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REVIEW

Recognition and Response in Plant–Pathogen Interactions

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Most plants are resistant to the majority of pathogens. Susceptibility is the exception to the more common state of resistance, i.e., being refractory to infection. However, plant pathogens cause serious economic losses by reducing crop yield and quality. Although such organisms are relatively simple genetic entities, in plants, the mechanisms underlying the generation of disease symptoms and resistance responses are complex and, often, unknown. The study of genes associated with plant-pathogen resistance addresses fundamental questions about the molecular, biochemical, cellular, and physiological means of these interactions. Over the past 10 years, the cloning and analysis of numerous plant resistance genes has led researchers to formulate unifying theories about resistance and susceptibility, and the co-evolution of plant pathogens and their hosts. In this review, we discuss the identification of response genes that have been characterized at the molecular level, as well as their putative links to various signaling pathways. We also summarize the knowledge regarding crosstalk among signaling pathways and plant resistance genes.

Keywords: defense-signaling pathway, disease resistance, HR, *R* gene, SAR

PATHOGEN RECOGNITION

Resistance to invading microorganisms is often governed by specific recognition between plant and pathogen proteins. Here, we will describe examples of the best characterized recognition systems in plants, which mediate pathogen perceptions either through an awareness of "virulent determinants" (Avr), which act as specific elicitors and are unique for a particular pathogen, or via conserved microbial structures, i.e., pathogen-associated molecular patterns (PAMPs).

R-gene-mediated pathogen recognition

The defense strategy of plants is based on dominant *resistance* (*R*) genes, in which disease resistance is elicited by the products of *avirulence* (*Avr*) genes from the pathogen (Flor, 1971). The R-proteins are variably expressed within a species, thus, allowing its distinct members to differ in their resistance to a particular organism. In general, the plant–pathogen interaction is highly specific. If a plant or a pathogen lacks the appropriate *R* or *avr* gene, respectively, then activation of the plant-defense responses may be delayed or ineffective (Nimchuk et al., 2003). R-protein-mediated defense responses are frequently associated with a type of programmed cell death, i.e., the hypersensitive response (HR), that is believed to limit the spread of pathogens (Heath, 2000).

Several *R* genes have now been cloned from a wide range of plant species. Despite the broad spectrum of resistance imparted by R proteins, these gene products can be categorized into five classes, according to their domain structures (Martin et al., 2003; Fig. 1). The majority of those proteins contains a nucleotide-binding site (NBS) and leucine rich repeats (LRRs); these are classified as NBB-LRR R proteins. The *Arabidopsis* genome has over 150 genes that encode this class of proteins (Jones, 2001). NBS-LRR proteins can be further divided based on their amino (N)-termini, which may share homology with Toll and interleukin-1 receptor (TIR) proteins (TIR-NBS-LRR), or else contain a leucine-zipper motif (LZ-NBS-LRR) or a coiled-coil motif (CC-NBS-LRR). Other conserved motifs found in the R-proteins include serine/threonine kinase domains and transmembrane domains (Martin et al., 2003).

Although many pathogen effector genes and the *R* genes that respond to them have been cloned, any direct binding between the effectors and R proteins has rarely been demonstrated. This suggests that, contrary to predicted models, the recognition of bacterial effectors by plants, and the subsequent signaling responses, result from an indirect mechanism (Bonas and Lahaye, 2002; Schneider, 2002). Dangl and Jones (2001) have proposed a 'guard' model, in which R proteins detect changes in the host targets of pathogen elicitors. Molecular evidence for indirect pathogen recognition has come from studies of the R protein RPM1-interacting protein 4 (RIN4), which confers resistance against strains of *Pseudomonas syringae* that carry the avirulence factors AvrRpm1 or AvrB. The interaction of RIN4 with AvrRpm1 and AvrB lead to RIN4 phosphorylation, while the interaction of RIN4 with AvrRpt2 results in the degradation of RIN4, as well as the R proteins RPM1 and RPS2. Both RPM1 and RPS2 serve as molecular guards of RIN4. The former monitors changes in RIN4 induced by AvrRpm1 or AvrB (Mackey et al., 2002), while the latter monitors the elimination of RIN4 caused by AvrRpt2 (Axtell and Staskawicz, 2003; Mackey et al., 2003; Day et al., 2005). Thus, RIN4 functions as a common target of several pathogen elicitors, and is guarded by more than one R protein. The initiation of defense-signaling arises because of alterations in the host targets of those elicitors, rather than by direct binding of the elicitors to R proteins. Mackey et al. (2002) have suggested that RIN4 is a negative regulator of basal defense responses, and that the pathogen elicitor-targeting of RIN4 increases its

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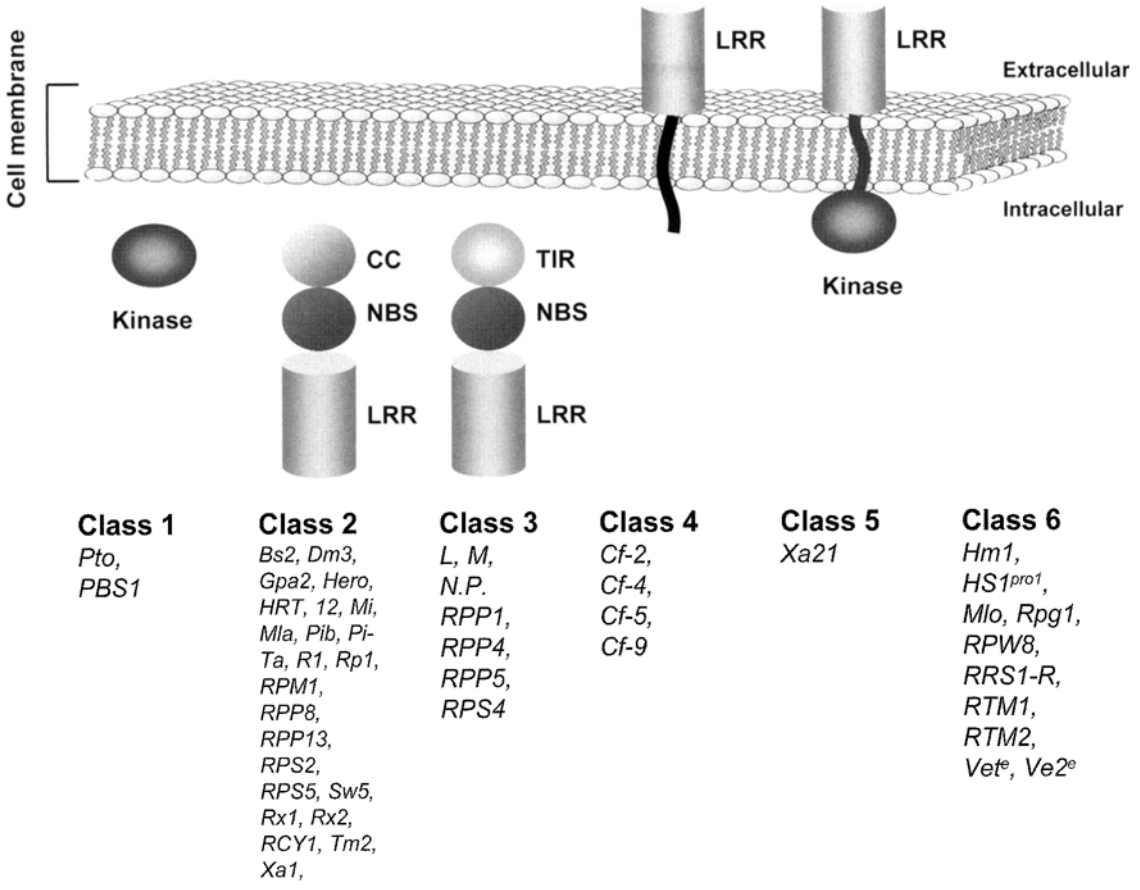

Figure 1. Structure and location of six main classes of plant disease resistance proteins. Classes 1 through 5 are defined based on combinations of a limited number of structural motifs. Class 6 includes R proteins that do not fit into the other 5 classes. LRR, leucine-rich repeat; NBS, nucleotide-binding site; CC, coiled coil domain; TIR, Toll and interleukin 1 receptor domain.

activity and suppresses the plant's basal immunity level.

Recognition of PAMPs

PAMPs, also referred to as general elicitors, are highly conserved structurally across a wide range of microbes, but are not found in potential host plants (Nürnberger et al., 2004). They often constitute indispensable structural components of the pathogen, and contain a conserved feature that is recognized by pathogen receptors. A variety of surface-exposed and cytoplasmic bacterial molecules contain PAMPs (Nürnberger et al., 2004). Their recognition by the plant receptors triggers mitogen-activated protein kinase (MAPK)-mediated signaling cascades that cause the rapid and transient phosphorylation of specific nuclear, cytosolic, and membrane-bound proteins (Dietrich et al., 1990; Felix et al., 1991; Jonak et al., 2002; Peck, 2003; He et al., 2006). The first complete MAPK cascade in plants was described for *Arabidopsis* (Asai et al., 2002). This cascade was shown to function downstream of the flagellin receptor FLS2, and to activate two plant-specific transcription factors. Transient overexpression of the components of that cascade confers resistance to bacterial and fungal pathogens (Asai et al., 2002). Treating *Arabidopsis* suspension cells with lipopolysaccharide (LPS), a cell-surface component of Gram-negative bacteria, results in the production of nitric oxide (NO) through the activation of an NO synthase, Atnos1, that was previously associated with hormonal signaling (Zeidler et al., 2004). In that earlier study, the expression of certain defense genes was nearly abolished in LPS-treated *Atnos1* mutants, and those plants were more susceptible than the wild type to a virulent strain of *P. syringae*. These reports highlight the importance of NO production in responses to LPS.

INDUCED RESISTANCE MECHANISMS

There is considerable overlap between early physiological and biochemical events and the signaling requirements for different types of plant pathogen-defense responses. Interactions that result in resistance to a pathogen induce either an HR or an effective basal defense, while those that lead to the spread of the pathogen (compatible interactions) are characterized by an ineffective basal-defense response. While these responses to each type of interaction (resistance or compatible) may have many similarities, they differ in their timing and strength.

The hypersensitive response (HR)

The HR is characterized by localized, rapid death of host cells, and is believed to confine the growth of biotrophic pathogens during an incompatible interaction by inducing the production of antimicrobial compounds and limiting

nutrient uptake. Regulation of the HR involves an oxidative burst (Heath, 2000), ion channel activity (Atkinson et al., 1996), and NO (Wendehenne et al., 2004), as well as interaction among some of these various signals (Delledonne et al., 2001). Certain relative levels of both NO and H_2O_2 induced in the host may be required for proper HR regulation (Delledonne et al., 2001), and the pattern of NO generation might play a role in cell-signaling and cell death as an infection proceeds (Zhang et al., 2003). In support of this proposed function for nitric oxide, it has been shown that inhibition of NO synthesis or activity attenuates the HR. Interestingly, an *Arabidopsis AtbohF/AtbohD* double mutant, which is deficient in components of the NADPH oxidase complex that are thought to be involved in generating the HR-associated oxidative burst, lacks any detectable H_2O_2 accumulation during resistance (Torres et al., 2002). In this double mutant, some early cell death is activated, suggesting that this event occurs independent of H_2O_2, and subsequent death requires H_2O_2 generation. Thus, initial cell death during the HR may be both NO- and H_2O_2-independent.

Other signaling molecules implicated in the HR include salicylic acid (SA), jasmonic acid (JA), and ethylene (ET). Transgenic *Arabidopsis* plants that express the *Pseudomonas putida* gene for salicylate hydroxylase (*nahG*), which converts SA to catechol, are unable to accumulate SA and do not generate an HR (Heath, 2000). The phenotype of some lesion-mimic mutants, which develop spontaneous lesions that imitate HR-mediated cell death, can be suppressed when these mutants are placed in a *NahG* background, and the lesions can be restored in these plants by adding SA (Lorrain et al., 2003). Other lesion-mimic mutants exhibit intensified lesions in plants that are defective in JA- or ET-signaling (Lorrain et al., 2003). These differences in the effects of SA, JA, and ET on lesion formation could be due to synergistic or antagonistic relationships among their respective signaling pathways.

Systemic defense responses

In addition to the HR, plants have general resistance responses that are induced after an HR, or during a successful infection, to either combat secondary infections from a broad spectrum of pathogens or to prevent an existing infection from spreading further. One such general defense mechanism is known as systemic acquired resistance (SAR) (Ryals et al., 1996). The accumulation of SA is required prior to this onset of SAR. In transgenic plants expressing salicylate hydroxylase, which fail to accumulate SA, the establishment of SAR is prevented (Gaffney et al., 1993). For some plants, such as tobacco, cucumber, and *Arabidopsis*, treatment with SA, or its functional analogs 2,6-dichloroisonicotinic acid (INA) and benzo (l,2,3) thiadiazole-7-carbothioic acid S-methyl ester (BTH), is sufficient to induce SAR (Métraux et al., 1991; Görlach et al., 1996). Thus, salicylic acid is sometimes both necessary and sufficient for the induction of SAR. Such acquired resistance is believed to be a result of the concerted activation of *PR* genes (Yalpani et al., 1991; Uknes et al., 1992) because the overexpression of a single *PR* gene confers only limited protection to the plant (Alexander et al., 1993). Even though their roles in disease resistance have yet to be clearly elucidated, the expression levels of *PR* genes serve as convenient markers for monitoring SAR. It has become obvious that plants utilize multiple pathways of transduction to activate the HR, SAR, and other resistance responses upon exposure to pathogenic signals. Likewise, it is now clear that SA-mediated SAR is not the only pathway that can lead to broad-spectrum disease resistance. Evidence is emerging to strongly suggest that JA and ethylene function as alternative signals in the induction of resistance against microbial pathogens, in addition to their well-characterized roles in the wounding response of plants.

DISSECTION OF DEFENSE-SIGNALING PATHWAYS

Three signaling molecules, SA, JA and ET, have now been identified as key factors in a variety of plant-defense responses. These include reactions to abiotic stresses, such as wounding and exposure to ozone, as well as to insect and microbial attacks (Dong, 1998; Feys and Parker, 2000). Here, we summarize our current understanding of the roles of SA-, JA- and ET-mediated signaling pathways in pathogen defense, and the considerable amount of synergistic or antagonistic cross talk between SA-dependent and JA/ET-dependent defense responses (Schenk et al., 2000; Kunkel and Brooks, 2002).

SA-dependent signaling

Salicylic acid plays a central role in local plant defense responses, and is required for the establishment of SAR. SA levels increase in plant tissues following pathogen infection, and exogenous applications result in enhanced resistance to a broad range of organisms (Ryals et al., 1996).

Several mutants have been isolated with altered SA levels or defects in their SA sensitivity. These have been useful in determining the relative positioning of various signaling components in the SA-signaling pathway. For example, in the *eds5–1* mutant (enhanced disease susceptibility), the level of *PR-1* mRNA accumulation following virulent *P. syringae* infection is approximately 10% of that in the wild type (WT), but the mutant plants are capable of mounting a partial SAR response, with levels of *PR-2* and *PR-5* mRNA equivalent to the WT (Glazebrook et al., 1996; Rogers and Ausubel, 1997). Other mutants with reduced *PR-1* gene expression levels following pathogen attack include *sid1* (allelic to *eds5–1*) and *sid2* (salicylic acid induction deficient) (Nawrath and Métraux, 1999), which are deficient in their accumulations of SA following infection. Expression of *SID1/EDS5* increases with SA treatment, suggesting that a positive feedback mechanism exists (Nawrath et al., 2002). SID1 encodes a membrane-spanning transporter protein (Nawrath et al., 2002), and *SID2* encodes a putative isochorismate synthase, which might be involved in the synthesis of SA from chorismate (Wildermuth et al., 2001).

The *pad1*, *pad2*, *pad3*, and *pad4* mutants (phytoalexin-deficient) have defects in their phytoalexin and SA accumulations, and reduced *PR* expression following pathogen attack by virulent *P. syringae* (Glazebrook and Ausubel, 1994; Glazebrook et al., 1996). *PAD4* acts upstream of SA, encoding a protein with predicted similarity to triacyl glyc-

erol lipases, resemblant of *EDS1* (Zhou et al., 1998; Falk et al., 1999; Jirage et al., 1999). Lipases are hydrolytic enzymes that break down triacylglycerols into fatty acids and glycerols. Thus, it has been suggested that PAD4 may participate in the synthesis or degradation of a molecule involved in defense-signaling.

JA-dependent signaling

JA is a fatty-acid-derived signaling molecule that is associated with several aspects of plant biology, including pollen and seed development, plus defenses against wounding, ozone, insect pests, and microbial pathogens (Creelman and Mullet, 1997; Reymond and Farmer, 1998; Li et al., 2001). Mutants of *A. thaliana* that are either impaired in their ability to produce JA, such as the *fad3/fad7/fad8* triple mutant (fatty acid desaturase), or unable to detect JA, such as *coi1* (coronatine insensitive1) and *jar1* (JA resistant), exhibit enhanced susceptibility to a variety of pathogens, including the fungi *Alternaria brassicicola*, *Botrytis cinerea*, and *Pythium* sp., and the bacterium *Erwinia carotovora* (Staswick et al., 1998; Thomma et al., 1998; Vijayan et al., 1998; Stintzi et al., 2001). These organisms, often referred to as 'necrotrophs', employ a common virulence strategy that involves rapidly killing plant cells to obtain nutrients (Jackson and Taylor, 1996). Several JA-dependent genes that encode PR proteins, including plant defensin1.2 (PDF1.2), thionin2.1 (THI2.1), hevein-like protein (HEL), and chitinaseb (CHIB), are commonly used in monitoring JA-dependent defense responses (Reymond and Farmer, 1998)

JA-mediated defense pathways are constitutively activated in the *cev1* mutant (constitutive expressor of *VSP1*), and in *cet* mutants (constitutive expressor of thionin). The *cev1* mutant shows constitutive expression of *Thi2.1*, *PDF1.2*, and *CHI-B*, and increased levels of JA and ET (Ellis and Turner, 2001; Ellis et al., 2002), while the *cet* mutants exhibit constitutive expression of JA-dependent genes, increased levels of JA, and spontaneous lesion development (Hilpert et al., 2001; Nibbe et al., 2002). It appears that this lesion formation in different *cet* mutants may result from cell-death pathways that are dependent and independent of SA. The *cev1* mutant has increased resistance to *Erisyphe* sp. (Ellis and Turner, 2001), but the response to pathogen infection by constitutively active JA mutants has not been investigated. However, it seems likely that constitutive activation of JA-mediated signaling confers enhanced resistance to necrotrophic pathogens that are normally controlled by the JA pathway.

ET-dependent signaling

ET production is regulated by developmental signals, and in response to biotic and abiotic stimuli (Wang et al., 2002). Several mutants have been isolated with defects in their ET-mediated responses, as manifested in seedling morphological characteristics known as the triple response. These include *ein* (ET insensitive) and *etr* (ET resistant) mutants (Bleecker et al., 1988; Guzman and Ecker, 1990). Components of the ET-signaling pathway include the nuclear-localized transcription factor EIN3, which activates ethylene response factor1 (ERF1). ERF1 is a member of the family of plant-specific ethylene-responsive element binding proteins (EREBPs); it binds to GCC box promoter elements to activate such defense genes as *PDF1.2* and *CHI-B* (Chao et al., 1997; Solano et al., 1998). The GCC box motif is associated with ET, and is found in the promoters of many pathogen-responsive genes (Ohme-Takagi and Shinshi, 1995; Büttner and Singh, 1997; Chen et al., 2002). *ERF1* expression can be induced by ET or JA; signaling from both pathways appears to be required for expression because mutations that block either the JA- or the ET-mediated signaling pathway prevent its expression in response to JA or ET, respectively (Lorenzo et al., 2003). Microarray analysis of plants over-expressing ERF1 have shown that ERF1 regulates the expression of both ET- and JA-responsive genes, indicating that ERF1 likely functions downstream of the intersection between those ET- and JA-signaling pathways (Lorenzo et al., 2003).

Interactions between signaling pathways

Although SA and JA/ET induce the expression of different subsets of *PR* genes, and are involved in resistance against specific pathogens, there is evidence of both synergism and antagonism between their pathways (Schenk et al., 2000; Glazebrook, 2001; Kunkel and Brooks, 2002).

The SA and JA pathways often appear to act antagonistically. Salicylic acid has an inhibitory effect on JA biosynthesis and JA-responsive gene expression (Penninckx et al., 1996; Gupta et al., 2000). NahG-transgenic plants exhibit increased levels of JA and JA-responsive gene expression in response to biotrophic pathogens, indicating that pathogen-induced SA accumulation suppresses JA production and the expression of JA-responsive genes (Spoel et al., 2003). Jasmonate is also reportedly involved in the negative regulation of SA-signaling. For example, *mpk4* and *ssi2*, which are impaired in their JA-signaling, constitutively express SA-mediated defense responses (Petersen et al., 2000; Shah et al., 2001; Kachroo et al., 2003).

SA and JA can also act synergistically to induce the expression of defense-associated genes (Schenk et al., 2000). In the *ssi1* mutant (suppressor of SA insensitivity), constitutive expression of *PDF1.2* and *NPR1*-independent expression of *PR-1* require not only SA, but also the JA- and ET-signaling pathways. This suggests that SSI1 plays a role in regulating crosstalk between the SA- and JA/ET-signaling pathways (Shah et al., 1999; Nandi et al., 2003). In addition, NPR1-independent resistance in *cpr5* and *cpr6* mutants (constitutive expressor of PR genes) requires SA and components of the ET and JA pathways (Clarke et al., 2000).

The ET and JA pathways often appear to act synergistically. In microarray analysis, Schenk et al. (2000) have found that most of the genes induced by ET are also induced by MeJA. Furthermore, both JA and ET are necessary for *PDF1.2* expression (Penninckx et al., 1996; Ellis and Turner, 2001), and SA-independent systemic resistance requires both JA- and ET-mediated signaling (Pieterse et al., 1998).

Using microarray analysis of mutants defective in their SA-, JA-, and/or ET-mediated defense-signaling, Glazebrook et al. (2003) have been able to identify components of these signal-transduction pathways, and have grouped those mutants according to their gene expression profiles induced by infec-

tion with virulent *P. syringae*. Their results suggest that, in response to virulent bacterial pathogen attack, SA- and JA-mediated signaling oppose each other, JA- and ET-mediated signaling generally act together, and SA- and ET-mediated signaling tend to oppose each other.

CONCLUDING REMARKS

Significant progress has been made in the identification of *R* genes from various plants. In contrast to early speculation that mutations resulting in plant resistance would occur in many different types of genes, the evidence to date demonstrates a remarkable degree of conservation of both dominant and recessive resistance in plants. Most of the genes isolated and characterized fall into related categories of NBS-LRR domain-containing proteins. Given the striking overall conservation among many of the *R* genes already identified, it becomes very compelling to investigate how those genes function to produce resistance because insights drawn from one system are likely to be broadly applicable. One promising area currently under examination is the identification of host proteins that interact with the products of pathogen genes during infection. This topic of interest is focused primarily on understanding the mechanisms of infection and pathogenesis, rather than of resistance, and has exploded with the advent of yeast two- and three-hybrid assays, as well as other assays designed to detect specific protein–protein interactions. An important challenge in this research is to determine the degree to which an interaction identified in yeast or *in vitro* also occurs *in planta*. The next generation of candidate genes will undoubtedly come from these studies. A major discovery that has emerged in the past decade, one with profound implications, is the role of gene-silencing in pathogenesis and resistance. This has led to the development of a powerful genetics approach, i.e., reverse genetics, in which genes are identified by the phenotypes associated with their silencing. Reverse genetics is becoming increasingly important in projects involving high-throughput functional genomics analyses of plant species.

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