Journal of Chemical Ecology, Vol. 30, No. 12, December 2004 (© 2004)

REVIEW ARTICLE

GENE-FOR-GENE DISEASE RESISTANCE: BRIDGING INSECT PEST AND PATHOGEN DEFENSE

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(Received September 6, 2004; accepted September 12, 2004)

Abstract—Active plant defense, also known as gene-for-gene resistance, is triggered when a plant resistance (*R*) gene recognizes the intrusion of a specific insect pest or pathogen. Activation of plant defense includes an array of physiological and transcriptional reprogramming. During the past decade, a large number of plant *R* genes that confer resistance to diverse group of pathogens have been cloned from a number of plant species. Based on predicted protein structures, these genes are classified into a small number of groups, indicating that structurally related *R* genes recognize phylogenetically distinct pathogens. An extreme example is the tomato *Mi-1* gene, which confers resistance to potato aphid (*Macrosiphum euphorbiae*), whitefly (*Bemisia tabaci*), and root-knot nematodes (*Meloidogyne* spp.). While *Mi-1* remains the only cloned insect *R* gene, there is evidence that gene-for-gene type of plant defense against piercing-sucking insects exists in a number of plant species.

Key Words—resistance genes, piercing-sucking insects, active plant defense, resistance response, *Mi-1*.

Plants are exposed to a large number of pests and pathogens. However, only a small proportion of these attacks and invasions are successful and result in disease. This is because plants have evolved to defend themselves from invading pests and pathogens (reviewed in Walling, 2000; Dangl and Jones, 2001). The first line of defense is passive and includes physical barriers like waxy or thick cuticles and the presence of specialized trichomes that inhibit insects or pathogens from settling, penetrating plant surfaces, and successfully colonizing plants. In addition to these

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physical barriers, there are two overlapping yet different forms of active plant defense. The first is known as the basal plant defense that restricts the invasion of a virulent pathogen or insect. The second involves specific recognition of the invading pest or pathogen by plant resistance (*R*) genes. Upon recognition of the attacking organism, plant defenses are initiated that serve to localize the invasion of the pathogen or deter feeding of the insect. This review focuses on *R* genes and the active form of plant defense against piercing-sucking insects, and highlights how these defense responses relate to those against plant–pathogens.

The genetic basis of plant resistance was first elucidated by Flor in the early 1940s (Flor, 1955). Studying the flax pathogen, *Melampsora lini*, Flor demonstrated that resistance to this fungus is due to the simultaneous presence of a *R* gene in the host and a matching avirulence (*Avr*) gene in the fungus. The absence of either the *R* gene or the *Avr* gene results in disease. This observation led to the theory of gene-for-gene complementarity between host and pathogen (Keen, 1990). The specific recognition of the *Avr* gene product facilitated by the plant resistance gene product triggers a signal transduction cascade that activates plant defenses. The gene-for-gene system is undoubtedly an oversimplification of the phenomenon; however, it has been a useful starting point for predicting plant–pathogen interactions (Dangl and Jones, 2001; Hammond-Kosack and Parker, 2003; Innes, 2004).

Insect R Genes

Resistance to insects has been identified in various plant species (Panda and Khush, 1995; Quisenberry and Clement, 2002). A number of single dominant *R* genes have been mapped, and molecular markers linked to these loci have been identified (Venter and Botha, 2000; reviewed in Yencho et al., 2000; Klingler et al., 2001; Liu et al., 2001; Jena et al., 2002; Liu et al., 2002a; Tan et al., 2004). The majority of the mapped genes are in staple crops like wheat and rice. The largest number of these mapped genes confer resistance to Hessian fly, *Mayetiola destructor*, which in addition to the Russian wheat aphid, *Diuraphis noxia*, is considered one of the most serious insect pests of wheat (Webster et al., 2000). In addition to these mapped genes, several single dominant aphid *R* genes have been identified that confer resistance to a single species of aphid. An example is the *Nr* (resistance to *Nasanova ribisnigri*) gene in lettuce conferring resistance to *N. ribisnigri* (Reinink and Dieleman, 1989).

During the last decade, a large number of *R* genes have been cloned from a number of plant species (reviewed in van't Slot and Knogge, 2002; Hammond-Kosack and Parker, 2003). Although these genes confer resistance to diverse groups of organisms, such as bacteria, virus, fungi, oomycetes, nematodes, and insects, their products share striking structural similarities. These structural similarities are also shared among *R* gene products from monocots and dicots, indicating that

recognition and activation of plant defense signal transduction has been maintained throughout evolution.

The most common structural motif shared by *R* genes is presence of the leucine-rich-repeat (LRR), which in other proteins facilitates protein–protein interactions (Kobe and Deisenhofer, 1994). In addition to the LRR domain, the largest class of *R* genes cloned to date contains a nucleotide binding site (NBS) of P-loop proteins (Traut, 1994) and a variable amino terminal region. Another less common class of R proteins, contains extracellular LRR with a transmembrane domain and either a kinase domain or a short intracellular carboxyl terminus (Hammond-Kosack and Parker, 2003; Nimchuk et al., 2003). A rare class of *R* genes encodes serine/threonine protein kinases (Martin et al., 1993; Swiderski and Innes, 2001). To date, the only cloned insect resistance gene is *Mi-1* (resistance to *Meloidogyne incognita*) from tomato. *Mi-1* belongs to the NBS–LRR class of *R* genes (Milligan et al., 1998; Rossi et al., 1998; Nombela et al., 2003).

The race to clone additional insect *R* genes has been accelerated by the advent of high throughput molecular tools, such as genome mapping, sequencing, and gene cloning. In addition, information gained from the sequences of currently cloned *R* genes is assisting in the search for candidate insect *R* genes (Brotman et al., 2002). With increasing numbers of molecular markers and high throughput methods, mapping *R* gene candidates and resistant phenotypes to each other is feasible. However, structural organization of *R* loci indicates that insect and disease *R* genes are clustered in plant genomes, making it more difficult to identify the gene family member conferring the resistance (McMullen and Simcox, 1996).

Clustering of members of multigene families in plant genomes is common for plant *R* genes. Examples exist where only a single gene in the cluster determines resistance. This is true for a number of loci including the *Mi* locus, the rust resistance locus *M*, the fungal resistance locus *Cf9 (resistance to Cladosprorium fulvum)*, the tobacco mosaic virus (TMV) resistance locus *N*, and the bacterial resistance locus *Pto (*resistance to *Pseudomonas syringae* pv. *tomato*), where an array of related genes is present in a cluster with only one member conferring disease resistance (Martin et al., 1993; Jones et al., 1994; Whitham et al., 1994; Anderson et al., 1997, Kaloshian et al., 1998). Therefore, cloning and transformation of candidate genes is required to identify their functional role.

The Structural Organization of the Mi-1 Locus

Resistance to root-knot nematodes mediated by the *Mi-1* gene was identified in a wild relative of tomato *Lycopersicon peruvianum*. *Mi-1* was introgressed from *L. peruvianum* into cultivated tomato, *Lycopersicon esculentum*, by using embryo rescue of an interspecific cross between these two *Lycopersicon* species (Smith, 1944). Progeny of a single F1 plant is the sole source of nematode resistance in currently available fresh-market and processing tomato cultivars (Medina-Filho

and Stevens, 1980). The *Mi-1* locus was localized to the short arm of tomato chromosome 6.

In addition to nematode resistance, resistance to potato aphid, *Macrosiphum euphorbiae,* was also identified within a 650-kb region of the short arm of chromosome 6 (Kaloshian et al., 1995). In this same region, two clusters of NBS–LRR type of *R* genes were identified (Vos et al., 1998), and the resistance to aphids and nematodes was localized to one of these clusters (Kaloshian et al., 1998). Within this cluster, two transcribed NBS–LRR type of *R* genes, *Mi-1.1* and *Mi-1.2*, with over 91% amino acid sequence identity and an apparent pseudogene, were identified. Even though the two genes were highly similar, only *Mi-1.2* (referred to in this article as *Mi-1*) conferred resistance to both root-knot nematodes and potato aphids (Milligan et al., 1998; Rossi et al., 1998). Later, it was shown that *Mi-1* also conferred resistance to both Q- and B- biotypes of *Bemisia tabaci* (Nombela et al., 2003). The function of *Mi-1.1* has not yet been identified.

The Mi-1 Surveillance System

The tomato gene *Mi-1* encodes a cytoplasmic protein of 1257 amino acids with putative coiled coil (CC) NBS–LRR domains (Milligan et al., 1998). Based on animal models, CC domains are presumed to be regions of protein–protein interacting domains and, therefore, may interact with partners involved in resistance signaling (Dubin et al., 2004). Recently, it was shown that the NBS domain has the ability to specifically bind and hydrolyze ATP (Tameling et al., 2002). ATP hydrolysis might provide the energy needed for a possible conformational change of NBS–LRR proteins, required to initiate signaling. ATP binding and hydrolysis have been shown to be necessary for signaling by proteins with NBS domains that regulate cell death in animal systems (van der Biezen and Jones, 1998).

Using genetics and functional studies, the LRR region of R proteins has been shown to determine recognition specificity (Botella et al., 1998; Meyers et al., 1998; Ellis et al., 1999; Bittner-Eddy et al., 2000; Dodds et al., 2001). This region is under selection for divergence, and it is the most variable region in closely related R proteins (Meyers et al., 1998). However, other protein domains in the LRR-containing *R* genes also have been implicated in determining recognition specificity (Luck et al., 2000). More recently, LRR and NBS regions have been implicated in intra- and intermolecular signaling and interaction with plant signal transduction components (Moffett et al., 2002; Liu et al., 2004). Mutations in NBS and LRR domains have resulted in either nonfunctional alleles or *R* gene products that are constitutively active in the absence of pathogen effector molecules (Bendahmane et al., 2002; Shirano et al., 2002). These data indicate that these *R* genes are under negative regulation.

Similarly, *Mi-1* is negatively regulated in the absence of nematodes or insects. Several chimeric constructs were made between the functional *Mi-1.2* allele

and the nonfunctional *Mi-1.1* allele (Hwang et al., 2000). Constructs were transformed into *Agrobacterium rhizogenes* and used in both transformation assays, which result in hairy root formation, and in transient expression in leaves. One of these constructs is Mi-DS4, produced by introducing the *Mi-1.2* LRR encoding region into *Mi-1.1*. Infiltration of *Nicotiana benthamina* leaves with *A. rhizogenes* containing Mi-DS4 results in cell death due to constitutive activation of the *Mi-1*-mediated cell death pathway (Hwang et al., 2000). Similarly,Mi-DS4 when used in *A. rhizogenes*-mediated transformation of cotyledons, failed to produce transformed roots due to the lethal phenotype. Using Mi-DS4 and other chimeric constructs between *Mi-1.2* and *Mi-1.1*, it was shown that intramolecular interaction in *Mi-1* regulates cell death, where the LRR region is involved in signaling cell death and the amino terminus region, which includes the CC and possibly the NBS domains, negatively regulating this signal (Hwang et al., 2000; Hwang and Williamson, 2003). In addition, these studies narrowed down the region of *Mi-1* important for recognition of the nematode effector protein or a plant protein that determines specificity to a segment of three amino acid residues, 984–986, which are located in the LRR domain of *Mi-1*.

Additional genetic evidence indicates that another gene, *Rme1* (required for resistance to *Meloidogyne*), is required for the *Mi-1*-mediated resistance to aphids, whiteflies, and nematodes (Martinez de Ilarduya et al., 2001, 2004). The *rme1* mutant was isolated in a genetic screen of mutagenised *Mi-1* tomato populations. The *rme1* mutant had a functional *Mi-1* gene, but was compromised in resistance to root-knot nematodes (Martinez de Ilarduya et al., 2001). Later, this mutant was also shown to be compromised in resistance to potato aphids and whiteflies (Martinez de Ilarduya et al., 2001, 2004).

To determine if *Rme1* acted upstream or downstream of *Mi-1*, the phenotype of plants expressing the mutant *rme1* allele and the chimeric Mi-DS4 were evaluated (Martinez de Ilarduya et al., 2004). Mi-DS4 was introduced into *rme1* cotyledons via *A. rhizogenes*-mediated transformation. These plants failed to produce transformed roots, indicating that while resistance was compromised in the *rme1* mutant, the cell death pathway remained active. Therefore, it is possible that *Rme1* interacts with *Mi-1* at amino acid residues 984–986 of the LRR.

The "Guard Theory" and R Protein Complexes

The gene-for-gene hypothesis predicts direct interaction between R proteins and Avr effector proteins (Keen, 1990). Direct interaction of NBS–LRR type of R proteins with corresponding effector proteins remains the exception rather then the rule (Jia et al., 2000; Deslandes et al., 2003). According to the emerging "guard theory," NBS–LRR plant R proteins monitor the interaction of another plant protein with the pathogen or pest Avr determinant (Dangl and Jones, 2001). The pathogen or pest Avr determinant targets this host protein, which might be

part of general plant defense, to suppress defense responses. It is speculated that Avr–host protein interaction results in conformational change in the target host protein, which allows binding by the plant R protein. The binding of the R protein to this target protein or complex in turn triggers the incompatible response. In the absence of the R protein, the host defenses are suppressed by the pathogen or pest virulence determinant, and disease or compatible response follows.

Several examples supporting the guard theory exist. A notable one is the *Arabidopsis* NBS–LRR gene *RPS5* (Resistance to *Pseudomonas syringae),* which confers resistance to *P. syringae* expressing the *Avr* gene A*vrPphB*. The resistance mediated by *RPS5* requires a protein kinase *PBS1* (*AvrPphB* susceptible) (Warren et al., 1999; Swiderski and Innes, 2001). Recently, it has been shown that AvrPphB, a cysteine protease, binds PBS1 and cleaves it. This cleavage triggers *RPS5*-mediated resistance, indicating that RPS5 might sense the integrity of PBS1 (Shao et al., 2002, 2003).

The guard hypothesis proposes indirect interaction between NBS–LRR type of R proteins and their corresponding Avr determinants. Both *Arabidopsis* RPM1 (Resistance to *P. syringae* pv. *maculicola*) and RPS2 (Resistance to *P. syringae* expressing *AvrRpt2*) R proteins interact with their corresponding Avr proteins through RIN4 (RPM1 interacting protein), and RIN4 is the target of three different bacterial effector proteins AvrRpt2, Avr RPM1, and AvrB (Mackey et al., 2002, 2003; Axtell and Staskawicz, 2003).

Based on these and other models, it is intriguing to postulate a role for *Rme1* in resistance to both aphids and nematodes. It is possible that *Rme1* is the target of the nematode and insect effector molecules (Figure 1). These animal Avr products may induce a conformational change in *Rme1*. *Mi-1* could be monitoring these changes in *Rme1* brought about by the interaction with nematode, aphid, or whitefly Avr determinants and trigger rapid activation of defenses (Figure 1). In the absence of *Mi-1* or *Rme1*, the feeding by insects or by nematodes is not detected and attack continues.

The interaction between *Mi-1* and *Rme1* is likely to be more complex. Recent data suggest that R proteins are associated in multimeric complexes with a number of plant proteins that are involved in both signaling and regulation (reviewed in Shirasu and Schulze-Lefert, 2003; Schulze-Lefert, 2004). One of these plant proteins present in a number of R protein complexes is the molecular chaperone Hsp90 (heat shock protein 90). Chaperonins, like Hsp90, are known to play a role in assembly and stability of multisubunit complexes. Requirement for Hsp90 has been shown for the function of NBS–LRR type of *R* genes *RPS2* and *RPM1* of *Arabidopsis*, the tobacco *N*, and the potato virus X (PVX) resistance gene, *Rx* (resistance to PVX) (Hubert et al., 2003; Lu et al., 2003; Takahashi et al., 2003; Liu et al., 2004). Similarly, by using virus-induced gene silencing of *Hsp90* transcripts, a role for *Hsp90* in *Mi-1*-mediated

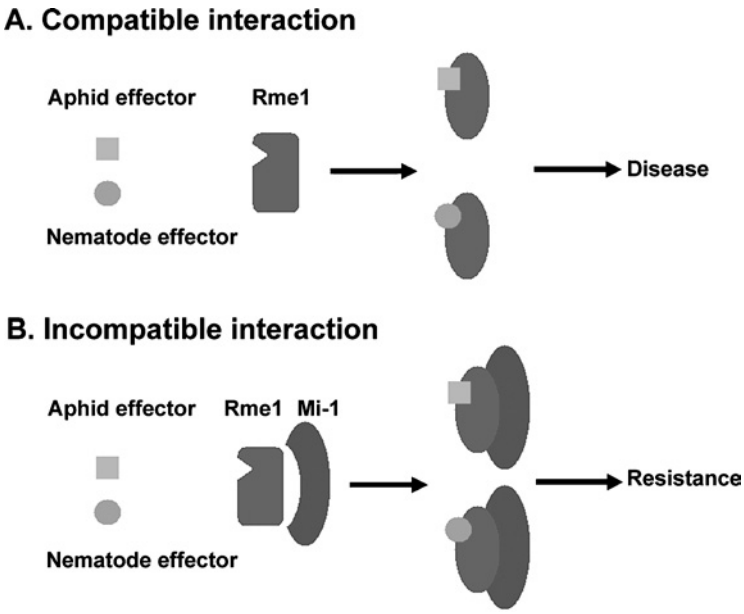

FIG. 1. A schematic model diagram, depicting early interactions in the *Mi-1* signaling pathway. Based on the guard theory, Rme1 is depicted as the target for the insect and nematode effector molecules. Interaction with both aphid and nematode effector molecules results in a conformational change of Rme1 protein. (A) In the absence of *Mi-1*, insect and nematode effector molecules interact with Rme1 which initiates a compatible interaction resulting in disease. (B) In the presence of *Mi-1*, a conformational change in Rme1 due to these interactions is detected, and defense responses or an incompatible interaction is triggered resulting in resistance.

resistance to both nematodes and aphids has been identified (Kaloshian, unpublished results).

Protein complexes containing R protein and Hsp90 could also contain other plant proteins, like Sgt1 (suppressor of G_2 allele of SKP1) and Rar1 (required for *Mla*12 resistance). These proteins might assist in proper assembly of the R complex into a stable signaling competent complex (Schulze-Lefert, 2004). The requirement for *Sgt1* and *Rar1* has been implicated in a number of NBS–LRR *R* gene-mediated resistance in plants as diverse as barley, tobacco, and *Arabidopsis* (reviewed in Shirasu and Schulze-Lefert, 2003). The requirement for *Sgt1* and *Rar1* implicates a role for the ubiquitination pathway, which targets proteins for degradation, in regulating *R* gene signaling (Azevedo et al., 2002; Liu et al., 2002b).

Avirulence Effectors

Complex communications occur between host and the invading pest or pathogen. To successfully infect and colonize host plants, microbial plant pathogens deliver effector molecules into their host cells. In order to reach their feeding sites and deliver these effector molecules, both piercing-sucking insects and nematodes penetrate their hosts with a combination of mechanical penetration and hydrolytic enzymes (reviewed in Miles, 1999; Rosso et al., 1999; Wang et al., 1999; Popeijus et al., 2000; reviewed in Davis et al., 2004). They use their stylets as a mechanical tool, as well as for delivery of various types of molecules to plant tissues and for ingestion of nutrients from phloem or feeding sites.

During the penetration and feeding processes, two types of saliva, gelling and watery saliva, are secreted by aphids and whiteflies. Gelling saliva, also known as the sheath saliva, is secreted along the path of the stylet and contains mainly proteins, phospholipids, and conjugated carbohydrates (reviewed in Miles, 1999). In addition to these components, enzymes like phenoloxidases and peroxidases, and 1,4-glucosidases has also been reported to occur in the sheath saliva (Urbanska et al., 1998; Miles, 1999; Cherqui and Tjallingii, 2000). Watery saliva contains variable and complex arrays of enzymes including phenoloxidases, peroxidase, pectinase, amylases, alkaline and acidic phosphatases, and lipases (Miles, 1999; Cherqui and Tjallingii, 2000). It is likely that piercing-sucking insect Avr determinants are present and delivered by the watery saliva into plant cells, or salivary components aid in generating oligosaccharides and cell wall fragments or other defense signals *in planta* that activate plant defenses.

There is ongoing research to uncover Avr effectors of insects and nematodes (Semblat et al., 2001; Rider et al., 2002; Williamson and Gleason, 2003). To date, no insect or nematode Avr effector proteins have been identified conclusively. In plant pathogen systems, both proteinaceous and nonproteinaceous effectors have been identified (reviewed in van't Slot and Knogge, 2002). The functional role of only a subset of these Avr molecules has been identified. In viral pathogens coat proteins, replicase proteins and movement proteins have been shown to act as Avr effectors (reviewed in van't Slot and Knogge, 2002). Recently, in bacterial and fungal pathogens, Avr proteins possessing protease activity have been identified (Jia et al., 2000; Shao et al., 2002, 2003). Because of the diversity of known effector molecules from bacteria, fungi, and viruses, it is difficult to speculate the nature of these molecules in insects and nematodes. Most likely, the nature of Mi-1 effectors from nematode, aphid and whitefly are different. However, conserved signature motifs in the effector molecules from root-knot nematodes, potato aphids, and whiteflies may interact directly with *Mi-1* or with *Rme1*, or in association with other plant components, to trigger the resistance response. It is also possible that *Mi-1* or *Rme1* recognizes more than one effector molecule as is the case with *RIN4* and the tomato *R* gene *Pto*, conferring resistance to *P. syringae* pv. *tomato* with two different *Avr* genes (Kim et al., 2002).

Since the plant surveillance system detects Avr molecules, why would a pathogen or pest maintain these? It is becoming increasing apparent that some of the effector molecules are maintained in populations of pathogens because they also function as virulence factors (reviewed in Kjemtrup et al., 2000). Virulence factors are required for the full success of a pest or pathogen on a susceptible host. Therefore, in both resistant and susceptible plants, a plant protein is targeted by the pathogen or pest virulence effector molecules. In plants lacking a *R* gene, disease ensues or pest attack continues. While in resistant plants, the Avr–host protein interaction is detected by the R protein, and defense responses are rapidly activated. This is the basis of the "guard theory" described above (Dangl and Jones, 2001) (Figure 1).

A number of insects of the order Hemiptera have endosymbionts which play an essential role in the life of these insects (reviewed in Baumann et al., 1995). The potential role of these microorganisms in plant–insect interactions has not yet been uncovered but cannot be ignored. It is plausible that avirulent effectors from this group of insects could be of bacterial origin.

R Gene-mediated Specificity and Resistance Mechanisms

Plants are in a continuous race with their pests and pathogens. As plant *R* genes evolve to acquire new recognition specificities, pathogens and pests find new ways to circumvent this new recognition machinery. Consequently, any particular single source of resistance, when used in monoculture, is only effective in the field for a short period of time. Most gene-for-gene type insect resistance deployed in crops behave in the same way. In addition, they confer resistance to a single species and limited biotypes of the insect (Hatchett and Gallun, 1970; Ratcliffe and Hatchett, 1997). This is also true for aphid resistance mediated by *Mi-1* where resistance is limited to only *M. euphorbiae* and certain biotypes of this aphid (Goggin et al., 2001).

Recognition of the Avr effectors by the host R protein initiates a defense response that is often, but not always, characterized by hypersensitive response (HR). The HR is a programmed cell death that is initiated at the site of the infection or feeding (Morel and Dangl, 1997). HR is associated with the resistance response mediated by the *Mi-1* gene, in roots, against root-knot nematodes (Dropkin, 1969). Localized necrotic spots are seen near the head of the infective-stage of the nematode, soon after it initiates feeding near the vasculature, presumably limiting access to nutrients. However, in the resistance response to potato aphid, no HR is seen in tomato leaflets infested by the aphid (Martinez de Ilarduya et al., 2003). Nevertheless, induction of HR is not absolutely necessary for activation of plant defense to pathogens. Absence of HR has been reported in plant–pathogen interactions where induction of defense responses was not correlated with initiation of HR (Jakobek and Lindgren, 1993; Cameron et al., 1994; Jia and Martin, 1999).

It is not clear whether HR is a common resistance response to piercing-sucking insects. For example, both presence and absence of HR have been reported in incompatible interactions between wheat and Hessian fly (Hatchett et al., 1993; Grover, 1995; C. Williams, personal communication). Irrespective of presence or absence of HR, a common mechanism of *R* gene-mediated resistance to piercing-sucking insects seems to be limited phloem-feeding (van Helden et al., 1993; Klingler et al., 1998; Kaloshian et al., 2000). Interestingly, the mechanisms of resistance mediated by *Mi-1* to potato aphids and whiteflies appear to be different. Electrical penetration graph studies show that on *Mi-1* plants, aphids do not ingest phloem and die from starvation (Kaloshian et al., 2000). In contrast, whiteflies are able to feed on resistant tomato phloem sap, but have difficulty reaching the phloem element in resistant plants (Jiang et al., 2001). This indicates that *Mi-1*-mediated defense responses are perceived differently by these two insects.

R GENE-MEDIATED PLANT DEFENSE TO INSECTS

There is increasing evidence that *R* gene-mediated resistance is a hyperactivity of basal plant defense. In other words, *R* gene-mediated resistance is a more efficient defense response than the basal response. The existence of basal plant defense responses was genetically dissected during the last decade (reviewed in Glazebrook, 1999, 2001). Using mutational analysis, it was discovered that it is possible to obtain plants that are more susceptible than existing susceptible genotypes. One of the initial screens was performed with *P. syringae* pv. *maculicola*. A high dose of the moderately pathogenic bacterium *P. syringae* pv. *maculicola* results in water-soaked lesions on *Arabidopsis* leaves. In contrast, a low dose results in limited chlorotic spots. Using a low dose of this bacterium and a mutagenized *Arabidopsis* population, several mutants were identified with enhanced disease susceptibility. Among those were the *eds* (enhanced disease susceptibility) mutants, *pad* (phytoalexin deficient) mutants, and the *npr1* (nonexpresser of pathogenesis related gene) mutant (Cao et al., 1994; Glazebrook and Ausubel, 1994; Glazebrook et al., 1996).

Microarray analysis of gene expression profiling comparing *R* gene-mediated incompatible responses to compatible responses, indicates that defense genes are activated faster and to higher levels in incompatible compared to compatible interactions (Tao et al., 2003). Indeed the hallmark of *R* gene-mediated resistance historically has been faster and higher level accumulation of pathogenesis-related (*PR*) gene transcripts in incompatible interactions compared to compatible interactions (Somssich et al., 1989). This pattern is also seen for *PR-1* gene expression in the *Mi-1*-mediated incompatible interaction compared to the compatible interaction after potato aphid infestation (Martinez de Ilarduya et al., 2003). Similarly, increases in chitinases and β-1,3-glucanases activity have been reported in

incompatible interactions of monocots infestation with aphids (van der Westhuizen et al., 1998; Forslund et al., 2000). Recent gene expression profiling by array analysis indicates that resistance in wheat to Russian wheat aphid activates the oxidative stress pathway similar to pathogen-induced *R*-mediated resistance responses (E. Boyko, personal communication).

Plant defense responses to pathogens include pathways dependent on salicylate (SA), jasmonate (JA), and ethylene (ET) signaling molecules. These pathways are not independent of each other, rather a complex network of communication between these pathways results in modulation of plant defense. Both synergistic and antagonistic interactions between SA, JA, and ET signaling pathways have been reported (reviewed in Felton and Korth, 2000; Kunkel and Brooks, 2002). These interactions and consequent modulation of plant defenses are different in different plant species and plant–pathogen or plant–pest interactions. In nature, plants are often simultaneously attacked by a number of different organisms. The cross talk between SA, JA, and ET signaling pathways allows the plant to choose the optimum plant defense, depending on the nature and combination of the attackers.

Both SA- and JA-dependent pathways have been implicated in basal defense responses to phloem- and sap-feeding insects (Fidantsef et al., 1999; Walling, 2000; Moran and Thompson, 2001; Moran et al., 2002; Martinez de Ilarduya et al., 2003; Zhu-Salzman et al., 2004). Using *Arabidopsis* genetic mutants *eds5*, *eds9*, and *npr-1*, defective in SA signaling, resulted in no change in aphid reproduction from that on wild-type plants (Moran and Thompson, 2001). In contrast, higher reproduction of aphids was observed on a *coi-1* (coronatine insensitive) mutant (defective in JA response) and lower reproduction on *cev-1* (constitutive expression of vegetative storage protein) mutant (constitutive JA and ET response) compared to wild-type plants, indicating a role for jasmonate pathway in aphid defense (Feys et al., 1994; Ellis and Turner, 2001; Ellis et al., 2002). Taken together, these results indicate that both JA and SA pathways might be involved in aphid resistance in *Arabidopsis*.

Accumulation of *PR-1* transcripts after aphid feeding on *Mi-1*-containing tomato plants, also indicates a role of SA in resistance to aphids (Martinez de Ilarduya et al., 2003). Stronger evidence for the role of SA in *Mi-1*-mediated resistance was recently demonstrated. *NahG* transgene, which encodes salicylate hydroxylase and degrades SA into catchecol, was introduced into *Mi-1*-containing tomato (Branch et al., 2004; Kaloshian, unpublished results). Expression of *NahG* reduced the levels of SA in both root and leaf tissues and significantly reduced the *Mi-1*-mediated resistance to root-knot nematodes and potato aphids (Branch et al., 2004; Kaloshian, unpublished results). The loss of *Mi-1*-mediated resistance was rescued using a SA functional analogue, benzothiadiazole, indicating that SA and not yet undetermined defense pathways, which are also affected by *NahG* expression, are involved in *Mi-1*-mediated resistance (Heck et al., 2003; Branch et al., 2004; Kaloshian, unpublished results).

JA and ET have also been shown to regulate basal defense to whiteflies in tomato and to silverleaf whiteflies in squash, indicating that, generalization of involvement of a specific defense pathway cannot be made based solely on insect guild (van de Ven et al., 2000; Walling, 2000).

Evaluation of plant defense by SA signaling pathway is being reconsidered because of a significant recent finding (Wildermuth et al., 2001). The known route for SA synthesis was by converting chorismate, synthesized by the shikimate pathway, through the phenylpropanoid pathway into SA. However, recent reports indicate a minor role of the phenylpropanoid pathway in SA biosynthesis for plant defense (Metraux, 2002). Wildermuth et al. (2001), suggested that for plant defense, SA is synthesized in the chloroplast from chorismate by isochorismate synthase 1 into isochorismate, which in turn is converted into SA. It remains to be seen whether this novel branch of SA synthesis, which is known to operate in prokaryotes, is also present in other plant species (Serino et al., 1995).

In addition to these known pathways, plant defenses independent of JA, SA, or ET have been also identified (Glazebrook et al., 2003). In sorghum, novel defense pathway(s) independent of JA and SA have also been implicated in aphid defense (Zhu-Salzman et al., 2004). Similarly, messages of a novel whitefly defense gene, *SLW3* (silverleaf whitefly-induced 3), do not accumulate after defense or wound-induced signals, indicating the presence of yet unidentified insect defense pathway(s) (van de Ven et al., 2000; Walling, 2000).

A number of transcription factors seem to be involved in regulation of defense responses (reviewed in Rushton and Somssich, 1998; Eulgem et al., 2000). Further evidence for involvement of these transcription factors in activation of plant defenses comes from the presence of putative binding sites in *PR* gene and other defense gene promoters (reviewed in Rushton and Somssich, 1998). Similarly, the plant-specific WRKY-type transcription factor has been implicated in control of *Hfr-1* (Hessian fly-response gene 1), which encodes a mannose-binding jacalin-like lectin (Williams et al., 2002; C. Williams, personal communication). *Hrf-1* is up-regulated in the incompatible response to Hessian fly mediated by *H*9 wheat resistance gene. Although it is not clear if *Hrf-1* encoded protein has lectin activity, this type of lectins may coat the midgut of the larvae, reducing absorption of nutrients (Foissac et al., 2000; Williams et al., 2002).

Future Directions

Development and accessibility of molecular tools during the past decade has resulted in the generation of a significant amount of information about plant–insect interactions. However, there is still much to be learned about these interactions. Cloning additional insect *R* genes should be a top priority and will allow an understanding of the spectrum of *R* gene motifs and domains in *R* genes that are specific for insect recognition. This will assist in exploiting the natural diversity of insect

R genes and facilitate the identification of resistance sources in wild germplasms. Incorporation of resistance sources by pyramiding *R* genes in cultivated species will assist in developing durable resistance. In addition, identifying nonbiotype specific *R* genes like the *Arabidopsis RPW8* (resistance to powdery mildew8) locus, which confers resistance to a wide range of powdery mildews, will be a very useful tool in the fight against insect pests (Xiao et al., 2001).

Gene expression profiling is generating a large amount of information about insect plant defense and identifying novel genes and pathways. It is clear that plants perceive and respond to different stimuli by modulating a number of defense pathways, and the interactions between these pathways vary among plant species. Therefore, it will be important to study plant–insect interactions in more than a single plant species. The next and important phase of research is to assess the functional roles of the upregulated genes, identified from expression profiling studies, and determine their contribution to plant defense. Recent advances in gene silencing that use virus-induced gene silencing or RNA interference techniques will allow these questions to be addressed (Ruiz et al., 1998; Chuang and Meyerowitz, 2000).

Acknowledgments—I thank Christie Williams and Elena Boyko for sharing unpublished results and QiGuang Xie for help with the figure. Research in Kaloshian lab is supported partly by USDA/NRI grant 00-02876 and Hatch Funds from University of California, Riverside.

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