Plant strategies for resistance to pathogens

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Genetic dissection of the various responses that plants activate upon recognition of pathogen attack have made clear that the plant is able to induce not only local defenses but also a carefully regulated mixture of different systemically induced defense mechanisms. In *Arabidopsis*, much progress in defining the underlying molecular mechanisms of systemic acquired resistance has been achieved and additional disease resistant mutants have been identified from diverse screens.

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Current Opinion in Biotechnology 1998, **9**:208–213

http://biomednet.com/elecref/0958166900900208

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Abbreviations

HR	hypersensitive response
ISR	induced systemic resistance
JA	Jasmonic acid
LLS	lethal leaf spot
lsd	lesions simulating disease resistance
NIM	non-inducible immunity
NPR	no PR-gene expression
pad	phytoalexin deficient
PR	pathogenesis-related
R	disease resistance
RIP	ribosome inactivating proteins
SA	salicylic acid
SAR	systemic acquired resistance

Introduction

Plants, like humans, actively defend themselves against pathogenic organisms. Plant defense can be triggered by gene-for-gene interactions (see Ji, Smith-Becker and Keen, this issue, pp 202–207) but other recognitions of non-self exist. Plants respond to pathogens by activating broad-spectrum innate immune responses that can be expressed locally at the site of pathogen invasion as well as systemically in the uninfected tissue. Here, we review advances in biochemical and molecular genetic analysis of previously identified, inducible disease-resistance systems and also recent descriptions of novel plant strategies for systemic pathogen protection.

Locally induced defense responses

Plants try to restrict pathogen infections to the site of attempted ingress by inducing local defenses. Included in this defensive repertoire are a fast, local cell collapse called the hypersensitive response (HR), H_2O_2 production, callose deposition and phytoalexin accumulation. Phytoalexins are antimicrobial molecules that may be pathogen-induced and have an impact on pathogen fitness in some plant–pathogen interactions. In the Graminaeae, the cyclic hydroxamic acids 2,4-dihydroxy-7-methoxy-1,4-benzoaxin-3-one (DIMBOA) and its precursor 2,4-dihydroxy-1,4-benzoxazin-3-one (DIBOA) are crucial for plant resistance to both insect and fungal pathogens (e.g. European corn borer, *Helminthosporium*). Plants with mutations in the biosynthesis of these phytoalexins grow normally but exhibit enhanced susceptibility to these pathogens. The biosynthetic pathway of DIMBOA has been identified by a combination of reverse and classical genetics [1•].

In *Arabidopsis*, a mutant screen was carried out to identify mutants which were unable to accumulate the phytoalexin camalexin after challenge by a virulent *Pseudomonas* strain. Interestingly, some of these phytoalexin deficient (*pad*) mutants were not impaired in camalexin biosynthesis but in more general regulatory pathways of local plant defense. *Pad4* mutants are compromised in resistance responses mediated by several different resistance (R) genes, while another *pad* mutant is allelic to *nim1/npr1* (see below) [2•,3••]. Mutants that exhibit enhanced disease susceptibility to virulent pathogens [4] also include *pad* mutants, indicating a possible function of camalexin in limiting pathogen ingress.

In barley, in addition to the ubiquitous non-host and R-gene mediated race-specific resistances, a generalized, local resistance exists that is mediated by the absence of a functional *MLO* gene. *Mlo* mutants exhibit resistance to all races of the powdery mildew *Erysiphe graminis* f.sp. *hordei*. *mlo*-mediated resistance is associated with the tendency of the plants to produce chlorotic and/or necrotic leaf spotting. Furthermore, *mlo*-conferred resistance is histologically distinguishable from R-gene mediated necrosis (i.e. HR). Upon fungal challenge of *mlo* mutants, papillae formation and enhanced pathogenesis-related (PR) gene expression are induced. In addition, *mlo* resistance requires the activity of two loci, ROR1 and ROR2 (required for *mlo* resistance), whereas the induction of an HR does not [5•,6]. An important step toward understanding this agronomically important phenomenon has been achieved by cloning the *MLO* gene [7••]. The presence of several membrane-spanning segments led to the prediction that MLO might be a novel G-protein-coupled receptor, helping to explain the presence of multiple *MLO* homologs detected in the *Arabidopsis* genome.

Systemically inducible resistance strategies

An important part of the local response to pathogen attack is the systemic triggering of enhanced resistance against secondary infections. To date, the best-characterized systemically induced disease resistance strategy is systemic acquired resistance (SAR; for recent reviews see [8,9]).

The salicylic acid-dependent inducible resistance pathway: systemic acquired resistance

SAR can be distinguished from other inducible resistances based upon the spectrum of pathogen protection and the associated changes in gene expression. The hallmarks of SAR in dicotyledons are long-lasting, broad-spectrum disease resistance that is dependent upon salicylic acid (SA) accumulation and correlated with the expression of the so-called SAR genes. In nature, SAR is induced following infection by necrotizing pathogens (e.g. *Colletotrichum lagenarium*, Tobacco Mosaic Virus); however, SAR is also associated with other types of cell death, including the spontaneous appearance of necrotic lesions in certain mutants. SAR induction depends on a functional NIM1/NPR1 gene product. Recently, the gene encoding this key regulatory protein involved in SAR signal transduction has been cloned.

NIM1/NPR1 is an ankyrin repeat containing protein with homology to IκB

Nim1/npr1 mutants cannot activate SAR gene expression or SAR-associated disease resistance, although SA levels are normal or slightly higher than in wildtype. Such mutants can also support the growth of normally avirulent pathogens. Induction of SAR by necrotizing factors and the chemical SAR activators SA, 2,6-dichloroisonicotinic acid and benzothiadiazole, requires a functional NIM1/NPR1 protein. The *NIM1/NPR1* gene has been cloned by two groups using a map-based cloning strategy [3••,10••]. Sequence analysis reveals interesting homologies to IκB, a class of mammalian nuclear factor κB transcription factor inhibitors. The predicted NIM1/NPR1 protein contains four regions with similarity to ankyrin domains (protein motifs involved in protein–protein interactions) as well as other conserved motifs that suggest it belongs to the α subclass of IκB. By analogy to the *Drosophila* and mammalian models, SAR signal transduction is likely to be mediated by successive phosphorylation events. This idea is supported by the finding that the NIM1/NPR1 sequence contains canonical mitogen activated protein kinase kinase activation loop motifs (SXXXS, where S is serine and X is any amino acid) suggesting direct phosphorylation. Further support for the idea of an SA-activated kinase cascade has recently been obtained by the purification of a SA-induced mitogen activated protein kinase from tobacco [11]; however, evidence of its involvement in SAR signal transduction remains to be demonstrated.

Multiple roles for salicylic acid

Simultaneous injection of subclinical concentrations of SA and an avirulent bacterial pathogen results in the earlier appearance of reactive oxygen species, HR and SAR gene expression than when either inducer is applied independently [12•]. Shirasu *et al.* [12•] propose that SA is acting via an agonist-dependent gain control (an increase in response that requires a chemical substance capable of combining with a receptor) and the persisting, inactive conjugated β-O-D-glucosylsalicylic acid pool may be important to rapidly provide free SA. These and similar results [9] have lead to the suggestion of a so-called priming effect resulting in a faster and stronger activation of disease resistance strategies in response to a second trigger (e.g. a necrogenic pathogen). Apparently, lower levels of SA than are required for exogenous *de novo* induction of SAR gene expression are sufficient to maintain an assembled signaling cascade, by (speculative) analogy to recent findings in the mammalian NFκB signal transduction pathway, it is conceivable that an enhanced ability to combat pathogens is the result of an assembled signaling complex that can be maintained by lower levels of SA than are required for *de novo* induction of SAR.

SA appears to be a common signaling molecule in both the HR and SAR responses. Thus, SA may play multiple roles in the initial plant defense response including potentiation of H_2O_2 production [13], HR induction [14], as well as activation of *NIM1/NPR1*-dependent gene expression. Although the molecular mechanism of the enhanced H_2O_2 formation is still unclear, recent results suggest that the increase is not caused by inhibition of catalase activity [14].

Since activation of SAR in certain so-called ‘lesion mimic’ mutants is correlated with the spontaneous appearance of necrotic lesions, this type of cell death alone appears to provide a sufficient trigger for SAR. The involvement of SA in lesion formation was shown in experiments with crosses between the dominant lesion mimic mutants, *lesions simulating disease resistance* (*lsd)6* and *lsd7* and transgenic NahG plants that cannot accumulate SA due to the constitutive expression of the *Pseudomonas putida nahG* gene that encodes salicylate hydroxylase. In the resulting F1 plants, spontaneous lesion formation was suppressed but exogenous SA application restored lesion formation. Because SA is necessary and sufficient to trigger lesion formation in these mutants, the wild type gene products are probably involved in limiting SA-dependent cell-death. In contrast, when the mutants *lsd2* and *lsd4* are crossed with NahG plants, the lesion phenotype is not suppressed but SAR-gene expression and disease resistance are eliminated [15]. In this case, SA is not required to trigger cell death. Taken together, these results suggest the existence of both SA-dependent and SA-independent cell death mechanisms.

Lesion mimic genes: LSD1 and LLS1

The molecular cloning of two genes involved in the regulation of cell death, *LSD1* from *Arabidopsis* and lethal leaf spot (*LLS*)1 from maize, might further our understanding of the link between cell death mechanisms, SA and resistance.

When *lsd1* mutants are grown under lesion-inducing conditions, lesion formation cannot be confined; the entire leaf eventually becomes necrotic. Apparently, an unknown cell-to-cell signal triggers a chain reaction in the

neighboring cells independently of the original inducer that results in cell death. Thus, LSD1 may play a role as a negative regulator of cell death activation, both by confining the spread of lesion formation and by altering the level of inducers required for programmed cell death. The sequence of *LSD1* shows homology to a zinc-finger transcription factor [16•]. In maize, the *LLS1* gene has been cloned by Mutator-tagging [17•]. The *LLS1* sequence shows homology to aromatic ring-hydroxylating dioxygenases that may be involved in catabolizing phenolic compounds. Since many phenolics accumulate in plants following pathogen ingress it is conceivable that one of these phenolic compounds may function as a mediator of cell death. An obvious candidate phenolic is SA but other possibilities as well as other cell death mechanisms may exist.

SA-independent pathways

Another systemically induced resistance can be triggered in certain hosts by the biocontrol bacteria *Pseudomonas flourescens* WCS 417 [18••], by *Serratia macescens* [19] or by cell wall preparations of these microorganisms (i.e. lipopolysaccharides and other molecules) [20]. This induced resistance response has been termed 'induced systemic resistance' (ISR) to distinguish it from the previously described SAR. ISR is SA-independent, is not associated with SAR gene expression and confers quantitative resistance (40–60% protection) to fungal and bacterial pathogens (see Table 2).

In addition, the necrotrophic bacteria, *Erwinia carotovora*, has been shown to induce expression of certain PR genes via an SA-independent, and potentially even SA-antagonistic, pathway during an early phase of infection. This systemic response can be distinguished from SAR by the pattern of induced PR gene expression [21].

Although their regulation and natural contribution to plant resistance is less well understood, other small, cysteine-rich antimicrobial peptides, such as lipid transfer proteins and thionins, accumulate following pathogen infection. Transgenic plant experiments indicate that these peptides play a role in disease resistance. In *Arabidopsis* and tobacco, constitutive high level expression of barley lipid transfer protein 2 confers resistance to bacterial pathogens [22]. Similarly, transgenic plants with high constitutive levels of thionins are resistant to a number of pathogens. Recently, it has been shown that overexpression of an endogenous thionin in Arabidopsis results in increased resistance to *Fusarium oxysporum* [23]; however, the mechanism by which these small peptides confer resistance has not yet been established.

Another small peptide of the defensin class is PDF1.2. This plant defensin is induced by jasmonic acid (JA), ethy-

Table 1

Disease resistance mutants in *Arabidopsis thaliana*.

Biochemical position and mutant	Name	Screen and possible function	Reference
Avr-R gene interaction			
eds1	Enhanced disease susceptibility	Susceptibility to avirulent *Peronospora parasitica* isolates, member of the converging (Tol/IL-1) R gene signaling pathway	[34]
ndr1	Non-race-specific disease resistance	Susceptiblity to avirulent *Pseudomonas syringae* strains, convergence of (leucine rich) R-gene signaling	[35•]
lsds1 *lsds6*	Lesions simulating disease resistance	Identification of spontaneous lesion fromation Wild-type alleles are involved in limiting initiation or spreading of cell death	[16••]
acds2	Accelerated cell deaths	Same as *lsds*	[36]
Cell death			
cims/cpr	Consitutive immunity/ constitutive PR gene expression	Marker gene overexpression (PR1 or PR2); role in SA biosynthesis or SR upregulation	[25•]
dnd1	Defense, no death	Absence of HR when inoculated with avirulent *Pseudomonas syringae, constitutive immunity*	[33] (A Bent, personal communication)
pad	Phytoalexin deficient	No phytoalexin accumulation after infection by the moderate virulent pathogen *Pseudomonas syringae* pv *maculicola* ES4326. Genes may be involved in phytoalexin biosynthesis or in general pathogen recognition and signaling	[2]
SA accumulation			
nim/npr/sai	No immunity/no PR genes/ SA insensitive	Suscpetibility to virulent *Peronospora parasitica* isolates after chemical immunization, hypersensitive to *Pseudomonas syringae*, counter selection using a SA-inducible promoter; Nim seems to be a central component of SAR	[3••,10••,37]
PR gene expression non SAR mutants			
edr1	Enhanced disease resistance	Resistance to virulent *Pseudomonas syringae* pathovars; also resistant to *Erisyphe cichoracearum*	[33] (R Innes, personal communication)

Table 2

Pathways of induced disease resistance.

Induced resistance	Signal molecule	Induced by	Marker genes*	Type of pathogen (not exclusively)†
Systemic acquired resistance	SA	Necrosis	SAR genes (PR1,2,5)	Obligate biotrophs/ avr/R gene interactions (*P. parasitica*)
Induced systemic resistance	?	PGPR (biocontrol bacteria), LPS and cell wall fractions	?	*Fusarium oxysporum* spraphani, *Pseudomonas* syringae pv *tomato* (*Pst*)
Small antimicrobial peptides	JA/C_2H_4	Wounding/insect feeding/ *Alternaria brassicicola*	Defensins (Pdf1.2) Thionins LPTs Protease inhibitors	Insect larvae, *Fusarium oxysporum*, *Botrytis cinera*, *Pst*
Erwinia	?	*Erwinia carotovoral* PAP-over-expression?	Subclass PR genes (including basic isoforms)	*Rhizoctonia solani?*
Silencing	(RNA?)	Viral infection	na	CaMV, nepovirus

*Marker genes are genes whose expression or protein activity is tightly correlated with the maintenence of resistance. †The spectrum of the different induced resistance mechanisms is overlapping, pathogens encounter always a mixture of several defense responses. CaMV, Cauliflower Mosaic Virus; na, not applicable.

lene, and superoxide, and also accumulates systemically following inoculation with *Alternaria brassicicola* [24••]. Furthermore, PDF1.2 mRNA levels are elevated in the lesion mimics *acd2* and *cpr5* [24••,25•]. In double mutants of *cpr5* and NahG or *npr1*, where the SAR pathway is suppressed, the level of PDF1.2 remains elevated and the plants retain resistance to *Peronospora parasitica* [25•]. In fact, PDF1.2 mRNA accumulation is twofold higher in NahG plants than in wild type, possibly through the elimination of either SA-mediated antagonism or of metabolic sinks [24••]. Whether *P. parasitica* resistance is conferred directly through the antimicrobial activity of PDF1.2 or as part of a broader, SA-independent resistance response remains an open question. In either case, crosstalk between the different signaling pathways is likely. For instance, it has been shown that JA induces phenylalanine ammonia lyase and chalcone synthase gene expression [26] and that *A. brassicicola* induces both SA and JA dependent plant responses [24••]; however, previous work has shown that in some cases SA- and JA-mediated signaling are mutually antagonistic.

Induced resistance to viruses

In cases where an HR is induced following viral infection (e.g. tobacco mosaic virus, turnip crinkle virus), an SA-dependent, cyanide-insensitive mechanism might be involved in limiting virus movement. In these cases, it has been suggested that the alternative oxidase respiratory pathway is induced by salicylhydroxamic acid, thus raising the local temperature (i.e. plant fever) [27]. This is further supported by experiments that show a SA- and tobacco mosaic virus-induced flux through the alternative oxidase pathway in tobacco [28].

Virus infections may persist for a long time in plants without causing lesions, but hampering plant growth and proliferation. Plants can recover from at least some viral infection. In the case of cauliflower mosaic virus and nepoviruses, it has been shown that the plant uses a post-transcriptional silencing mechanism to limit systemic movement [29•,30•]. The ‘gene silencing’ phenomenon was initially observed in transgenic plant experiments. The gene is actively transcribed by the nucleus but the mRNA does not accumulate to high levels, apparently due to specific degradation in the cytoplasm. It is currently unknown whether this silencing mechanism is the cause of resistance or the consequence of another, virus-specific plant defense strategy.

Ribosome inactivating proteins (RIP) cleave the N-glycosidic bond of adenine in a specific ribosomal RNA sequence thereby rendering them incapable of protein synthesis. RIPs have been shown to possess antiviral activity *in vitro*, presumably by inhibiting viral replication. When an inactive form of the pokeweed antiviral protein, a type I RIP, is overexpressed in transgenic tobacco plants, broad range virus resistance is induced and PR-genes are expressed in the absence of lesion formation. Furthermore, this induction appears to be SA-independent because SA does not accumulate in these plants [31] nor is the expression of PR genes systemically induced [32]. In grafting experiments, although the scion grafted onto a PAP-overexpressing rootstock maintained virus resistance, resistance against a fungal pathogen, *Rhizoctonia solani*, was inactivated. Because RIPs are expressed in a tissue-specific manner, it is questionable whether they have a role in broad-spectrum pathogen resistance in nature.

Conclusions

During the past year, our knowledge about the variety of inducible plant defense strategies has increased substantially; however, for most of the underlying signal transduction pathways a molecular understanding is still missing. Systematic approaches for the identification of marker genes and mutants are needed. A first step in this direction is the identification of non-SAR mutants, such as the enhanced disease resistance 1 mutant [33]. A better understanding of plant resistance strategies, their timing and localization will allow an assessment of the relative contributions of the different defense mechanisms to disease resistance. Manipulating the expression of crucial genes (e.g. *NIM1*, *MLO* and DIMBOA biosynthesis genes) and applying inducers (e.g. benzothiadiazol) has already proven to be effective in protecting plants against pathogens.

Acknowledgements

We apologize to the scientists whose excellent work could not be cited due to space limitations. We would like to thank M Hunt, M Tanzer and E Ward for critically reading the manuscript.

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