MPMI Vol. 25, No. 7, 2012, pp. 862–868. http://dx.doi.org/10.1094/MPMI-01-12-0024-IA. *e*-Xtra*

CURRENT REVIEW

Effector-Triggered Immunity Signaling: From Gene-for-Gene Pathways to Protein-Protein Interaction Networks

Walter Gassmann and Saikat Bhattacharjee

Division of Plant Sciences, Christopher S. Bond Life Sciences Center and Interdisciplinary Plant Group, University of Missouri, Columbia 65211, U.S.A.

Submitted 31 January 2012. Accepted 9 March 2012.

In its simplicity and testability, Flor's gene-for-gene hypothesis has been a powerful driver in plant immunity research for decades. Once the molecular underpinnings of gene-for-gene resistance had come into sharper focus, there was a reassessment of Flor's hypothesis and a name change to effector-triggered immunity. As implied by the name change and exemplified by pioneering studies, plant immunity is increasingly described in terms of protein rather than genetic interactions. This progress leads to a reinterpretation of old concepts of pathogen recognition and resistance signaling and, of course, opens up new questions. Here, we provide a brief historical overview of resistance gene function and how a new focus on protein interactions can lead to a deeper understanding of the logic of plant innate immunity signaling.

Gene-for-gene.

Despite the rapid adoption of the term "effector-triggered immunity" to replace "gene-for-gene resistance", it is probably fair to say that the historic and visual image of the gene-for-gene hypothesis is still with many of us. Gene-for-gene implies a one-on-one relationship between a pathogen avirulence (*avr*) gene and a plant resistance gene. "Recognition" of the *avr* gene by the resistance gene was envisioned to trigger a classical signal-transduction cascade to effect plant resistance (Flor 1971). The gene-for-gene hypothesis is an undisputed success. Apart from providing a conceptual framework, it gave investigators the confidence to approach the black box of plant innate immunity with the powerful tools of genetics and molecular biology. Since the first cloning of an *avr* gene (Staskawicz et al. 1984) and of a resistance gene (Martin et al. 1993), many gene-for-gene pairs have been characterized in a large variety of plant–pathogen combinations.

Despite or perhaps because of the success of the gene-for-gene hypothesis, it may be time to remind ourselves that Flor, before developing his hypothesis with its implied binary "resistant/susceptible" classification, started off with a larger number of phenotype classes; for example (with descending level of resistance), "immune, resistant, semi-resistant, moderately susceptible, and susceptible" (Flor 1942). It is a testament to Flor's powers of observation and abstraction, not a criticism, that out of this he distilled the binary system that allowed a genetic approach to characterizing plant immunity. However, as in many fields of endeavor, it is looking at the gray areas where new insights can now be made. Many excellent reviews summarize our current understanding of effector-triggered immunity (ETI) and its interconnections with pathogen-associated molecular pattern-triggered immunity (PTI) (Bent and Mackey 2007; Chisholm et al. 2006; Dodds and Rathjen 2010; Jones and Dangl 2006; Maekawa et al. 2011), and we will not attempt to duplicate them here. Rather, we would like to present an opinionated retrospective on gene-for-gene resistance and a conceptual framework for current research. Given the vast scope of the field, we had to be selective with examples, and we apologize for the many important contributions to the field that are not mentioned here.

Genes-for-gene.

A large part of the research effort in the field was geared toward understanding resistance gene specificity. Gene-for-gene immediately suggested a receptor–ligand interaction as a reasonable hypothesis. That things were not quite that simple was exemplified by the cloning of the *Arabidopsis* RPM1 resistance gene, which recognizes the sequence-unrelated effectors AvrRpm1 from *Pseudomonas syringae* pv. *maculicola* and AvrB from *P. syringae* pv. *glycinea* (Grant et al. 1995). How could one highly specific receptor interact with two different proteins? Based on the pioneering work of Dangl and colleagues, we now know that *RPM1* recognizes not the structure of AvrB or AvrRpm1 but the function of these effectors mediated by the mutually interacting protein RIN4 (Mackey et al. 2002). RIN4 interacts with at least two additional bacterial effectors (Axtell and Staskawicz 2003; Mackey et al. 2003; Wilton et al. 2010) but only the interaction with AvrB or AvrRpm1 leads to phosphorylation of RIN4, which appears to be the signal to activate RPM1 (Liu et al. 2011). And, although the effectors have not been identified yet, the fact that the tomato Mi protein provides resistance to several species of root-knot nematodes (*Meloidogyne* spp.) (Milligan et al. 1998), the aphid *Macrosiphum euphorbiae* (Rossi et al. 1998), and the whitefly *Bemisia tabaci* (Nombela et al. 2003) is a graphic example of multispecific resistance proteins.

Gene-for-genes.

As for increased complexity on the plant side, several examples of dual resistance protein systems have been described in recent years. In the tobacco species *Nicotiana benthamiana*, the *Tobacco mosaic virus* Toll-interleukin-1 receptor nucleotide-

Corresponding author: W. Gassmann; Telephone: +1.573.884.7703; Fax: +1.573.884.9676; E-mail: gassmannw@missouri.edu

*The *e*-Xtra logo stands for "electronic extra" and indicates that Figure 1 appears in color online.

binding leucine-rich repeat (TNL) resistance protein N requires the coiled-coil nucleotide-binding leucine-rich repeat (CNL) protein NRG1 for function (Peart et al. 2005). Similarly, the two linked *Arabidopsis* TNL resistance genes *RPS4* and *RRS1* are required for resistance to avirulent strains of the bacteria *P. syringae* and *Ralstonia solanacearum* and the fungal pathogen *Colletotrichum higginsianum* (Birker et al. 2009; Narusaka et al. 2009), and the two linked TNL genes *RPP2A* and *RPP2B* together provide resistance to the *Hyaloperonospora arabidopsidis* isolate Cala2 (Sinapidou et al. 2004). Therefore, this is probably more common than recognized. When identifying a resistance gene by mutagenesis or natural variation, genetics often identifies a single gene that is nonfunctional or missing in the susceptible mutant or variety. Functional genes in common in the resistant and susceptible plants are not recognized by this approach.

However, these dual resistance gene systems, where resistance is compromised in the absence of either resistance gene, are not the equivalent of RPM1 recognizing both AvrRpm1 and AvrB. One example of diverse resistance proteins recognizing the same effector was provided by the cloning of the soybean resistance gene *Rpg1-b* that recognizes AvrB (which, after all, had been isolated from *P. syringae* pv. *glycinea*). As it turned out, *Rpg1-b* and *RPM1* are not orthologous genes. In effect, therefore, two different resistance genes recognize AvrB. *Rpg1-b* most likely guards a soybean RIN4 ortholog or RIN4-like protein, because *Rpg1-b*-mediated resistance to AvrB is compromised by AvrRpt2 (Ashfield et al. 2004). The AvrRpt2 protease cleaves several *Arabidopsis* proteins that share amino acid sequences with the RIN4 cleavage motif (Chisholm et al. 2005; Kim et al. 2005). Any one of these virulence targets could be guarded by a resistance protein, and different plant species may convergently evolve recognition of a particular effector protein by guarding different virulence targets, similar to the convergent evolution of effectors exemplified by *avrRpm1* and *avrB* (McDowell 2004).

Perhaps more straight-forward in terms of cross-talk is the situation described by Kim and associates (2009): even though there seems to be a clear specificity of RPM1 for AvrRpm1/AvrB and of RPS2 for AvrRpt2, Kim and associates observed that *rpm1 RPS2* plants are more resistant to bacteria expressing AvrRpm1 than *rpm1 rps2* plants. In other words, RPS2 provides some level of AvrRpm1 recognition, most likely because both RPM1 and RPS2 interact with the effector target RIN4. Although the plant is pretty good at distinguishing between RIN4 phosphorylation in response to the presence of AvrB/AvrRpm1 that triggers RPM1, and RIN4 cleavage by AvrRpt2 that triggers RPS2, this distinction is not perfect because these proteins reside in a common complex.

Genes-for-genes.

It is easy to extrapolate from observations made with RPM1, RPS2, and RIN4 to resistance proteins that show more overlap in their recognition specificity. We should expect that no resistance protein displays absolute specificity, whether recognition occurs indirectly, as with RPM1 and RPS2, or directly, as with L6 (Dodds et al. 2006). Perhaps the gene-for-gene hypothesis has led us to view ETI a bit too cleanly, reinforced by genetics where pursuit of low-hanging fruit favors cloning of uniquely strong resistance gene specificities. It is perhaps time to go back to Flor's original classifications, recognizing that some quantitative resistance may, in fact, constitute weaker resistance gene specificities. But how do we sort this all out?

It is becoming clear that genetics, as powerful as it has been to get the foot in the door, can only go so far in working out the molecular mechanisms of ETI. Instead, determining the immune interactome will provide a more direct way to describe molecular mechanisms of specificity and signaling. It is tempting to fit genetic data into schematic pathways with arrows that can be misleading. For example, based on the observation that mutations in *NDR1* abolish resistance mediated by the three resistance genes *RPM1, RPS2*, and *RPS5* (Century et al. 1995), it is natural to assume that *NDR1* encodes a signaling component that transduces the resistance signal from these resistance proteins. A very different model is proposed by findings that suggest NDR1 is a glycosylphosphatidyl inositol-modified protein anchored to the extracellular side of the plasma membrane that interacts with RIN4 via its cytoplasmically localized N-terminus (Coppinger et al. 2004; Day et al. 2006). RIN4, in turn, interacts with RPS2 and RPM1 (Axtell and Staskawicz 2003; Mackey et al. 2003, 2002) and, interestingly, the pathogen-associated molecular pattern recognition receptor FLS2 may be an additional component of this protein complex (Qi et al. 2011). NDR1, rather than a signaling intermediate, appears to function as an adaptor protein that assures proper localization and assembly of an immune recognition complex that likely includes resistance proteins guarding basal immune receptors. Interestingly, NDR1 may have acquired this function because of its involvement in maintaining plasma membrane integrity, a cellular process likely to be targeted by pathogens (Knepper et al. 2011).

Similarly, *ENHANCED DISEASE SUSCEPTIBILITY1* (*EDS1*) was proposed to encode a bona fide signaling component based on genetics. *EDS1* was originally identified in a screen for susceptible mutants to several isolates of *H. arabidopsidis* (Parker et al. 1996) and is highly conserved in plants (Gao et al. 2010; Hu et al. 2005; Liu et al. 2002; Peart et al. 2002). As the name implies, mutations in *EDS1* reduce the basal level of plant resistance to virulent pathogens. Subsequently, *EDS1* was also shown to be specifically required for immunity mediated by resistance proteins of the TNL class, whereas *NDR1* was genetically necessary for resistance mediated by some CNL proteins (Aarts et al. 1998). *EDS1* encodes a lipase-like protein but the biochemical function (if any) is unknown (Falk et al. 1999; Wiermer et al. 2005).

Because of the dependence of multiple TNL proteins on EDS1, it was again assumed that EDS1 constituted a common downstream signaling component for TNL proteins. Recently, however, it was shown that EDS1 is a direct target of at least two sequence-unrelated effectors, AvrRps4 and HopA1, and is guarded by the TNL proteins RPS4, RPS6, and SNC1 (Bhattacharjee et al. 2011; Heidrich et al. 2011). The co-localization of both RPS4 and SNC1 with the effector target EDS1 is likely to provide the basis for the observation that, in the absence of RPS4, SNC1 contributes to AvrRps4-triggered resistance (Kim et al. 2010).

Therefore, if both NDR1 and EDS1 are constituents of protein complexes with their respective class of resistance proteins, can they still be considered "downstream" signaling components? And, is it even appropriate to talk about "upstream" and "downstream" within a complex, or within a signaling module that upregulates itself in a circular feed-back loop, as does the EDS1 module (Rustérucci et al. 2001)? In essence, how is the wiring for effector-triggered signaling configurated?

Short-circuiting signaling.

Ever since the isolation of the first resistance genes, elucidation of downstream signaling pathways has been the focus of much research. Genetics, however, failed to deliver a linear arrangement of stepwise signaling components in ETI. Two major factors likely contribute to the difficulty in identifying signaling proteins in ETI: redundancy and a short signaling pathway. Redundancy is very common across evolutionary di-

verged genomes. Signal transducers such as kinases, phosphatases, and transcription factors are often encoded by large gene families. In the yeast genome, nearly a third of gene families function in signal transduction (Kafri et al. 2009). Plants are not much different in composition of redundant signaling components (Chory and Wu 2001; Cutler and McCourt 2005).

In addition to gene redundancy, it is also more relevant to think of signaling webs rather than a linear signaling pathway, which can lead to robustness against single gene loss because of the network architecture (Salathé and Soyer 2008). Just as a spider web can overcome the loss of individual strands, robust signaling systems can mostly compensate for losses of single constituents or sectors. With its essential but also potentially deleterious function in protecting the plant from invaders, ETI signaling is a prime example of a process that needs to be embedded in a robust and well-controlled system that can withstand the loss of individual elements due to effector attack. Indeed, the ETI response network recently was shown experimentally to possess a robust architecture (Tsuda et al. 2009), and the characteristic features of such plant signal transduction processes have been excellently outlined in several review articles (Katagiri and Tsuda 2010; Trewavas 2002).

However, gene redundancy and network robustness cannot explain everything in ETI signaling, and is usually not an insurmountable problem. If no signaling intermediates can be identified, perhaps they simply do not exist. It is difficult to prove the absence of something but a number of short signaling pathways have been characterized. The functioning of the glucocorticoid receptor (GR) in animals, a ligand-activated nuclear hormone receptor, is a classic example (Yudt and Cidlowski 2002). In addition to the ligand-binding domain, the GR itself also contains a DNA-binding domain. Conformational changes induced by ligand association promote nuclear uptake, binding to specific DNA elements, and promotion of target gene transactivation. Such a dual function of a receptor as a sensor and transducer protein obviates the need for signaling intermediates. Closer to home, an example of a signaling process displaying both redundancy and short pathway length is phytochrome signaling. Light-dependent translocation of PhyA and PhyB to the nucleus promotes interaction and subsequent degradation of members of the PHYTOCHROME INTERACTING FACTOR protein family, which repress photomorphogenesis (Leivar et al. 2009; Shen et al. 2008; Shen et al. 2007b).

Could the robust and rapid nature of ETI defenses recruit guards or guardees as direct messengers? The presence of many effectors is first sensed in the cytoplasm, and a frequent result of ETI is transcriptional reprogramming of hundreds of genes (Caldo et al. 2004; Tao et al. 2003). Interestingly, an increasing number of resistance proteins have been shown to interact with transcription factors once activated. For example, the barley MLA10 resistance protein interacts with WRKY1 and WRKY2 when activated by the powdery mildew effector AvrA10. Both WRKY proteins function as transcriptional repressors of PTI responses. Interaction of these WRKY proteins with MLA10 inhibits transcriptional repression, hence activating immune responses (Shen et al. 2007a). Therefore, a nuclear pool of MLA10 is required for ETI defenses. An even more direct connection between signal reception and transcriptional regulation may occur with *Arabidopsis* RRS1, a TNL resistance protein with a unique WRKY transcription factor-type DNA-binding domain at the C-terminus. When activated by the corresponding effector PopP2, RRS1 relocalizes to the nucleus (Deslandes et al. 2003; Rivas 2011). However, it has not been established yet whether the RRS1 WRKY domain induces ETI genes, and the vast majority of resistance proteins do not contain known DNA-binding domains.

Several resistance proteins in addition to MLA10 were found to be enriched or required in the nucleus following activation for mounting an effective ETI; for example, N, SNC1, and RPS4 (Burch-Smith et al. 2007; Cheng et al. 2009; Wirthmueller et al. 2007; Zhu et al. 2010a). In almost all of these cases, resistance proteins are located in both the cytoplasm and the nucleus at resting state. Effector-dependent activation results in changes in the equilibrium distribution of these proteins. Mutating potential nuclear localization sequences of RPS4 abolishes its function in AvrRps4-triggered immunity (Wirthmueller et al. 2007). Forced partitioning of barley MLA10 and tobacco N to the cytoplasm by fusions with nuclear exclusion sequences (NES) results in the loss of ETI responses to the corresponding elicitors AvrA10 and p50, respectively (Burch-Smith et al. 2007; Shen et al. 2007a). These examples raise the possibility that, in at least some systems, an effector-induced alteration in the nucleo-cytoplasmic distribution of the resistance protein is necessary to trigger ETI responses. However, because these resistance proteins exist in multiple cellular pools even before elicitation, it has been difficult to prove that individual resistance protein molecules move to the nucleus. Nevertheless, a tight correlation between nuclear localization and activation of constitutive defenses was observed with the autoactivated resistance protein snc1-1 and intramolecular suppressor mutants of this protein (Zhu et al. 2010a).

Also, it does not have to be the resistance protein that relocalizes as a direct signal carrier. At least for one RIN4 guard, RPM1, activation and signaling does not require a change in localization away from the plasma membrane (Gao et al. 2011). Conceptually, direct signaling by relocalization could also be achieved by an accessory protein of the resistasome guarded by a resistance protein. Excitingly, RIN4 fragments were recently shown to persist, and one of the fragments to change localization, after processing by AvrRpt2, the protease effector that triggers RPS2 via RIN4 cleavage (Afzal et al. 2011). RIN4 cleavage was originally interpreted as inactivating and removing RIN4, because RPS2 is constitutively active in an *rin4* null mutant. However, unlike full-length RIN4, which is tethered to the plasma membrane via C-terminal palmitoylation, an active fragment of RIN4 is soluble and, therefore, has an altered localization after effector perception. In the case of RIN4, the AvrRpt2-generated fragments are potent suppressors of PTI but, in other cases, guardee fragments could be the activators of ETI. Interestingly, in the presence of wild-type RIN4, RPM1, and RPS2, modified RIN4 proteins that cannot attach to the plasma membrane are constitutive activators of ETI-type responses (Afzal et al. 2011).

The recent identification of EDS1 as a direct target of at least two unrelated bacterial effectors may also necessitate a reevaluation of EDS1's signaling role (Bhattacharjee et al. 2011; Heidrich et al. 2011). EDS1 has multiple interaction partners in several cellular compartments: it forms homo-dimers and hetero-dimers with PAD4 in the nucleus and cytoplasm (Feys et al. 2001), and ternary complexes with PAD4 and SAG101 in the nucleus (Zhu et al. 2011). An *eds1* mutant is severely impaired in defenses to multiple virulent pathogens, implicating EDS1 as a central regulator of basal defenses. In this function, the EDS1-PAD4 complexes are essential (Rietz et al. 2011). However, EDS1 also has a central function in ETI specifically triggered by the TNL family of resistance proteins (Aarts et al. 1998). This limited role of EDS1 in ETI may, in large part, be based on the physical association of distinct EDS1 pools with only the TNL family of resistance proteins such as RPS4, RPS6, and SNC1 (Bhattacharjee et al. 2011; Heidrich et al. 2011; Kim et al. 2010); in essence, a guard–guardee relationship between EDS1 and TNL proteins. Thus, distinct EDS1

complexes have defined roles in PTI and ETI. To complicate matters more, nuclear pools of not only the EDS1-interacting resistance proteins RPS4 and SNC1 but also of EDS1 itself have been implicated in ETI. The nuclear pool of EDS1 is increased during activated ETI, and reducing nuclear EDS1 accumulation using NES fusions reduced ETI mediated by RPS4 and RPP4 (García et al. 2010). Therefore, EDS1 may provide an example for a defense protein that does double duty as a direct messenger in ETI.

The signaling web.

Whereas ETI signaling might be characterized by short and direct signaling, basal immunity and the resulting response to pathogens are characterized by a redundant web-like structure. Katagiri and Tsuda (2010) recently described this communication network, consisting of signaling sectors that channel information toward induction of plant defenses. PTI responses, according to these authors, are characterized by slow responses and by sector cooperativity, features that make PTI vulnerable to perturbation by pathogen effectors. However, effector-mediated alterations are proposed to be less effective in preventing ETI because the signaling sectors are adapted to function in a compensatory mode, a property the authors called sector-switching. For this switching to occur, signals through the proposed sectors are likely integrated and interpreted at highly connected nodes, or hubs. Major hubs in plant systems have been described in several excellent reviews and can represent proteins of diverse functions such as cytoskeletal components and transcription factors (Dietz et al. 2010; Leivar and Quail 2010; Nibau et al. 2006).

Given this network structure, it would make sense for a pathogen to target hubs in its attempt to block plant immunity. This is what was recently found in a large-scale protein interaction study probing the *Arabidopsis* interactome with effectors (Mukhtar et al. 2011). One such hub, PREFOLDIN6, is an interactor of EDS1, and is a direct target of several effectors (Mukhtar et al. 2011). In addition to sector switching, the robustness of ETI was proposed to derive from the speed with which defenses are triggered (Katagiri and Tsuda 2010). We propose that this is achieved by resistance proteins guarding hubs, or by resistance proteins directly intercepting effectors that target hubs, and relying on a short and direct signaling pathway. In this way, ETI jumps the gun and bypasses most of the signaling network to rapidly induce an assembly of sectors (Fig. 1). Such a direct signaling system has the added advantage of being less prone to interception and disruption by effectors. The difference between cooperative (PTI) and switching (ETI) sector modes may also be the result of signal strength: whereas a weak signal needs to be reinforced by the joined output of several sectors, a strong signal has enough energy to overflow into other sectors. It will be important to identify the molecular mechanisms of these different network behaviors.

The importance of adaptor proteins in an interconnected signaling web.

In such an interconnected web of protein interactions and booby-trapped hubs, what prevents random fluctuations and innocuous perturbations from triggering a full-blown response? An important safeguard is that the abundance of signaling-competent resistance and defense proteins is carefully titrated with the help of co-chaperones and by regulating protein turnover (Cheng et al. 2011; Lu et al. 2011; Shirasu 2009). A related question is how resistance protein specificity in ETI is maintained if multiple effectors attack hubs like RIN4 or EDS1. A certain level of cross-talk is to be expected but, in general, the specificity of ETI is quite remarkable and provides

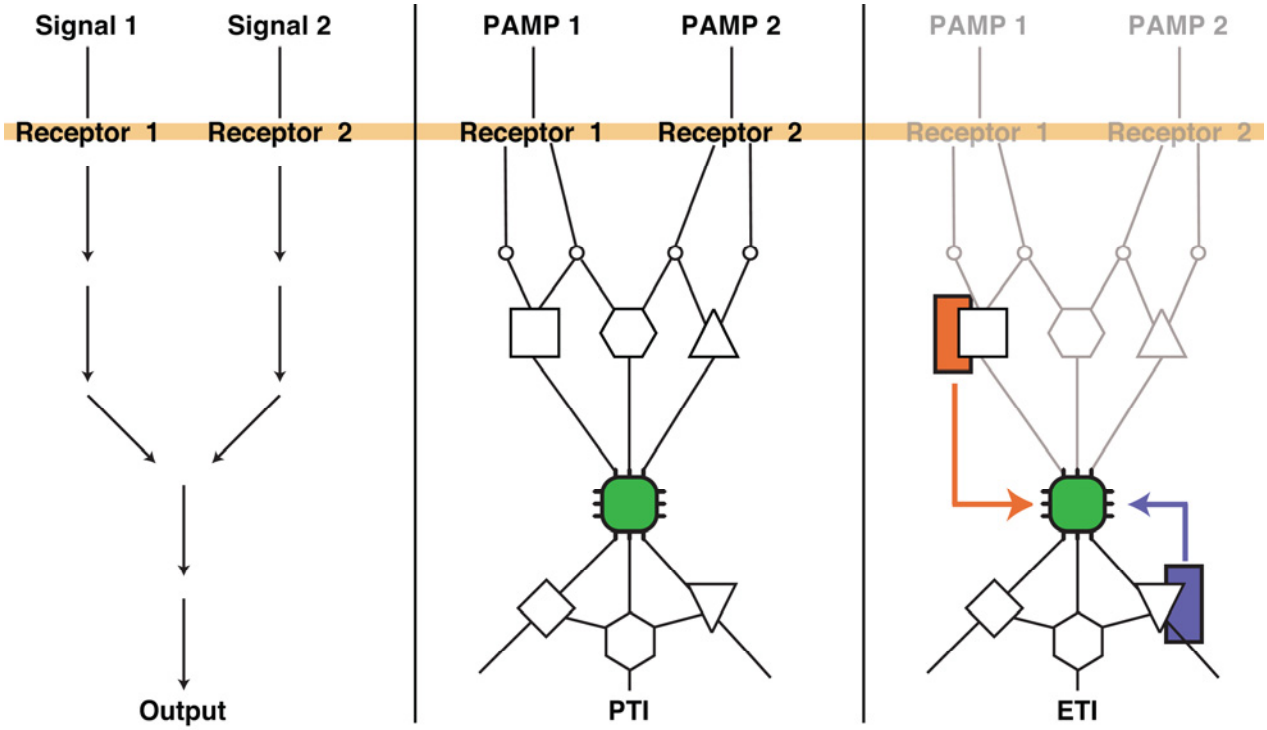

Fig. 1. Schematic and simplified model of plant immune signaling. Left: Genetic model of a generic signal transduction cascade. Middle: Pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI) mediated by plasma membrane receptors that feed into a signaling web (top). Signals are transduced to cellular processing units (middle) that convert incoming signals into appropriate outputs such as transcriptional reprogramming or protein trafficking (bottom). Right: Effector-triggered immunity (ETI) mediated by resistance proteins (rectangles) bypasses signal transduction steps and directly activates defenses. These resistance proteins guard hubs in the signal transduction or in the output network, or intercept effectors targeting such hubs (not shown). For clarity, only a single cellular process is shown in this simplified scheme. In reality, several interconnected processes would orchestrate the plant defense response, increasing the complexity of the web.

some protection against an inappropriate response to noise. As discussed above, in the case of RIN4, resistance protein specificity arises from markedly different modifications to RIN4 caused by effectors that target this guardee. With a guardee like EDS1, an additional molecular basis of specificity may consist of guarding separate EDS1 subpools with different resistance proteins. Effectors targeted to different cellular compartments would then trigger distinct resistance proteins. The specificity and distribution of resistance proteins would lead to a reduction in background noise emanating from any one complex in the absence of pathogens. However, in a way, that only pushes the problem of specificity back one level. To understand specificity of protein interactions in eukaryotes, one needs to consider the important function of adaptor proteins.

The term "adaptor protein" was coined for scaffold proteins mainly in the animal innate immune system such as SLP-76, LAT, Dok, NLRC4, and others that regulate signaling by mediating protein interactions at specific times and locations in the cell (Isakov 2008; Jordan et al. 2003; Kofoed and Vance 2011; Medeiros et al. 2007). Such adaptor proteins can positively regulate immune responses by assembling functional signalosomes, or negatively regulate them by, for example, sequestering proteins or stabilizing protein interactions that need to be disrupted for signaling to occur. The *Arabidopsis* immune regulator SRFR1 seems to fit the latter role, and led to the characterization of the EDS1 resistasome. SRFR1 is a tetratricopeptide repeat (TPR) containing protein that was initially identified as a negative regulator of TNL-specific plant defenses (Kim et al. 2010; Kwon et al. 2009). SRFR1 forms cytoplasmic complexes with the resistance protein co-chaperone SGT1; the TNL resistance proteins RPS4, SNC1, and RPS6; and EDS1 (Bhattacharjee et al. 2011; Kim et al. 2010; Li et al. 2010). This diversity of SRFR1 interactors is suggestive of an adaptor-like function of SRFR1 although, to date, not all of these interactions have been shown to be direct. SRFR1 interaction with SGT1 may affect resistance protein accumulation (Li et al. 2010). However, it was also found that the effectors AvrRps4 and HopA1 directly target EDS1, the cognate resistance proteins RPS4 and RPS6 guard EDS1, and the presence of effectors disrupts EDS1 interactions with RPS4 and RPS6 (Bhattacharjee et al. 2011; Heidrich et al. 2011). Therefore, SRFR1 associations with these TNL proteins and with EDS1 may influence resistance protein specificity by regulating how easily EDS1-TNL protein interactions are disrupted by effectors (Bhattacharjee et al. 2011; Kim et al. 2010). This would explain why *srfr1* mutants are able to mount a certain level of ETI to some effectors in the absence of the corresponding resistance protein.

Interestingly, it may be disordered regions in the SRFR1 protein that help it maintain order in the ETI network. Interactomics studies with eukaryotic organisms have identified disordered proteins as over-represented among protein interaction hubs (Gsponer et al. 2008; Haynes et al. 2006). Disordered domains do not fold into defined rigid structures but adopt conformations that are constantly modulated to form diverse interaction interfaces, or only adopt a defined structure once the disordered domain interacts with a binding partner. For SRFR1, two disordered regions predicted by computational analysis, one between TPR repeats 2 and 3 and the other at the C terminus, may enable SRFR1 to interact with multiple proteins. Another feature of disordered proteins is a phenomenon known as dosage sensitivity, meaning that they are deleterious to the host when overexpressed (Vavouri et al. 2009). When the steady state balance of these proteins is shifted by overexpression, the disordered domains are thought to engage in indiscriminate ectopic interactions, resulting in lethality. This process has been linked to several types of cancer and neurodegenerative diseases (Uversky et al. 2008). Therefore, it may be relevant to the function of SRFR1 that attempts to overexpress SRFR1, whether transiently or stably, failed repeatedly (S. Bhattacharjee and W. Gassmann, *unpublished*).

In addition to the cytoplasmic complexes, a fraction of SRFR1-EDS1 complexes are located in the nucleus. This pool may further contribute to the nature of signaling by interacting with specific nuclear proteins. Interestingly, one of the SRFR1-interacting resistance proteins, SNC1, was shown to interact with the transcriptional co-repressor TOPLESS-RELATED 1 in the nucleus (Zhu et al. 2010b). As was pointed out previously (Katagiri and Tsuda 2010), ETI responses are, therefore, likely to be determined by multiple factors, among which are the strength and timing of effector sensing by the cognate resistance protein, and alteration in the host protein interactome that these effectors cause.

Conclusions.

The last decades have provided us with a huge increase in our understanding of the plant innate immune system. As is often the case, this influx of information has necessitated a reassessment of neat and orderly hypotheses that might fit select cases but do not capture the messiness of a live biological system. One thing is certain: the complexity will increase. The challenge in the field will be to understand the spatial and temporal dynamics of ETI protein interactions and activities, and how these processes are embedded in the wider underlying matrix of the plant innate immune system. We believe that understanding the function of adaptor proteins will be one important aspect in sorting this out. By regulating adaptor proteins, the plant may have flexibility in fine-tuning the trigger point and specificity of ETI, thus optimizing resource allocation to the immune system. This would be a way to build some malleability into an immune system that has to rely on genetically predetermined recognition specificities. From this angle, systemic acquired resistance could be viewed as a state of ramped-down immune specificity in response to previous pathogen attack, making the plant more likely to respond to any foreign elicitor for which it does not actually possess a highly specific receptor. Despite much progress, there is no end in sight in what we can learn from the plant innate immune system.

ACKNOWLEDGMENTS

We thank J. McDowell, D. Mackey, and an anonymous reviewer for helpful comments on our manuscript; V. Bryan for help with the figure; and the National Science Foundation (IOS-0715926 and IOS-1121114) for funding for work on the plant innate immune system.

LITERATURE CITED

Aarts, N., Metz, M., Holub, E., Staskawicz, B. J., Daniels, M. J., and Parker, J. E. 1998. Different requirements for *EDS1* and *NDR1* by disease resistance genes define at least two *R* gene-mediated signaling pathways in *Arabidopsis*. Proc. Natl. Acad. Sci. U.S.A. 95:10306-10311.

Afzal, A. J., da Cunha, L., and Mackey, D. 2011. Separable fragments and membrane tethering of *Arabidopsis* RIN4 regulate its suppression of PAMP-triggered immunity. Plant Cell 23:3798-3811.

Ashfield, T., Ong, L. E., Nobuta, K., Schneider, C. M., and Innes, R. W. 2004. Convergent evolution of disease resistance gene specificity in two flowering plant families. Plant Cell 16:309-318.

Axtell, M. J., and Staskawicz, B. J. 2003. Initiation of RPS2-specified disease resistance in *Arabidopsis* is coupled to the AvrRpt2-directed elimination of RIN4. Cell 112:369-377.

Bent, A. F., and Mackey, D. 2007. Elicitors, effectors, and *R* genes: The new paradigm and a lifetime supply of questions. Annu. Rev. Phytopathol. 45:399-436.

Bhattacharjee, S., Halane, M. K., Kim, S. H., and Gassmann, W. 2011. Pathogen effectors target *Arabidopsis* EDS1 and alter its interactions

with immune regulators. Science 334:1405-1408.
Birker, D., Heidrich, K., Takahara, H., Narusaka, M., Deslandes, L., Narusaka, Y., Reymond, M., Parker, J. E., and O'Connell, R. 2009. A locus conferring resistance to *Colletotrichum higginsianum* is shared by four geographically distinct *Arabidopsis* accessions. Plant J. 60:602-613.
Burch-Smith, T. M., Schiff, M., Caplan, J. L., Tsao, J., Czymmek, K., and Dinesh-Kumar, S. P. 2007. A novel role for the TIR domain in association with pathogen-derived elicitors. PLoS Biol. 5:e68. Published online.
Caldo, R. A., Nettleton, D., and Wise, R. P. 2004. Interaction-dependent gene expression in Mla-specified response to barley powdery mildew. Plant Cell 16:2514-2528.
Century, K. S., Holub, E. B., and Staskawicz, B. J. 1995. NDR1, a locus of *Arabidopsis thaliana* that is required for disease resistance to both a bacterial and a fungal pathogen. Proc. Natl. Acad. Sci. U.S.A. 92:6597-6601.
Cheng, Y. T., Germain, H., Wiermer, M., Bi, D., Xu, F., Garcia, A. V., Wirthmueller, L., Després, C., Parker, J. E., Zhang, Y., and Li, X. 2009. Nuclear pore complex component MOS7/Nup88 is required for innate immunity and nuclear accumulation of defense regulators in *Arabidopsis*. Plant Cell 21:2503-2516.
Cheng, Y. T., Li, Y., Huang, S., Huang, Y., Dong, X., Zhang, Y., and Li, X. 2011. Stability of plant immune-receptor resistance proteins is controlled by SKP1-CULLIN1-F-box (SCF)-mediated protein degradation. Proc. Natl. Acad. Sci. U.S.A. 108:14694-14699.
Chisholm, S. T., Dahlbeck, D., Krishnamurthy, N., Day, B., Sjolander, K., and Staskawicz, B. J. 2005. Molecular characterization of proteolytic cleavage sites of the *Pseudomonas syringae* effector AvrRpt2. Proc. Natl. Acad. Sci. U.S.A. 102:2087-2092.
Chisholm, S. T., Coaker, G., Day, B., and Staskawicz, B. J. 2006. Host-microbe interactions: Shaping the evolution of the plant immune response. Cell 124:803-814.
Chory, J., and Wu, D. 2001. Weaving the complex web of signal transduction. Plant Physiol. 125:77-80.
Coppinger, P., Repetti, P. P., Day, B., Dahlbeck, D., Mehlert, A., and Staskawicz, B. J. 2004. Overexpression of the plasma membrane-localized NDR1 protein results in enhanced bacterial disease resistance in *Arabidopsis thaliana*. Plant J. 40:225-237.
Cutler, S., and McCourt, P. 2005. Dude, where's my phenotype? Dealing with redundancy in signaling networks. Plant Physiol. 138:558-559.
Day, B., Dahlbeck, D., and Staskawicz, B. J. 2006. NDR1 interaction with RIN4 mediates the differential activation of multiple disease resistance pathways in *Arabidopsis*. Plant Cell 18:2782-2791.
Deslandes, L., Olivier, J., Peeters, N., Feng, D. X., Khounlotham, M., Boucher, C., Somssich, L., Genin, S., and Marco, Y. 2003. Physical interaction between RRS1-R, a protein conferring resistance to bacterial wilt, and PopP2, a type III effector targeted to the plant nucleus. Proc. Natl. Acad. Sci. U.S.A. 100:8024-8029.
Dietz, K. J., Jacquot, J. P., and Harris, G. 2010. Hubs and bottlenecks in plant molecular signalling networks. New Phytol. 188:919-938.
Dodds, P. N., and Rathjen, J. P. 2010. Plant immunity: Towards an integrated view of plant–pathogen interactions. Nat. Rev. Genet. 11:539-548.
Dodds, P. N., Lawrence, G. J., Catanzariti, A. M., Teh, T., Wang, C. I. A., Ayliffe, M. A., Kobe, B., and Ellis, J. G. 2006. Direct protein interaction underlies gene-for-gene specificity and coevolution of the flax resistance genes and flax rust avirulence genes. Proc. Natl. Acad. Sci. U.S.A. 103:8888-8893.
Falk, A., Feys, B. J., Frost, L. N., Jones, J. D. G., Daniels, M. J., and Parker, J. E. 1999. *EDS1*, an essential component of *R* gene-mediated disease resistance in *Arabidopsis* has homology to eukaryotic lipases. Proc. Natl. Acad. Sci. U.S.A. 96:3292-3297.
Feys, B. J., Moisan, L. J., Newman, M. A., and Parker, J. E. 2001. Direct interaction between the *Arabidopsis* disease resistance signaling proteins, EDS1 and PAD4. EMBO (Eur. Mol. Biol. Organ.) J. 20:5400-5411.
Flor, H. H. 1942. Inheritance of pathogenicity in *Melampsora lini*. Phytopathology 32:653-669.
Flor, H. H. 1971. Current status of the gene-for-gene concept. Annu. Rev. Phytopathol. 9:275-296.
Gao, F., Shu, X., Ali, M. B., Howard, S., Li, N., Winterhagen, P., Qiu, W., and Gassmann, W. 2010. A functional *EDS1* ortholog is differentially regulated in powdery mildew-resistant and -susceptible grapevines and complements an *Arabidopsis eds1* mutant. Planta 231:1037-1047.
Gao, Z., Chung, E. H., Eitas, T. K., and Dangl, J. L. 2011. Plant intracellular innate immune receptor resistance to *Pseudomonas syringae* pv. *maculicola* 1 (RPM1) is activated at, and functions on, the plasma membrane. Proc. Natl. Acad. Sci. U.S.A. 108:7619-7624.
García, A. V., Blanvillain-Baufumé, S., Huibers, R. P., Wiermer, M., Li, G., Gobbato, E., Rietz, S., and Parker, J. E. 2010. Balanced nuclear and cytoplasmic activities of EDS1 are required for a complete plant innate immune response. PLoS Pathog. 6:e1000970. Published online.
Grant, M. R., Godiard, L., Straube, E., Ashfield, T., Lewald, J., Sattler, A., Innes, R.W., and Dangl, J. L. 1995. Structure of the *Arabidopsis RPM1* gene enabling dual specificity disease resistance. Science 269:843-846.
Gsponer, J., Futschik, M. E., Teichmann, S. A., and Babu, M. M. 2008. Tight regulation of unstructured proteins: From transcript synthesis to protein degradation. Science 322:1365-1368.
Haynes, C., Oldfield, C. J., Ji, F., Klitgord, N., Cusick, M. E., Radivojac, P., Uversky, V. N., Vidal, M., and Iakoucheva, L. M. 2006. Intrinsic disorder is a common feature of hub proteins from four eukaryotic interactomes. PLoS Comput. Biol. 2:e100. Published online.
Heidrich, K., Wirthmueller, L., Tasset, C., Pouzet, C., Deslandes, L., and Parker, J. E. 2011. *Arabidopsis* EDS1 connects pathogen effector recognition to cell compartment-specific immune responses. Science 334:1401-1404.
Hu, G. S., deHart, A. K. A., Li, Y. S., Ustach, C., Handley, V., Navarre, R., Hwang, C. F., Aegerter, B. J., Williamson, V. M., and Baker, B. 2005. *EDS1* in tomato is required for resistance mediated by TIR-class *R* genes and the receptor-like *R* gene *Ve*. Plant J. 42:376-391.
Isakov, N. 2008. A new twist to adaptor proteins contributes to regulation of lymphocyte cell signaling. Trends Immunol. 29:388-396.
Jones, J. D. G., and Dangl, J. L. 2006. The plant immune system. Nature 444:323-329.
Jordan, M. S., Singer, A. L., and Koretzky, G. A. 2003. Adaptors as central mediators of signal transduction in immune cells. Nat. Immunol. 4:110-116.
Kafri, R., Springer, M., and Pilpel, Y. 2009. Genetic redundancy: New tricks for old genes. Cell 136:389-392.
Katagiri, F., and Tsuda, K. 2010. Understanding the plant immune system. Mol. Plant-Microbe Interact. 23:1531-1536.
Kim, H. S., Desveaux, D., Singer, A. U., Patel, P., Sondek, J., and Dangl, J. L. 2005. The *Pseudomonas syringae* effector AvrRpt2 cleaves its C-terminally acylated target, RIN4, from *Arabidopsis* membranes to block RPM1 activation. Proc. Natl. Acad. Sci. U.S.A. 102:6496-6501.
Kim, M. G., Geng, X., Lee, S. Y., and Mackey, D. 2009. The *Pseudomonas syringae* type III effector AvrRpm1 induces significant defenses by activating the *Arabidopsis* nucleotide-binding leucine-rich repeat protein RPS2. Plant J. 57:645-653.
Kim, S. H., Gao, F., Bhattacharjee, S., Adiasor, J. A., Nam, J. C., and Gassmann, W. 2010. The *Arabidopsis* resistance-like gene *SNC1* is activated by mutations in *SRFR1* and contributes to resistance to the bacterial effector AvrRps4. PLoS Pathog. 6:e1001172. Published online.
Knepper, C., Savory, E. A., and Day, B. 2011. *Arabidopsis* NDR1 is an integrin-like protein with a role in fluid loss and plasma membrane-cell wall adhesion. Plant Physiol. 156:286-300.
Kofoed, E. M., and Vance, R. E. 2011. Innate immune recognition of bacterial ligands by NAIPs determines inflammasome specificity. Nature 477:592-595.
Kwon, S. I., Kim, S. H., Bhattacharjee, S., Noh, J. J., and Gassmann, W. 2009. SRFR1, a suppressor of effector-triggered immunity, encodes a conserved tetratricopeptide repeat protein with similarity to transcriptional repressors. Plant J. 57:109-119.
Leivar, P., and Quail, P. H. 2010. PIFs: Pivotal components in a cellular signaling hub. Trends Plant Sci. 16:19-28.
Leivar, P., Tepperman, J. M., Monte, E., Calderon, R. H., Liu, T. L., and Quail, P. H. 2009. Definition of early transcriptional circuitry involved in light-induced reversal of PIF-imposed repression of photomorphogenesis in young *Arabidopsis* seedlings. Plant Cell 21:3535-3553.
Li, Y., Li, S., Bi, D., Cheng, Y.-T., Li, X., and Zhang, Y. 2010. SRFR1 negatively regulates plant NB-LRR Resistance protein accumulation to prevent autoimmunity. PLoS Pathog. 6:e1001111. Published online.
Liu, J., Elmore, J. M., Lin, Z. J., and Coaker, G. 2011. A receptor-like cytoplasmic kinase phosphorylates the host target RIN4, leading to the activation of a plant innate immune receptor. Cell Host Microbe 9:137-146.
Liu, Y. L., Schiff, M., Marathe, R., and Dinesh-Kumar, S. P. 2002. Tobacco *Rar1, EDS1* and *NPR1/NIM1* like genes are required for N-mediated resistance to tobacco mosaic virus. Plant J. 30:415-429.
Lu, D., Lin, W., Gao, X., Wu, S., Cheng, C., Avila, J., Heese, A., Devarenne, T. P., He, P., and Shan, L. 2011. Direct ubiquitination of pattern recognition receptor FLS2 attenuates plant innate immunity. Science 332:1439-1442.
Mackey, D., Holt, B. F., Wiig, A., and Dangl, J. L. 2002. RIN4 interacts with *Pseudomonas syringae* type III effector molecules and is required for RPM1-mediated resistance in *Arabidopsis*. Cell 108:743-754.
Mackey, D., Belkhadir, Y., Alonso, J. M., Ecker, J. R., and Dangl, J. L. 2003. *Arabidopsis* RIN4 is a target of the type III virulence effector AvrRpt2 and modulates RPS2-mediated resistance. Cell 112:379-389.

Maekawa, T., Kufer, T. A., and Schulze-Lefert, P. 2011. NLR functions in plant and animal immune systems: So far and yet so close. Nat. Immunol. 12:817-826.
Martin, G. B., Brommonschenkel, S. H., Chunwongse, J., Frary, A., Ganal, M. W., Spivey, R., Wu, T., Earle, E. D., and Tanksley, S. D. 1993. Map-based cloning of a protein kinase gene conferring disease resistance in tomato. Science 262:1432-1436.
McDowell, J. M. 2004. Convergent evolution of disease resistance genes. Trends Plant Sci. 9:315-317.
Medeiros, R. B., Burbach, B. J., Mueller, K. L., Srivastava, R., Moon, J. J., Highfill, S., Peterson, E. J., and Shimizu, Y. 2007. Regulation of NF-κB activation in T cells via association of the adapter proteins ADAP and CARMA1. Science 316:754-758.
Milligan, S. B., Bodeau, J., Yaghoobi, J., Kaloshian, I., Zabel, P., and Williamson, V. M. 1998. The root knot nematode resistance gene *Mi* from tomato is a member of the leucine zipper, nucleotide binding, leucine-rich repeat family of plant genes. Plant Cell 10:1307-1319.
Mukhtar, M. S., Carvunis, A. R., Dreze, M., Epple, P., Steinbrenner, J., Moore, J., Tasan, M., Galli, M., Hao, T., Nishimura, M. T., Pevzner, S. J., Donovan, S. E., Ghamsari, L., Santhanam, B., Romero, V., Poulin, M. M., Gebreab, F., Gutierrez, B. J., Tam, S., Monachello, D., Boxem, M., Harbort, C. J., McDonald, N., Gai, L., Chen, H., He, Y., Vandenhaute, J., Roth, F. P., Hill, D. E., Ecker, J. R., Vidal, M., Beynon, J., Braun, P., and Dangl, J. L. 2011. Independently evolved virulence effectors converge onto hubs in a plant immune system network. Science 333:596-601.
Narusaka, M., Shirasu, K., Noutoshi, Y., Kubo, Y., Shiraishi, T., Iwabuchi, M., and Narusaka, Y. 2009. *RRS1* and *RPS4* provide a dual *Resistance*-gene system against fungal and bacterial pathogens. Plant J. 60:218-226.
Nibau, C., Wu, H. M., and Cheung, A. Y. 2006. RAC/ROP GTPases: 'Hubs' for signal integration and diversification in plants. Trends Plant Sci. 11:309-315.
Nombela, G., Williamson, V. M., and Muñiz, M. 2003. The root-knot nematode resistance gene *Mi-1.2* of tomato is responsible for resistance against the whitefly *Bemisia tabaci*. Mol. Plant-Microbe Interact. 16:645-649.
Parker, J. E., Holub, E. B., Frost, L. N., Falk, A., Gunn, N. D., and Daniels, M. J. 1996. Characterization of *eds1*, a mutation in *Arabidopsis* suppressing resistance to *Peronospora parasitica* specified by several different *RPP* genes. Plant Cell 8:2033-2046.
Peart, J. R., Cook, G., Feys, B. J., Parker, J. E., and Baulcombe, D. C. 2002. An *EDS1* orthologue is required for N-mediated resistance against *Tobacco mosaic virus*. Plant J. 29:569-579.
Peart, J. R., Mestre, P., Lu, R., Malcuit, I., and Baulcombe, D. C. 2005. NRG1, a CC-NB-LRR protein, together with N, a TIR-NB-LRR protein, mediates resistance against *Tobacco mosaic virus*. Curr. Biol. 15:968-973.
Qi, Y., Tsuda, K., Glazebrook, J., and Katagiri, F. 2011. Physical association of pattern-triggered immunity (PTI) and effector-triggered immunity (ETI) immune receptors in *Arabidopsis*. Mol. Plant Pathol. 12:702-708.
Rietz, S., Stamm, A., Malonek, S., Wagner, S., Becker, D., Medina-Escobar, N., Corina Vlot, A., Feys, B. J., Niefind, K., and Parker, J. E. 2011. Different roles of enhanced disease susceptibility1 (EDS1) bound to and dissociated from phytoalexin deficient4 (PAD4) in *Arabidopsis* immunity. New Phytol. 191:107-119.
Rivas, S. 2011. Nuclear dynamics during plant innate immunity. Plant Physiol. 158:87-94.
Rossi, M., Goggin, F. L., Milligan, S. B., Kaloshian, I., Ullman, D. E., and Williamson, V. M. 1998. The nematode resistance gene *Mi* of tomato confers resistance against the potato aphid. Proc. Natl. Acad. Sci. U.S.A. 95:9750-9754.
Rustérucci, C., Aviv, D. H., Holt, B. F., Dangl, J. L., and Parker, J. E. 2001. The disease resistance signaling components *EDS1* and *PAD4* are essential regulators of the cell death pathway controlled by *LSD1* in *Arabidopsis*. Plant Cell 13:2211-2224.
Salathé, M., and Soyer, O. S. 2008. Parasites lead to evolution of robustness against gene loss in host signaling networks. Mol. Syst. Biol. 4:202.
Shen, H., Zhu, L., Castillon, A., Majee, M., Downie, B., and Huq, E. 2008. Light-induced phosphorylation and degradation of the negative regulator PHYTOCHROME-INTERACTING FACTOR1 from *Arabidopsis* depend upon its direct physical interactions with photoactivated phytochromes. Plant Cell 20:1586-1602.
Shen, Q.-H., Saijo, Y., Mauch, S., Biskup, C., Bieri, S., Keller, B., Seki, H., Ülker, B., Somssich, I. E., and Schulze-Lefert, P. 2007a. Nuclear activity of MLA immune receptors links isolate-specific and basal disease-resistance responses. Science 315:1098-1103.
Shen, Y., Khanna, R., Carle, C. M., and Quail, P. H. 2007b. Phytochrome induces rapid PIF5 phosphorylation and degradation in response to red-light activation. Plant Physiol. 145:1043-1051.
Shirasu, K. 2009. The HSP90-SGT1 chaperone complex for NLR immune sensors. Annu. Rev. Plant Biol. 60:139-164.
Sinapidou, E., Williams, K., Nott, L., Bahkt, S., Tör, M., Crute, I., Bittner-Eddy, P., and Beynon, J. 2004. Two TIR:NB:LRR genes are required to specify resistance to *Peronospora parasitica* isolate Cala2 in *Arabidopsis*. Plant J. 38:898-909.
Staskawicz, B. J., Dahlbeck, D., and Keen, N. T. 1984. Cloned avirulence gene of *Pseudomonas syringae* pv. *glycinea* determines race-specific incompatibility on *Glycine max* (L.) Merr. Proc. Natl. Acad. Sci. U.S.A. 81:6024-6028.
Tao, Y., Xie, Z., Chen, W., Glazebrook, J., Chang, H. S., Han, B., Zhu, T., Zou, G., and Katagiri, F. 2003. Quantitative nature of *Arabidopsis* responses during compatible and incompatible interactions with the bacterial pathogen *Pseudomonas syringae*. Plant Cell 15:317-330.
Trewavas, A. 2002. Plant cell signal transduction: The emerging phenotype. Plant Cell 14 (Suppl.):S3-S4.
Tsuda, K., Sato, M., Stoddard, T., Glazebrook, J., and Katagiri, F. 2009. Network properties of robust immunity in plants. PLoS Genet. 5:e1000772. Published online.
Uversky, V. N., Oldfield, C. J., and Dunker, A. K. 2008. Intrinsically disordered proteins in human diseases: Introducing the D2 concept. Annu. Rev. Biophys. 37:215-246.
Vavouri, T., Semple, J. I., Garcia-Verdugo, R., and Lehner, B. 2009. Intrinsic protein disorder and interaction promiscuity are widely associated with dosage sensitivity. Cell 138:198-208.
Wiermer, M., Feys, B. J., and Parker, J. E. 2005. Plant immunity: The EDS1 regulatory node. Curr. Opin. Plant Biol. 8:383-389.
Wilton, M., Subramaniam, R., Elmore, J., Felsensteiner, C., Coaker, G., and Desveaux, D. 2010. The type III effector $HopF2_{Pto}$ targets *Arabidopsis* RIN4 protein to promote *Pseudomonas syringae* virulence. Proc. Natl. Acad. Sci. U.S.A. 107:2349-2354.
Wirthmueller, L., Zhang, Y., Jones, J. D. G., and Parker, J. E. 2007. Nuclear accumulation of the *Arabidopsis* immune receptor RPS4 is necessary for triggering EDS1-dependent defense. Curr. Biol. 17:2023-2029.
Yudt, M. R., and Cidlowski, J. A. 2002. The glucocorticoid receptor: Coding a diversity of proteins and responses through a single gene. Mol. Endocrinol. 16:1719-1726.
Zhu, S., Jeong, R. D., Venugopal, S. C., Lapchyk, L., Navarre, D., Kachroo, A., and Kachroo, P. 2011. SAG101 forms a ternary complex with EDS1 and PAD4 and is required for resistance signaling against turnip crinkle virus. PLoS Pathog 7:e1002318. Published online.
Zhu, Y., Qian, W., and Hua, J. 2010a. Temperature modulates plant defense responses through NB-LRR proteins. PLoS Pathog. 6:e1000844. Published online.
Zhu, Z., Xu, F., Zhang, Y., Cheng, Y. T., Wiermer, M., and Li, X. 2010b. *Arabidopsis* resistance protein SNC1 activates immune responses through association with a transcriptional corepressor. Proc. Natl. Acad. Sci. U.S.A. 107:13960-13965.

AUTHOR-RECOMMENDED INTERNET RESOURCE

The Database of Protein Disorder (DisProt) website: disprot.org