Available online at www.sciencedirect.com

SciVerse ScienceDirect

Current Opinion in Plant Biology

Genetic and molecular basis of nonhost disease resistance: complex, yes; silver bullet, no

Jun Fan[1,2] and Peter Doerner[3,4]

Nonhost resistance (NHR), in which a successful pathogen on some plants fails to overcome host barriers on others, has attracted much attention owing to its potential for robust crop improvement. Recent advances reveal that a multitude of underlying mechanisms contribute to NHR, ranging from components shared with recognition-based defenses up to recessive susceptibility factors involved in plant primary metabolism. Most NHR appears multi-factorial and quantitative. This implies that there is no single, 'silver bullet' NHR mechanism that can be used to broadly restrict pathogens in many or all crops.

Addresses
[1] Department of Plant Pathology, China Agricultural University, Beijing 100193, China
[2] John Innes Centre, Norwich NR4 7UH, United Kingdom
[3] University of Edinburgh, Institute of Molecular Plant Sciences, Mayfield Road, Edinburgh EH9 3JH, United Kingdom
[4] Laboratoire de Physiologie Cellulaire Végétale, CNRS (UMR5168)/INRA (UMR1200)/CEA Grenoble, and Université Joseph Fourier, F-38000 Grenoble, France

Corresponding authors: Fan, Jun (jfan@cau.edu.cn) and Doerner, Peter (peter.doerner@ed.ac.uk)

Current Opinion in Plant Biology 2012, **15**:400–406

This review comes from a themed issue on **Biotic interactions**

Edited by **Pamela C Ronald** and **Ken Shirasu**

For a complete overview see the Issue and the Editorial

Available online 22nd March 2012

1369-5266/$ – see front matter,

http://dx.doi.org/10.1016/j.pbi.2012.03.001

Introduction

Nonhost resistance (NHR) is a widespread phenomenon exhibited by most plant species that are able to resist microbes or viruses, which are successful pathogens on other plants. NHR is remarkable for its durability in nature and effectiveness against broad range of potential pathogen species, and thus is hoped to be a novel source of resistance mechanisms for improving crop plants against diseases caused by host-adapted pathogens. Current models of plant innate immunity involve two groups of surveillance receptors, pattern recognition receptors (PRRs) (Box 1) and nucleotide-binding and leucine-rich repeat (NB-LRR) proteins. These activate host plant defense responses following recognition of pathogen encoded non-specific microbial-associated molecular patterns (MAMPs) or specific effector proteins, respectively [1]. A conceptual framework has recently been proposed in which PRRs, NB-LRR proteins and effectors, the three core components operating in host immunity, also determine the outcomes of the interplay between plant and non-adapted pathogens [2]. Here, we summarise recent advances in understanding the roles of multiple genetic and molecular components in determining the outcome of diverse nonhost interactions.

Viruses and nonhost plants: not welcome

Plant viruses are biotrophic pathogens that are unique in that their multiplication and life cycle occurs entirely inside the host cell. As such, the incompatibility between a virus and its host can be as simple as the absence of host factors essential for the virus life cycle [3], or can be due to the presence of multiple layers of defense in the host plant that actively suppress viral pathogenesis [4]. Several recent reports reveal mechanisms underlying resistance of nonhost plant to virus infection: Mutations in genes encoding DICER-LIKE or Argonaute proteins allow non-adapted *Potato virus X* to infect *Arabidopsis thaliana*, indicating that RNA silencing plays an important role in restricting nonhost virus [5]. In tomato, the cellular protein tm-1 was shown to confer nonhost resistance to *Tobacco mild green mosaic virus* and *Pepper mild mottle virus* by interacting with their viral replication proteins to inhibit viral RNA replication [6]. By contrast, the recessive resistance in *Nicotiana benthamiana* to non-adapted *Melon necrotic spot virus* is owing to the absence of a compatible plant translation initiation factor, which hampers efficient translation of viral proteins required for RNA replication [7]. It is noteworthy that the above mentioned plant factors are also involved in plant defense against host-adapted viruses, hence, the molecular basis of NHR to viral pathogens may overlap with recognition-based or non-specific host resistance mechanisms and include both active and passive (lack of susceptibility factors) defense mechanisms.

Active defenses that determine NHR to microbial attacks: strength in diversity of host mechanisms

It is widely accepted that pre-formed and induced defenses condition plant NHR [8,9]. However, considering the enormous diversity in life cycle and infection biology of microbial pathogens, it is not surprising that a multitude of complex, and sometimes opposing mechanisms are involved in NHR. This notion is supported by recent observations that nonhost resistance of barley to different fungal pathogens is associated with largely distinct transcriptional responses [10].

Box 1 Glossary

Disease susceptibility gene: A gene that makes plant susceptible to certain pathogens.

Susceptibility factor: Host factor that is not involved in defense suppression but necessary for an adapted pathogen to grow and develop *in planta*.

Effector: Microbial secreted small molecule or protein that modulates host cell functions to enable colonization.

Glucosinolates: A class of sulfur-containing and nitrogen-containing natural products widely distributed in crucifers. Tissue damage or pathogen infection can trigger enzymatic hydrolysis of glucosinolates into a range of bioactive metabolites, some of which contribute to plant defense against pathogens and herbivores.

Host status: The capacity of a plant being a host to certain pathogen species.

Host–pathogen compatibility: The ability of a given pathogen to infect a particular host.

Microbe-associated molecular pattern: A small molecular motif that is conserved within a class of microbes and that can stimulate host immune response following direct recognition by the pattern recognition receptors.

Pathovar: A pathovar is a bacterial strain that is differentiated from other strains of the same species on the basis of their distinct pathogenicity to one or more plant hosts.

Pattern recognition receptors: Typically membrane-bound receptor-like kinases that detect the conserved microbe-associated molecular patterns and initiate the first active layer of plant innate immunity.

Phytoalexins: Low-molecular-weight antimicrobial natural products that are synthesized by and accumulated in plants following pathogen infection.

Table 1

Arabidopsis genes involved in pre-invasive and post-invasive resistance to selected non-adapted fungal pathogens

Genes	Penetration			Hyphal growth			Reference
	Bgh	*Mo*	*Cg*-HTE	*Bgh*	*Mo*	*Pcu*	
PEN1	+	–	–	+		–	[11–13,16]
PEN2	+	+	+	+	+	+	[11–13,14•,16,17]
PEN3	+	–	+	+		+	[12,13,17]
EDS1		–		+			[11,13]
PAD2		–				+	[13,17]
PAD3		–	–			+	[16,17]
PAD4		–		+			[11,13]
SAG101				+			[11]
AGB1		+			+	+	[12,13,14•]
PMR5		+			+		[13,14•]
MLO2		+			+		[14•]
CYP79B2/B3			+			+	[16,17]
CYP81F2			+				[16]
EDR1			+				[21•]

+: genes required for inhibition of fungal entry or infection hyphal growth; –: genes dispensable for the outcome of interactions; *Bgh*: *Blumeria graminis* f. sp. *hordei*; *Mo*: *Magnaporthe oryzae*; *Pcu*: *Plectosphaerella cucumerina*; *Cg*-HTE: *Colletotrichum gloeosporioides* Hyphal Tip-based Entry

Recent advances in the genetic dissection of Arabidopsis NHR to a range of non-adapted fungal pathogens also suggest that overlapping and distinct genes or metabolic pathways are involved (Table 1). Earlier investigations revealed that three genes, *PEN1* (*Penetration 1*), *PEN2* and *PEN3*, are required for pre-invasive resistance to the obligate biotrophic fungus *Blumeria graminis* f. sp. *hordei* (*Bgh*), whereas the inhibition of hyphal growth largely relies on *EDS1* (*Enhanced disease susceptibility 1*), *PAD4* (*Phytoalexin deficient 4*) and *Senescence associated gene 101* (*SAG101*) [11,12]. Recent studies show that *PEN2* and three additional genes, *AGB1* (*Arabidopsis G-protein β-subunit*), *PMR5* (*Powdery mildew resistant 5*) and *Mildew resistance locus O 2* (*MLO2*), function in both pre-invasive and post-invasive resistance to the hemibiotrophic pathogen *Magnaporthe oryzae* [13,14•]. *PEN2*, required for pre-invasive resistance to broad spectrum of pathogens (Table 1), encodes an atypical β-thioglucoside glucohydrolase that metabolizes tryptophan derived indole glucosinolates (GSL) to produce antimicrobials in living plant cells following pathogen attack [15]. Hiruma *et al.* report that *Colletotrichum* species can take on two different entry modes during infection: a melanized appressorium-dependant invasion normally observed on intact plant surfaces, and a hyphal tip-based entry (HTE) that is predominant at wound sites of nonhost plants. Further studies show that Arabidopsis resistance to the HTE of *C. gloeosporioides* depends on the *PEN2*-related indole GSL metabolism pathway, whereas the mechanistic basis of resistance to appressorium-mediated invasion is still unknown [16].

The *CYP79 B2/B3* dependant tryptophan metabolism pathway is crucial in Arabidopsis resistance to the necrotrophic nonhost fungi *Plectosphaerella cucumerina* [17] and the oomycete host pathogen *Phytophthora brassicae* [18••]. Two branches of this pathway, *PEN2*-related indole GSL metabolism and *PAD3*-dependent camalexin biosynthesis, act in tandem to confer resistance. However, disruption of both *PEN2* and *PAD3* only partially compromises resistance, indicating that additional trp-derived metabolites contribute to resistance [17,18••]. These studies reveal a pivotal role of tryptophan-derived metabolites in Arabidopsis resistance to nonhost and host-adapted pathogens with distinct life cycles and infection biologies. A broader investigation of pathogen-inducible tryptophan-derived metabolism in Brassicaceae, reveals that the *PEN2*-related indole GSL metabolism is conserved, whereas other branches of the pathway, including camalexin synthesis may be phylogenetic clade specific [19]. Thus, they may belong to a catalytic landscape of secondary metabolism reflecting plant adaptation to complex interactions with a range of biotic challenges [20]. However, it should be noted that mechanisms independent of tryptophan metabolism also exist in Arabidopsis–fungi nonhost interactions. The gene *Enhanced disease resistance 1* (*EDR1*) that encodes a protein kinase, that

functions to at least partially, inhibit HTE of the nonhost anthracnose pathogen by upregulating expression of a group of defensin genes in Arabidopsis [21•].

Other plant species have also been used to characterize NHR to fungal infections. In barley, both *ROR1* (*Required for mlo-specified disease resistance 1*) and *ROR2* genes are involved to restrict cellular entry of non-adapted soybean rust fungi *Phakopsora pachyrhizi* [22]. *ROR2* is a barley *PEN1*-ortholog encoding syntaxin protein that is required for pre-invasive resistance to *Bgh* [23]. Recent findings that ADP-ribosylation factor GTPases are also required for both penetration-induced ROR2 focal accumulation and full resistance to fungal penetration, provide further links between ROR2-syntaxin and multi-vesicular bodies in surface defense in barley [24]. These studies suggest that the evolutionary conserved ROR2/PEN1 syntaxin-dependent secretory pathways are involved in defenses against diverse nonhost pathogens. Moreover, Bhuiyan *et al.* reported that the monolignol biosynthesis pathway is induced in wheat by powdery mildew infection and interfering with the pathway by RNAi-mediated gene silencing or enzyme specific inhibitors enhances penetration efficiency of both adapted and nonhost pathovars, indicating that this pathway contributes to fungal entry restriction in cereal plants [25]. By contrast, NHR in rice to cereal rust species is largely post-invasive and associated with active defense responses including callose deposition and production of reactive oxygen species, but the genetic basis of this durable resistance remains to be elucidated [26].

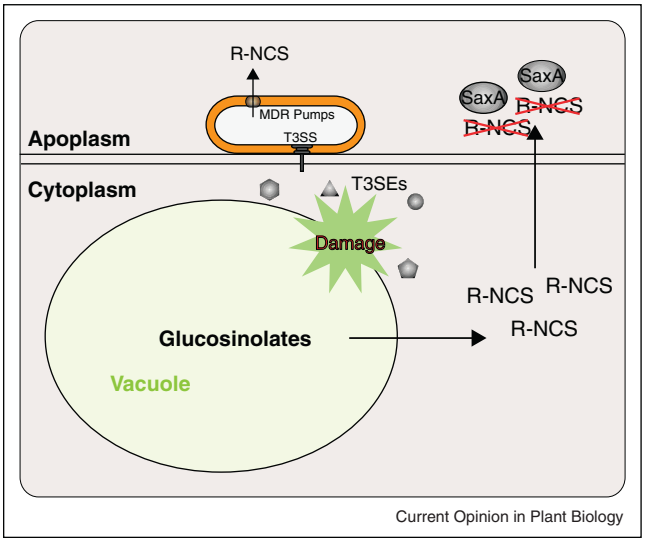
These examples represent the complex defense networks, probably activated following recognition of pathogen derived MAMPs or effectors, that quantitatively contribute to plant NHR to nonhost pathogens (see review [2,27]). A recent example demonstrates the role of MAMP perception in plant resistance to oomycete pathogen *Phytophthora infestans*. Resistance of *N. benthamiana* plants to different *Phytophthora* species varies from highly resistant to fully susceptible and *P. infestans* is moderately virulent on this plant. Silencing of genes in *N. benthamiana* homologous to Arabidopsis leucine-rich repeat receptor-like kinase *BAK1*/*SERK3*, previously shown to be a major modulator of defense responses triggered by oomycete MAMP protein INF1 [28], significantly enhances disease susceptibility to *P. infestans* [29].

While Arabidopsis is a natural host of a subspecies of oomycete pathogen *Albugo candida* causing the white rust disease, it is predominantly immune to many subspecies isolated from other cruciferous plants. By studying the low levels of resistance variation among Arabidopsis accessions Borhan *et al.* were able to identify an NB-LRR gene, *White rust resistance 4* (*WRR4*) that confers resistance to several subspecies of *A. candida*. The authors speculate that the prevalent resistance to non-adapted *A. candida* results from recognition of pathogen effectors by multiple *WRR4*-like genes in Arabidopsis [30].

The role of MAMP-triggered and effector-triggered immunity in NHR is well corroborated in many plant–bacteria interactions. Transgenic expression of the Arabidopsis MAMP receptor EFR that recognizes bacterial elongation factor Tu in *N. benthamiana* and tomato, confers MAMP-responsiveness and enhanced disease resistance to virulent pathogens from different bacterial genera [31••]. An investigation on natural variation of Arabidopsis resistance to nonhost bacteria reveals that the flagellin receptor gene *FLS2* confers resistance to *P. syringae* pv. *phaseolicola* [32]. These observations demonstrate a positive contribution of MAMP-triggered immunity in NHR to bacterial pathogens. Likewise, the hemibiotrophic bacterium *Pseudomonas syringae* pv. *tomato* (*Pto*) T1 is a tomato pathogen and unable to colonize Arabidopsis. Two type III secretion system-dependent effectors (T3SEs) from *Pto* T1, AvrRpt2 and HopAS1, elicit HR on Arabidopsis. Disruption of genes encoding either of these effectors in *Pto* T1 or the NB-LRR protein recognizing AvrRpt2 in Arabidopsis significantly enhance bacterial growth [33]. Moreover, the conserved T3SE protein Eop1 from *Rubus* strains of *Erwinia amylovora* is able reduce the virulence of *E. amylovora* strains in non-*Rubus* hosts and functions as a host-range-limiting factor [34]. These examples indicate that effector-triggered immunity plays an important role in restricting non-adapted bacterial pathogens. However, it is still not clear how exactly the nonhost bacterial growth is suppressed in the apoplastic environment. Nevertheless, the findings that MAMP treatment of plants restricts bacterial injection of T3SE and that T3SEs can relieve this restriction may shed light on and stimulate further investigations of the underlying mechanisms [35•].

Despite multiple lines of evidence showing engagement of PRRs and NB-LRR proteins in NHR, we have found a natural product-based mechanism that restricts non-adapted bacterial pathogens apparently independent of pathogen recognition. Our observations show that aliphatic isothiocyanates (ITCs), derived from GSL breakdown typically following tissue damage of crucifers, inhibit the growth of most *P. syringae* pathovars for which Arabidopsis is not a host, but have no effect on growth of pathovars that colonize Arabidopsis, such as *Pto* DC3000. Subsequent investigations revealed that in *Pto* DC3000, a putative enzyme encoded by the *saxA* gene, involved in metabolising ITCs, acts with a group of multidrug efflux transporters to protect bacteria against ITCs (Figure 1). Disruption of these protective *sax* genes from *Pto* DC3000 makes the mutant strain sensitive to ITC-treatment, thus leading to collapse of the bacterial population at the necrotrophic stage of infection when high levels ITCs are released in Arabidopsis young leaves. By contrast, Arabidopsis mutants carrying genetic lesions in aliphatic GSL biosynthesis, growth of the ITC-sensitive

Figure 1



Schematic diagram of ITC-based defense activation in the necrotrophic stage of infection and host bacterial strategies to overcome this chemical barrier. Bacterially derived factors, presumably T3SEs and/or toxins, trigger the cell death process and the release of glucosinolates from damaged vacuoles. Non-toxic glucosinolates are subsequently hydrolyzed by β-thioglucosidases derived from plant or bacteria to produce toxic isothiocyanates (R-NCS). R-NCS may further diffuse into the apoplasm to suppress bacteria. The host bacteria secrete SaxA-like enzymes to detoxify R-NCS in the apoplasm and the Sax-related MDR efflux pumps function to complement SaxA. Together, these confer bacterial tolerance to toxic ITCs.

mutant strain is rescued [36••]. The data demonstrate an important role of ITCs-based defense in suppression of bacterial invaders. The preferential distribution of *saxA*-like genes in crucifer pathovars implies that ITCs may be one of the driving forces that shape pathogen host adaptation. Notably, biotrophic growth of the ITC sensitive *sax* mutant is not suppressed, indicating that distinct mechanisms mediate restriction of biotrophic growth of nonhost bacteria.

Consistent with the observations that many defense responses are shared by both nonhost and host resistance, aliphatic GSL biosynthesis has been shown to be crucial for Arabidopsis basal resistance to a necrotrophic ascomycete, *Sclerotinia sclerotiorum* [37], indicating that it may be part of the complex defense metabolism networks that are activated differentially following attacks by pathogens with diverse life cycle and infection strategy [36••,37].

Plant factors passively affect NHR to microbial attacks: virtuously inhospitable

To colonize a host plant, pathogens have to overcome the complex defense networks and acquire nutrients necessary for their proliferation. To do this, many pathogens secrete effector molecules into the apoplast or inside host cells to directly quench plant defense [38] or reprogram host cell to suppress defenses [39–41] and elicit metabolic shifts [42] to benefit pathogens. Many plant genes are also required for disease process and their disruption often leads to recessive broad-spectrum disease resistance, thus revealing a role as susceptibility genes [43]. Our knowledge on how these factors mediate disease susceptibility is still very limited, although they may be targets of pathogen effectors that negatively regulate plant defense pathways or susceptibility factors required for pathogen growth and development [43]. Here we explore the role of recessive resistance in NHR and summarize new insights on how genes, such as *MLO* and *Xa13*, affect host status.

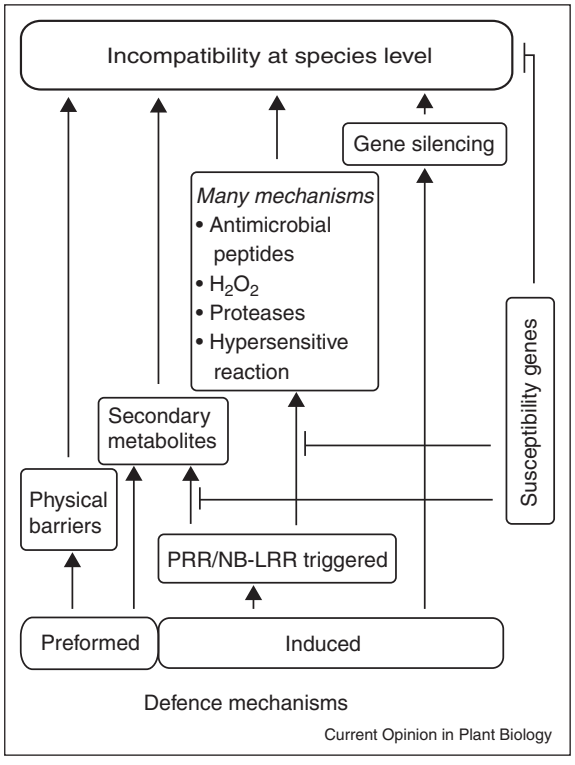
The downy mildew pathogen *Bremia lactucae* is pathogenic on lettuce (*Lactuca sativa*) but unable to cause disease on wild lettuce (*L. saligna*). These two species are inter-fertile, making it possible to analyze the inheritance of resistance in their progeny. Quantitative trait loci (QTLs) assays reveal that at least 15 QTLs, each effective at one or more plant developmental stages, determine nonhost resistance in *L. saligna* [44]. Some of these QTLs are recessive and pyramiding 3 of the recessive QTLs are sufficient to produce complete resistance to *B. lactucae* in young lettuce plants [45•]. These studies clearly demonstrate that NHR are polygenic, quantitative traits that rely on both genetically dominant and recessive plant components.

Loss-of-function mutations in *MLO* genes confer durable broad-spectrum powdery mildew resistance in monocot and dicot plants, reminiscent of NHR phenotypes. The molecular basis of *MLO* or *mlo* mediated disease responses are not fully understood. However, recent data show that (1) in Arabidopsis the *mlo2*-mediated pathogen resistance requires the pathways that produce tryptophan-derived metabolites [46]; (2) transcription of *MLO* genes is co-regulated in both Arabidopsis and barley with a common set of genes required for defenses against diverse fungal pathogens [47]; and (3) disruption of *MLOs* in barley and Arabidopsis enhance plant susceptibility to *M. oryzae* [14•,48]. Hence, *MLO* genes appear to have a key role in defense regulation in diverse plant–pathogen interactions. Interestingly, some of the previously identified Arabidopsis susceptibility genes, such as *PMR5* and *EDR1*, were shown to be required for resistance to non-adapted pathogens [13,21•], indicating that they have dual roles in mediating diverse plant defense responses.

Rice Xa13 protein is a member of a subgroup of SWEET transporter proteins [49••] that mediate sugar efflux, preferentially sucrose, into the leaf apoplast for phloem loading [50]. Pathogenic bacteria *Xanthomonas oryzae* pv *oryzae* (*Xoo*) secrete a specific transcription activator-like (TAL) effector that targets *Xa13* gene promoter and induces its expression to promote disease. Naturally occurring promoter mutations that disrupt bacterially induced Xa13 expression confer recessive resistance to this *Xoo* strain in a panel of geographically diverse rice

lines [51]. However, *Xoo* strains carrying other TAL effectors can overcome *xa13*-mediated resistance by targeting genes encoding Xa13 homologs that are also capable of mediating sucrose efflux [50,52•]. Moreover, multiple *SWEET* genes are found in Arabidopsis and rice genome and many of the Arabidopsis *SWEET* genes are upregulated by bacterial or fungal infections [49••]. These discoveries not only help us understand how *Xoo* bacteria hijack native host physiological process for their own growth, but also highlight a central role of nutrition-based mechanisms in plant–pathogen co-evolution. This is further corroborated by the observations that plant amino acid metabolic status can selectively determine the outcome of plant–pathogen interactions [53••]. We expect that numerous examples of such quantitatively acting, recessive susceptibility genes will be discovered, but as long as they are required for highly specific facets of the pathogen's infection biology, these may not all confer 'broad-spectrum' NHR (Figure 2).

Figure 2



Multiple plant factors lead to nonhost disease resistance. Both preformed and induced defense mechanisms confer NHR. Preformed defenses, such as release of antimicrobial secondary metabolites, can be activated at various stages of infection as described in this review. Many induced defense responses are probably triggered following pathogen recognition by PRRs or NB-LRR receptors. Gene silencing plays important role in restriction of non-adapted viruses. Some susceptibility genes negatively regulate plant defenses against otherwise non-adapted pathogens, whereas other susceptibility factors are required for the establishment and growth of the host-adapted pathogen.

Conclusions

NHR is a widespread phenomenon resulting from long-term co-evolution between plants and their numerous biotic associates. The genetic and molecular basis of pathogen resistance displayed at the species level overlaps with that mediating basal resistance to host-adapted pathogens. Plant species or clade-specific innovations of secondary metabolism have an important role in NHR. The NHR defense responses are predominantly triggered by perception of pathogen derived MAMPs or effectors, but recognition independent processes also function to limit non-adapted pathogens. An emerging role of plant primary metabolism in determining host–pathogen compatibility opens up new frontiers in studies of NHR. Understanding the genetic and molecular basis of NHR will inform future work on engineering crop plants with durable broad-spectrum resistance against adapted pathogens.

Acknowledgements

This research was partially supported by Chinese Universities Scientific Fund (2012RC007) provided to JF by China Agricultural University.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Jones JD, Dangl JL: **The plant immune system**. *Nature* 2006, **444**:323-329.

2. Schulze-Lefert P, Panstruga R: **A molecular evolutionary concept connecting nonhost resistance, pathogen host range, and pathogen speciation**. *Trends in Plant Science* 2011, **16**:117-125.

3. Robaglia C, Caranta C: **Translation initiation factors: a weak link in plant RNA virus infection**. *Trends in Plant Science* 2006, **11**:40-45.

4. Pallas V, Garcia JA: **How do plant viruses induce disease? Interactions and interference with host components**. *Journal of General Virology* 2011, **92**:2691-2705.

5. Jaubert M, Bhattacharjee S, Mello AFS, Perry KL, Moffett P: **ARGONAUTE2 mediates RNA-silencing antiviral defenses against potato virus X in Arabidopsis**. *Plant Physiology* 2011, **156**:1556-1564.

6. Ishibashi K, Naito S, Meshi T, Ishikawa M: **An inhibitory interaction between viral and cellular proteins underlies the resistance of tomato to nonadapted tobamoviruses**. *Proceedings of the National Academy of Sciences of the United States of America* 2009, **106**:8778-8783.

7. Nieto C, Rodriguez-Moreno L, Rodriguez-Hernandez AM, Aranda MA, Truniger V: **Nicotiana benthamiana resistance to non-adapted Melon necrotic spot virus results from an incompatible interaction between virus RNA and translation initiation factor 4E**. *Plant Journal* 2011, **66**:492-501.

8. Heath MC: **Nonhost resistance and nonspecific plant defenses**. *Current Opinion in Plant Biology* 2000, **3**:315-319.

9. Nürnberger T, Lipka V: **Non-host resistance in plants: new insights into an old phenomenon**. *Molecular Plant Pathology* 2005, **6**:335-345.

10. Zellerhoff N, Himmelbach A, Dong WB, Bieri S, Schaffrath U, Schweizer P: **Nonhost resistance of barley to different fungal pathogens is associated with largely distinct, quantitative transcriptional responses**. *Plant Physiology* 2010, **152**:2053-2066.

11. Lipka V, Dittgen J, Bednarek P, Bhat R, Wiermer M, Stein M, Landtag J, Brandt W, Rosahl S, Scheel D *et al.*: **Pre- and postinvasion defenses both contribute to nonhost resistance in Arabidopsis**. *Science* 2005, **310**:1180-1183.

12. Stein M, Dittgen J, Sánchez-Rodríguez C, Hou B-H, Molina A, Schulze-Lefert P, Lipka V, Somerville S: **Arabidopsis PEN3/PDR8, an ATP binding cassette transporter, contributes to nonhost resistance to inappropriate pathogens that enter by direct penetration**. *The Plant Cell Online* 2006, **18**:731-746.

13. Maeda K, Houjyou Y, Komatsu T, Hori H, Kodaira T, Ishikawa A: **AGB1 and PMR5 contribute to PEN2-mediated preinvasion resistance to *Magnaporthe oryzae* in *Arabidopsis thaliana***. *Molecular Plant-Microbe Interactions* 2009, **22**:1331-1340.

14. • Nakao M, Nakamura R, Kita K, Inukai R, Ishikawa A: **Non-host resistance to penetration and hyphal growth of *Magnaporthe oryzae* in Arabidopsis**. *Scientific Reports* 2011, **1**.

Apart from *PEN2* this study shows that additional genes that differ from those identified in the Arabidopsis–*Bgh* interaction quantitatively contribute to NHR to *M. oryzae*, of which *MLO2* and *PMR5* are widely required for host adapted mildews to colonize Arabidopsis.

15. Bednarek P, Pislewska-Bednarek M, Svatos A, Schneider B, Doubsky J, Mansurova M, Humphry M, Consonni C, Panstruga R, Sanchez-Vallet A *et al.*: **A glucosinolate metabolism pathway in living plant cells mediates broad-spectrum antifungal defense**. *Science* 2009, **323**:101-106.

16. Hiruma K, Onozawa-Komori M, Takahashi F, Asakura M, Bednarek P, Okuno T, Schulze-Lefert P, Takano Y: **Entry mode-dependent function of an indole glucosinolate pathway in Arabidopsis for nonhost resistance against anthracnose pathogens**. *Plant Cell* 2010, **22**:2429-2443.

17. Sanchez-Vallet A, Ramos B, Bednarek P, Lopez G, Pislewska-Bednarek M, Schulze-Lefert P, Molina A: **Tryptophan-derived secondary metabolites in Arabidopsis thaliana confer non-host resistance to necrotrophic Plectosphaerella cucumerina fungi**. *Plant Journal* 2010, **63**:115-127.

18. •• Schlaeppi K, Abou-Mansour E, Buchala A, Mauch F: **Disease resistance of Arabidopsis to *Phytophthora brassicae* is established by the sequential action of indole glucosinolates and camalexin**. *Plant Journal* 2010, **62**:840-851.

This investigation reveals that when normal appressorium-mediated invasion is impeded in Arabidopsis, the non-adapted anthracnose pathogens use a previously unknown hyphal tip-based entry (HTE) mode to break in. *PEN2*-related indole glucosinolate biosynthesis or metabolism is required for plant resistance to HTE but dispensable for restriction of appressorium-mediated invasion. This work also shows that sugars can potentially function as signals to enhance HTE on nonhost plants. Collectively the data highlight the diversity of NHR defense mechanisms associated with pathogen infection styles and the impact of micro-nutritional environment on fungal infection structure development on nonhost plants.

19. Bednarek P, Piślewska-Bednarek M, Ver Loren van Themaat E, Maddula RK, Svatoš A, Schulze-Lefert P: **Conservation and clade-specific diversification of pathogen-inducible tryptophan and indole glucosinolate metabolism in Arabidopsis thaliana relatives**. *New Phytologist* 2011, **192**:713-726.

20. Juergen K: **Natural diversity and adaptation in plant secondary metabolism**. *Current Opinion in Plant Biology* 2011, **14**:246-251.

21. • Hiruma K, Nishiuchi T, Kato T, Bednarek P, Okuno T, Schulze-Lefert P, Takano Y: **Arabidopsis ENHANCE DISEASE RESISTANCE 1 is required for pathogen-induced expression of plant defensins in nonhost resistance, and acts through interference of MYC2-mediated repressor function**. *The Plant Journal* 2011, **67**:980-992.

EDR1, previously identified as a negative regulator of resistance to adapted powdery mildews, is required for Arabidopsis to restrict HTE of the non-adapted anthracnose pathogens. EDR1 functions independently of *PEN2*-pathways and acts partially through inducing expression of a group of defensin proteins, which reveals a new role for antifungal proteins in NHR.

22. Hoefle C, Loehrer M, Schaffrath U, Frank M, Schultheiss H, Hukelhoven R: **Transgenic suppression of cell death limits penetration success of the soybean rust fungus Phakopsora pachyrhizi into epidermal cells of barley**. *Phytopathology* 2009, **99**:220-226.

23. Collins NC, Thordal-Christensen H, Lipka V, Bau S, Kombrink E, Qiu J-L, Huckelhoven R, Stein M, Freialdenhoven A, Somerville SC *et al.*: **SNARE-protein-mediated disease resistance at the plant cell wall**. *Nature* 2003, **425**:973-977.

24. Bohlenius H, Morch SM, Godfrey D, Nielsen ME, Thordal-Christensen H: **The multivesicular body-localized GTPase ARFA1b/1c is important for callose deposition and ROR2 syntaxin-dependent preinvasive basal defense in barley**. *Plant Cell* 2010, **22**:3831-3844.

25. Bhuiyan NH, Selvaraj G, Wei YD, King J: **Gene expression profiling and silencing reveal that monolignol biosynthesis plays a critical role in penetration defence in wheat against powdery mildew invasion**. *Journal of Experimental Botany* 2009, **60**:509-521.

26. Ayliffe M, Devilla R, Mago R, White R, Talbot M, Pryor A, Leung H: **Nonhost resistance of rice to rust pathogens**. *Molecular Plant-Microbe Interactions* 2011, **24**:1143-1155.

27. Dodds PN, Rathjen JP: **Plant immunity: towards an integrated view of plant–pathogen interactions**. *Nature Reviews. Genetics* 2010, **11**:539-548.

28. Heese A, Hann DR, Gimenez-Ibanez S, Jones AME, He K, Li J, Schroeder JI, Peck SC, Rathjen JP: **The receptor-like kinase SERK3/BAK1 is a central regulator of innate immunity in plants**. *Proceedings of the National Academy of Sciences of the United States of America* 2007, **104**:12217-12222.

29. Chaparro-Garcia A, Wilkinson RC, Gimenez-Ibanez S, Findlay K, Coffey MD, Zipfel C, Rathjen JP, Kamoun S, Schornack S: **The receptor-like kinase SERK3/BAK1 is required for basal resistance against the late blight pathogen *Phytophthora infestans* in *Nicotiana benthamiana***. *PLoS ONE* 2011, **6**.

30. Borhan MH, Gunn N, Cooper A, Gulden S, Tör M, Rimmer SR, Holub EB: **WRR4 encodes a TIR-NB-LRR protein that confers broad-spectrum white rust resistance in Arabidopsis thaliana to four physiological races of *Albugo candida***. *Molecular Plant-Microbe Interactions* 2008, **21**:757-768.

31. •• Lacombe S, Rougon-Cardoso A, Sherwood E, Peeters N, Dahlbeck D, van Esse HP, Smoker M, Rallapalli G, Thomma BPHJ, Staskawicz B *et al.*: **Interfamily transfer of a plant pattern-recognition receptor confers broad-spectrum bacterial resistance**. *Nature Biotechnology* 2010, **28**:365-369.

Brassicaceae specific PRR EFR, when expressed in *Solanaceae* plants, confers responsiveness to the PAMP molecule EF-Tu and protects transgenic plants from diseases caused by many genera of bacterial pathogens. This study demonstrates that PRRs have important roles in limiting pathogen host range and can be used to improve broad-spectrum disease resistance in crop plants.

32. Forsyth A, Mansfield JW, Grabov N, de Torres M, Sinapidou E, Grant MR: **Genetic dissection of basal resistance to Pseudomonas syringae pv. phaseolicola in accessions of Arabidopsis**. *Molecular Plant-Microbe Interactions* 2010, **23**:1545-1552.

33. Sohn KH, Saucet SB, Clarke CR, Vinatzer BA, O'Brien HE, Guttman DS, Jones JDG: **HopAS1 recognition significantly contributes to Arabidopsis nonhost resistance to Pseudomonas syringae pathogens**. *New Phytologist* 2012, **193**:58-66.

34. Asselin JE, Bonasera JM, Kim JF, Oh CS, Beer SV: **Eop1 from a rubus strain of Erwinia amylovora functions as a host-range limiting factor**. *Phytopathology* 2011, **101**:935-944.

35. • Crabill E, Joe A, Block A, van Rooyen JM, Alfano JR: **Plant immunity directly or indirectly restricts the injection of type III effectors by the Pseudomonas syringae type III secretion system**. *Plant Physiology* 2010, **154**:233-244.

The study reveals a potential mechanism for how PAMP-triggered immunity prevents infection by non-adapted bacterial pathogens.

36. •• Fan J, Crooks C, Creissen G, Hill L, Fairhurst S, Doerner P, Lamb C: **Pseudomonas sax genes overcome aliphatic isothiocyanate-mediated non-host resistance in Arabidopsis**. *Science* 2011, **331**:1185-1188.

The authors uncover a new role of the antibiotic natural products aliphatic ITCs as bacterial host range limiting factors and identify a group of bacterial genes from host pathogens that overcome ITC-based defense

and are necessary for bacterial survival during nectrotrophic infection. The study demonstrates that plant defense responses deployed at necrotrophic stage have an important role in NHR to hemibiotrophic pathogens.

37. Stotz HU, Sawada Y, Shimada Y, Hirai MY, Sasaki E, Krischke M, Brown PD, Saito K, Kamiya Y: **Role of camalexin, indole glucosinolates, and side chain modification of glucosinolate-derived isothiocyanates in defense of Arabidopsis against *Sclerotinia sclerotiorum***. *The Plant Journal* 2011, **67**:81-93.

38. Bozkurt TO, Schornack S, Win J, Shindo T, Ilyas M, Oliva R, Cano LM, Jones AME, Huitema E, van der Hoorn RAL *et al.*: ***Phytophthora infestans* effector AVRblb2 prevents secretion of a plant immune protease at the haustorial interface**. *Proceedings of the National Academy of Sciences of the United States of America* 2011, **108**:20832-20837.

39. Doehlemann G, Reissmann S, Aßmann D, Fleckenstein M, Kahmann R: **Two linked genes encoding a secreted effector and a membrane protein are essential for Ustilago maydis-induced tumour formation**. *Molecular Microbiology* 2011, **81**:751-766.

40. Williams B, Kabbage M, Kim HJ, Britt R, Dickman MB: **Tipping the balance: *Sclerotinia sclerotiorum* secreted oxalic acid suppresses host defenses by manipulating the host redox environment**. *PLoS Pathogens* 2011, **7**.

41. Kelley BS, Lee SJ, Damasceno CMB, Chakravarthy S, Kim BD, Martin GB, Rose JKC: **A secreted effector protein (SNE1) from *Phytophthora infestans* is a broadly acting suppressor of programmed cell death**. *Plant Journal* 2010, **62**:357-366.

42. Ward JL, Forcat S, Beckmann M, Bennett M, Miller SJ, Baker JM, Hawkins ND, Vermeer CP, Lu CA, Lin WC *et al.*: **The metabolic transition during disease following infection of Arabidopsis thaliana by Pseudomonas syringae pv. tomato**. *Plant Journal* 2010, **63**:443-457.

43. Pavan S, Jacobsen E, Visser RGF, Bai YL: **Loss of susceptibility as a novel breeding strategy for durable and broad-spectrum resistance**. *Molecular Breeding* 2010, **25**:1-12.

44. Zhang NW, Lindhout P, Niks RE, Jeuken MJW: **Genetic dissection of Lactuca saligna nonhost resistance to downy mildew at various lettuce developmental stages**. *Plant Pathology* 2009, **58**:923-932.

45. • Zhang NWW, Pelgrom K, Niks RE, Visser RGF, Jeuken MJW: **Three combined quantitative trait loci from nonhost Lactuca saligna are sufficient to provide complete resistance of lettuce against Bremia lactucae**. *Molecular Plant-Microbe Interactions* 2009, **22**:1160-1168.
This is one of the examples showing that NHR can be controlled by genetically recessive QTLs.

46. Consonni C, Bednarek P, Humphry M, Francocci F, Ferrari S, Harzen A, van Themaat EVL, Panstruga R: **Tryptophan-derived metabolites are required for antifungal defense in the Arabidopsis mlo2 mutant**. *Plant Physiology* 2010, **152**:1544-1561.

47. Humphry M, Bednarek P, Kemmerling B, Koh S, Stein M, Gobel U, Stuber K, Pislewska-Bednarek M, Loraine A, Schulze-Lefert P *et al.*: **A regulon conserved in monocot and dicot plants defines a functional module in antifungal plant immunity**. *Proceedings of the National Academy of Sciences of the United States of America* 2010, **107**:21896-21901.

48. Jarosch B, Kogel K-H, Schaffrath U: **The ambivalence of the barley Mlo locus: mutations conferring resistance against powdery mildew (Blumeria graminis f. sp. hordei) enhance susceptibility to the rice blast fungus Magnaporthe grisea**. *Molecular Plant-Microbe Interactions* 1999, **12**:508-514.

49. •• Chen L-Q, Hou B-H, Lalonde S, Takanaga H, Hartung ML, Qu X-Q, Guo W-J, Kim J-G, Underwood W, Chaudhuri B *et al.*: **Sugar transporters for intercellular exchange and nutrition of pathogens**. *Nature* 2010, **468**:527-532.
The authors identify a new class of sugar transporters, named as SWEETs, some of which are transcriptional up regulated following pathogen challenges. This and the paper [52•] collectively hint at an important role of nutrition acquisition in plant–pathogen co-evolution.

50. Chen L-Q, Qu X-Q, Hou B-H, Sosso D, Osorio S, Fernie AR, Frommer WB: **Sucrose efflux mediated by SWEET proteins as a key step for phloem transport**. *Science* 2012, **335**:207-211.

51. Chu Z, Yuan M, Yao J, Ge X, Yuan B, Xu C, Li X, Fu B, Li Z, Bennetzen JL *et al.*: **Promoter mutations of an essential gene for pollen development result in disease resistance in rice**. *Genes & Development* 2006, **20**:1250-1255.

52. • Antony G, Zhou J, Huang S, Li T, Liu B, White F, Yang B: **Rice xa13 recessive resistance to bacterial blight is defeated by induction of the disease susceptibility gene Os-11N3**. *The Plant Cell Online* 2010, **22**:3864-3876.
The authors show that at least two additional TAL effectors from *Xoo* target alternative *SWEET* genes in rice plants to defeat *xa13*-mediated resistance. This and the paper [49••] collectively suggest an important role of nutrition acquisition in plant–pathogen co-evolution.

53. •• Stuttmann J, Hubberten H-M, Rietz S, Kaur J, Muskett P, Guerois R, Bednarek P, Hoefgen R, Parker JE: **Perturbation of Arabidopsis amino acid metabolism causes incompatibility with the adapted biotrophic pathogen Hyaloperonospora arabidopsidis**. *The Plant Cell Online* 2011, **23**:2788-2803.
The authors show that overaccumulation of the amino acid Thr in two non-allelic Arabidopsis mutants disrupted in amino acid metabolism leads to enhanced resistance to downy mildew but not other adapted pathogens. This work highlights the impact of plant primary metabolism on host status determination.