corresponding effector, Avrpm3, is conserved in *Blumeria graminis* f. sp. *tritici, secalis*, and *dactylidis* that cause rust in wheat, rye, and wild grass (*Dactylis glomerata*), respectively. The Pm3 NLRs recognize all Avrpm3 effector homologs and confer resistance to the non-adapted rye mildew pathogen on wheat. Furthermore, Pm3-mediated resistance is suppressed by another effector, Svrpm3 of *B. graminis* f. sp. *tritici* [64], and Svrpm3 homologs are also conserved in *B. graminis* f. sp. *secalis* and *dactylidis*. Notably, while Pm3 recognizes all homologs of Avrpm3 derived from *B. graminis* f. sp. *tritici, secalis*, and *dactylidis*, Pm3-mediated HR cell death

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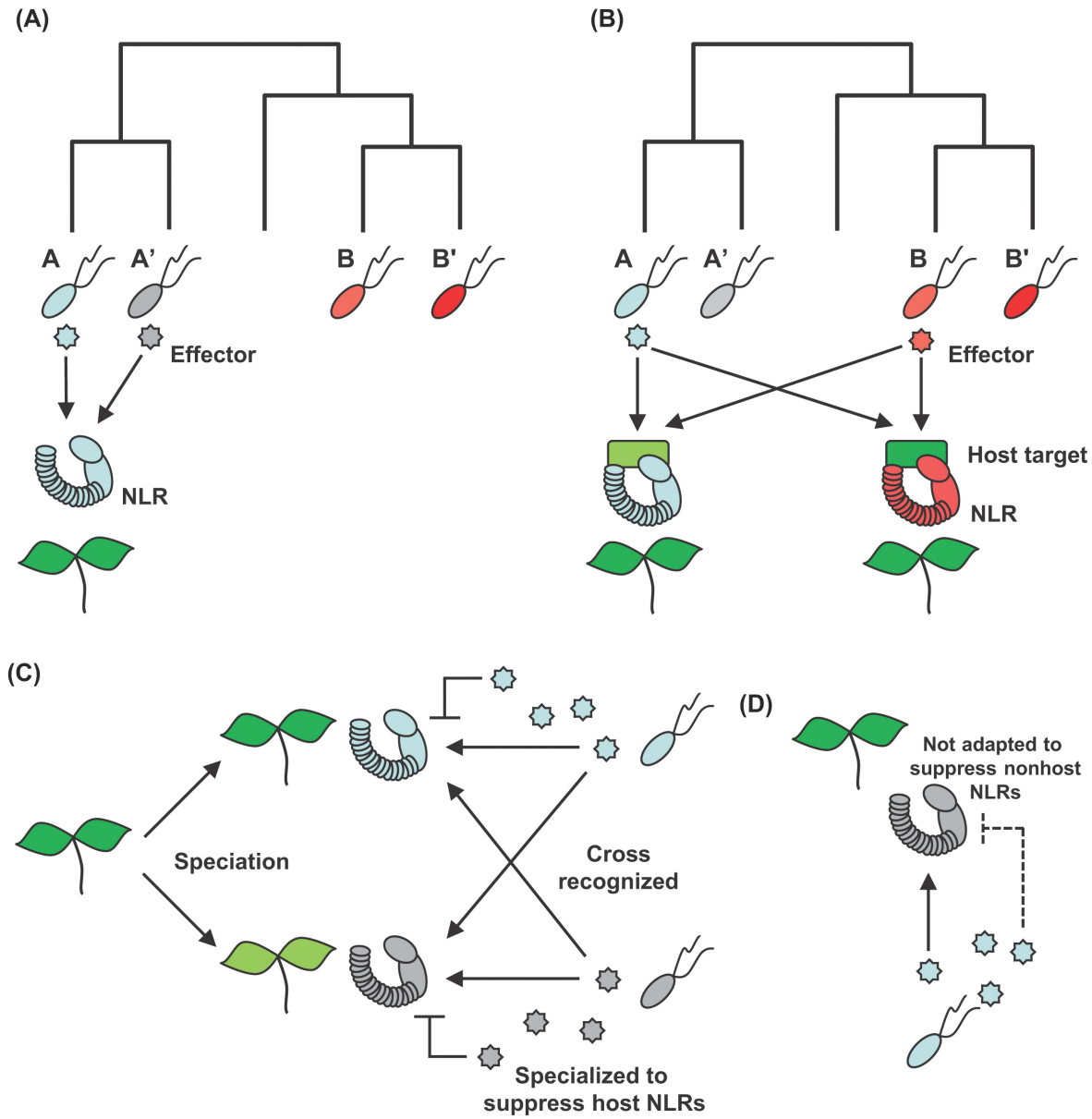

Figure 1. Mechanistic model of the NLR-mediated NHR

(**A**) NLRs evolved to recognize adapted pathogen effectors also recognize conserved homologous effectors of non-adapted pathogen. A, A′, B, and B′ indicate different strains (or species) of pathogen. (**B**) Effectors of distantly related non-adapted pathogens targeting similar host targets of adapted pathogens could be recognized by surveillance system of nonhost plants. (**C**) While non-adapted pathogens recognized by nonhost plants NLRs, non-adapted pathogens cannot efficiently suppress nonhost defense machineries, because of lack of adaptation. (**D**) Transfer of nonhost NLRs into susceptible host plants could be promising strategy for conferring durable resistance.

is not suppressed by Svrpm3 of *B. graminis* f. sp. *secalis* which is non-adapted pathogen of wheat [65]. These results imply that NLRs recognizing non-adapted pathogen effectors could be effective because non-adapted pathogen is not specialized to suppress nonhost NLR-mediated resistance while adapted pathogens have evolved suppressing mechanisms against it.

To date, a number of effectors have been identified that suppress NLRs or ETI signaling cascades, such as the *Phytophthora infestans* RxLR effector IPI-O4, which suppresses the wild potato-derived NLR Rpi-blb1 [66,67], and

the effector PITG_15278 which suppresses Rpi-blb2 [68]. The *Ralstonia solanacearum* effector RipAC interacted with SGT1 and prevented mitogen-activated protein kinase (MAPK)-mediated phosphorylation [69,70]; the *Xanthomonas axonopodis* pv. *manihotis* effectors XopE4 and XopAo1 suppress the ETI-mediated HR [71]. Although a few cases such as Pm3 have been reported, multiple NLRs that contribute to NHR and ETI suppressors also have been identified. Thus, further identification of functionally homologous NLRs from host and nonhost plants that recognize the same or similar effectors of both adapted and non-adapted pathogens will be necessary for the reciprocal approaches to test whether the NLRs derived from nonhost plants could be more robust against suppression by non-adapted pathogens.

We propose that similar to PTI in NHR, nonhost plants could recognize effectors of non-adapted pathogen using NLRs. Moreover, the NLRs or ETI signaling components of nonhosts could be more tolerant to effector-mediated suppression by non-adapted pathogens due to lack of adaptation (Figure 1C,D).

Perspectives

Helper NLRs that function in the downstream of sensor NLRs contribute to multiple cases of NLR-mediated resistance [72–74]. While NLR required for cell death (NRC)-type helper NLRs are conserved in the *Solanaceae* plants, the helper NLRs N-requirement gene 1 (NRG1) and activated disease resistance 1 (ADR1) are broadly conserved in almost all higher plants [75]. Helper NLRs have a critical role as signaling hubs. Thus, effector-mediated suppression of helper NLRs could lead to the collapse of multiple NLR-mediated resistance. Indeed, Avrcab1b of *P. infestans* is reported to suppress NRC2/3 [68]. In this context, functionally homologous helper NLRs derived from nonhost plants could be tested to determine whether they are more tolerant to the suppression by non-adapted pathogens. If so, nonhost helper NLRs might reinforce plant defenses in a pleiotropic manner.

In general, NHR cannot be transferred through crossing and largely depends on heterologous expression. Thus, compatibility between helper or sensor NLRs or NLR signaling components should be carefully considered for transferring NLRs. Indeed, transfer of BS2, a well-known NRC-dependent sensor NLR, from Solanaceae chili pepper to Euphorbiaceae Cassava failed to confer resistance against *Xanthomonas axonopodis* pv. *manihotis* [76]. In addition, complementation assays using EDS1-SAG101-NRG1 modules also suggest that components of *Arabidopsis* and *N. benthamiana* are not fully compatible with each other compared with their own combinations [77]. Therefore, co-transfer of nonhost helper NLRs or signaling components with identified nonhost receptors could be crucial for conferring the full potential of resistance in specific cases.

Recently, a number of studies have suggested that PTI and ETI function synergistically [78–80]. Considering that single gene-mediated NHR could be overcome by adaptation of pathogen, combinational approaches would be required to confer durable resistance for susceptible crops. Thus, more identification of genetic resources contributing to NHR would be essential for achieving this goal.

Summary

- NHR is conferred by the coordination of multiple layers of resistance. These layers range from physicochemical barriers to receptor-mediated responses. The contribution of each component in any interaction depends on context. Generally, the relative contribution of each component is related to the phylogenetic distances between the host and nonhost plant species.
- Receptor-mediated NHR could be transferred from nonhost to susceptible host plants.
- We suggest that receptor-mediated NHR is established by recognition and durability (possible to recognize non-adapted pathogens but more tolerant to immune suppression by non-adapted pathogens). Further characterization of receptors from nonhost plants and investigation on mechanisms of durability would be required for further application of NHR.

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Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Author Contribution

S.O. and D.C. conceptualized and wrote the manuscript, S.O. created the figures.

Abbreviations

AVR, avirulence; EDS1, enhanced disease susceptibility 1; ETI, effector-triggered immunity; HR, hypersensitive response; NHO1, nonhost 1; NHR, nonhost resistance; NLR, nucleotide-binding leucine-rich repeat receptor; NRC, NLR required for cell death; NRG1 , N-requirement gene 1; PAMP, pathogen-associated molecular pattern; PRR, pattern-recognition receptor; PTI, PAMP-triggered immunity; Rpi, resistance to *Phytophyhora infestans*; RPS, resistance to *Pseudomonas syringae*; SAG101, senescence-associated gene 101.

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