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SYSTEMIC ACQUIRED RESISTANCE

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■ **Abstract** Systemic acquired resistance (SAR) is a mechanism of induced defense that confers long-lasting protection against a broad spectrum of microorganisms. SAR requires the signal molecule salicylic acid (SA) and is associated with accumulation of pathogenesis-related proteins, which are thought to contribute to resistance. Much progress has been made recently in elucidating the mechanism of SAR. Using the model plant *Arabidopsis*, it was discovered that the isochorismate pathway is the major source of SA during SAR. In response to SA, the positive regulator protein NPR1 moves to the nucleus where it interacts with TGA transcription factors to induce defense gene expression, thus activating SAR. Exciting new data suggest that the mobile signal for SAR might be a lipid molecule. We discuss the molecular and genetic data that have contributed to our understanding of SAR and present a model describing the sequence of events leading from initial infection to the induction of defense genes.

INTRODUCTION

Plants have evolved a number of inducible defense mechanisms against pathogen attack. Recognition of a pathogen often triggers a localized resistance reaction, known as the hypersensitive response (HR), which is characterized by rapid cell death at the site of infection (40). In the 1960s, Ross showed that tobacco plants challenged with tobacco mosaic virus (TMV) subsequently developed increased resistance to secondary infection in distal tissues (86). This spread of resistance throughout the plant's tissues was termed systemic acquired resistance (SAR). We now know that SAR can be activated in many plant species by pathogens that cause necrosis, either as part of the HR or as a symptom of disease. The resistance conferred is long-lasting, sometimes for the lifetime of the plant, and effective against a broad-spectrum of pathogens including viruses, bacteria, fungi, and oomycetes (91, 102).

Molecularly, SAR is characterized by the increased expression of a large number of pathogenesis-related genes (*PR* genes), in both local and systemic tissues. PR proteins were first described in the 1970s by Van Loon, who observed accumulation of various novel proteins after infection of tobacco with TMV (108, 109). Although

many PR proteins have antimicrobial properties in vitro (109), the function of each in the defense response has not been clearly defined. It is generally thought that SAR results from the concerted effects of many PR proteins rather than a specific PR protein. Although their roles in establishing SAR are unclear, *PR* genes serve as useful molecular markers for the onset of SAR.

In 1979, White observed that PR protein accumulation and resistance to TMV could be induced by treatment of tobacco with salicylic acid (SA), aspirin (acetyl SA), or benzoic acid (116). Evidence that SA is a signal for the induction of SAR came from two studies published in 1990 (63, 70). Malamy et al. showed that the endogenous SA concentration rises in both local and systemic tissues after infection of tobacco with TMV and this rise correlates with *PR* gene induction (63). Métraux et al. found that cucumber plants infected with either *Colletotrichum lagenarium* or tobacco necrosis virus (TNV) have considerably elevated levels of SA in the phloem sap (70). In a search for SA analogues that were less phytotoxic than SA, 2,6-dichloroisonicotinic acid (INA) and benzothiadiazole S-methyl ester (BTH) were found to induce the same set of *PR* genes (34, 38, 55, 69, 114). A requirement for SA as an endogenous signal for SAR was proven by Gaffney et al. using a bacterial gene, *nahG*, encoding salicylate hydroxylase, which removes SA by conversion to catechol (35). Transgenic tobacco and *Arabidopsis* expressing *nahG* accumulate very little SA after pathogen infection, fail to express *PR* genes, and are impaired in SAR (17, 35).

In the past 10 years, genetic analyses in the model plant *Arabidopsis* have identified additional components of SAR downstream of SA. Plants that are non-responsive to SA were identified in a number of mutant screens and found to have mutations in the same gene, *NPR1/NIM1* (*NON-EXPRESSER OF PR GENES1/ NONINDUCIBLE IMMUNITY1*) (8, 16, 37, 94). Considerable progress has been made in elucidating the role of NPR1 and associated proteins in the induction of SAR since the last Annual Review on SAR in 1997 (102). We therefore focus on these recent molecular and genetic experiments that have contributed to our understanding of SAR.

NATURE OF THE SYSTEMIC SIGNAL

Early grafting experiments demonstrated that the infected leaf produces a systemic signal for SAR, and this signal is not species specific (15, 46). The nature of the systemic signal has been a subject of controversy for many years.

Salicylic Acid

The detection of increased SA levels in systemic leaves and in the phloem led many researchers to believe that SA might be a systemic signal for SAR. The evidence for and against this hypothesis has been the subject of previous reviews (18, 93). Labeling studies in TMV-infected tobacco showed that most of the SA (69%) accumulating systemically was made and exported from the inoculated

leaf (97). Similarly, in cucumber infected with TNV, SA found in systemic leaves was both imported from the infected leaf and synthesized de novo (71, 73). A more recent study suggests that signaling might occur through the conversion of SA to the volatile compound methyl salicylate, which could induce resistance not only in the uninfected parts of the same plant but also in neighboring plants (98).

A number of experiments argue against SA being the systemic signal. Detachment of *Pseudomonas syringae*-infected cucumber leaves before SA levels had increased in the petiole did not block the development of SAR (85). Furthermore, grafting experiments in tobacco between wild-type scions and *nahG*-expressing rootstocks showed that, although the rootstock was unable to accumulate SA, the SAR signal was still produced and translocated to the scion (113). The reciprocal grafting experiment showed that the systemic tissue must accumulate SA for the SAR signal to be perceived.

Lipid-Based Signal Molecule

Exciting new work suggests that a lipid-based molecule may be the mobile signal for SAR. Maldonado et al. showed that the *dir1* (*defective in induced resistance 1*) mutant has normal local resistance to pathogens but is unable to develop SAR or express *PR* genes in systemic leaves (64). Therefore, wild-type DIR1, which has sequence similarity to lipid transfer proteins (LTPs), might function in the generation or transmission of the mobile signal. Indeed, experiments using petiole exudate showed that the phloem sap from *dir1* is deficient in the mobile signal for SAR. However, the mutant plants could still respond to a signal contained in the sap from wild-type plants, ruling out a role for DIR1 in signal perception. Furthermore, the *dir1* plants have wild-type SA metabolism and a normal response to SA and INA.

The similarity of DIR1 to LTPs suggests that the mobile signal for SAR might be a lipid molecule. LTPs form a multigene family in *Arabidopsis* with 71 predicted members (3). Interestingly, they share sequence similarity with elicitins from *Phytophthora* spp., which are elicitors of plant defense responses (4). The extracellular location of LTPs and elicitins is consistent with a role in signaling and implies the presence of plasma membrane (PM) receptors involved in signal transduction. Indeed, wheat LTP1 binds to the same PM receptor as the *Phytophthora* elicitin cryptogein (7).

Further evidence for a lipid-based signal molecule comes from the characterization of the *eds1* and *pad4* mutants, which are both defective in lipase-like proteins (28, 47). The *eds1* (*enhanced disease susceptibility 1*) mutant was originally identified for its compromised local resistance to *Peronospora parasitica* mediated by several resistance (*R*) genes, whereas *pad4* (*phytoalexin deficient 4*) was isolated in a screen for mutants with enhanced susceptibility to a virulent strain of *P. syringae* pv. *maculicola* (37, 81). It was subsequently discovered that *pad4* weakens local resistance mediated by the same subset of *R* genes that are blocked by *eds1* (31). These *R* genes encode TIR-NB-LRR-type resistance proteins. However,

many other *R* genes act through an EDS1-independent signaling pathway (1). In *eds1* and *pad4* plants, even when a normal HR is elicited by pathogens that trigger the EDS1-independent pathway, SAR cannot be induced (L. Jorda & J. Parker, personal communication). Experiments using phloem exudates have shown that EDS1 is required for both production of the mobile signal in the local tissue and perception of the signal in the systemic tissue (C. Lamb, personal communication). Recently, it was discovered that a tobacco SA-binding protein, SABP2 (26), is also a lipase and that its lipase activity is increased four- to fivefold by addition of SA (53). Furthermore, silencing of the *SABP2* gene diminishes both local resistance and SAR. These observations led the authors to propose that SABP2 is a receptor for SA; however, the exact position of SABP2 in the SA signaling pathway is not clear. Mutation of another gene, *SFD1*, which encodes a dihydroxyacetone phosphate reductase involved in glycerolipid synthesis, also compromises SAR and decreases SA accumulation and *PR-1* expression in systemic tissue after infection with an avirulent strain of *P. syringae* (75). Although many important questions still need to be addressed, these data strongly suggest a role for lipid signaling in SAR.

Reactive Oxygen Species

Early studies could detect no reactive oxygen species (ROS) production in systemic tissues during the onset of SAR (78, 89). However, it has since been discovered by Alvarez et al. that H_2O_2 accumulates in small groups of cells in uninoculated leaves of *Arabidopsis* after infection with an avirulent strain of *P. syringae* (2). These microbursts occur within two hours after an initial oxidative burst in the inoculated tissue and are followed by the formation of microscopic HR lesions. Using catalase to scavenge H_2O_2, or DPI (diphenylene iodonium) to inhibit the NADPH oxidase, it was demonstrated that both the primary and secondary oxidative bursts are required for the onset of SAR. The authors propose that microbursts of ROS may activate defense responses at a low level throughout the plant and this contributes to the SAR-induced state.

Transport of the Systemic Signal

How does the SAR signal travel throughout the plant? Girdling experiments suggested that the SAR signal produced in inoculated leaves travels in the phloem to upper leaves (39, 87). If the mobile signal does travel through the phloem, the pattern of SAR induction should match the transport of sugars out of the infected leaf. When this was tested in *Arabidopsis*, it was observed that the movement of radioactively labeled sucrose did not exactly match the induction of SAR, SA accumulation, or *PR-1* expression (50). Induction of SAR was observed outside of the normal orthostichy defining phloem movement. This suggests the small amount of phloem moving between orthostichies contains enough signal to induce SAR. It seems likely that the phloem is the major conduit for the SAR signal(s), but some fraction of the signal may also be able to move by a different route.

THE ROLE OF SA IN SAR

The role of SA in SAR has been discussed extensively in a number of reviews (18, 24, 91, 93). As described above, in many plants SAR is preceded by an increase in SA concentration. However, some plants such as potato and rice have high endogenous levels of SA under noninducing conditions (14, 100, 120). Indeed, application of SA to potato does not protect it against *Phytophthora infestans* (14). However, expression of *nahG* in potato blocks resistance to *P. infestans* induced by arachidonic acid. This suggests that after treatment with arachidonic acid, instead of SA levels rising, the potato plants become more sensitive to SA (120). Thus, SA is an essential signal for SAR across a range of plants, although the mechanism by which SA induces SAR might differ.

SA Synthesis

It was previously assumed that SA for SAR is synthesized via the shikimate-phenylpropanoid pathway (57), although this was never proven. It has recently been shown that, like bacteria, plants can also synthesize SA from chorismate via isochorismate. Expression of the bacterial enzymes catalyzing these reactions, isochorismate synthase 1 (ICS1) and isochorismate pyruvate lyase 1 (IPL1), in tobacco and *Arabidopsis* results in increased SA accumulation and pathogen resistance (66, 112).

Using HPLC, Nawrath & Métraux isolated the SA induction-deficient *Arabidopsis* mutants *sid1* and *sid2*, which failed to accumulate SA after SAR induction (77). More alleles of *sid1* and *sid2*, called *eds5* and *eds16*, respectively, were identified independently by virtue of their enhanced disease-susceptibility phenotype (22, 37). A recent breakthrough in our understanding of SA biosynthesis came when *SID2/EDS16* was cloned by Wildermuth et al. and shown to encode a putative chloroplast-localized ICS1 (117). Mutations of the *ICS1* gene, in *sid2* and *eds16*, reduce SA accumulation after infection to only 5–10% of wild-type levels and compromise both basal and systemic resistance. This demonstrates that the isochorismate pathway in plants is the main source of SA synthesis during SAR. Consistent with this conclusion, *ICS1* expression is induced by infection in both local and systemic tissues. Wildermuth et al. proposed that the phenylpropanoid pathway is responsible for the rapid production of SA associated with local cell death, whereas the isochorismate pathway is more important for sustained SA synthesis during development of SAR (117). Since SA synthesis is not completely abolished in *sid2* plants, some SA must be produced either through the activity of another ICS-like protein, such as ICS2 (117), or through the phenylpropanoid pathway.

Arabidopsis ICS1 contains a putative plastid transit sequence, suggesting that SA synthesis occurs in the plastid. Interestingly, *EDS5/SID1* encodes another protein required for SA accumulation that has sequence similarity to the multidrug and toxin extrusion (MATE) family of transporter proteins (76). This suggests that

EDS5 might be involved in moving SA or a phenolic precursor out of the plastid after synthesis (68).

Control of SA Synthesis

In plants such as tobacco and *Arabidopsis*, regulation of SA biosynthesis is an essential regulatory step in SAR activation. Therefore, identification of upstream regulatory components required for the induction of SA biosynthesis genes, especially *ICS1*, will be an important step toward understanding the control of SAR. The induction of *ICS1* after infection by *Erysiphe orontii* and *P. syringae* pv. *maculicola* is not affected by depletion of SA in *nahG* plants, indicating that the *ICS1* gene is not regulated by SA (117).

Many components upstream of *ICS1* have been implicated in the regulation of SA synthesis, through characterization of various mutants with increased levels of SA. Most of these mutants form spontaneous HR-like lesions or have severe morphological phenotypes such as dwarfing (23). Expression of *ICS1* is constitutively elevated in three such gain-of-resistance mutants, *cpr1*, *cpr5*, and *cpr6* (*constitutive expresser of PR genes*) (117). However, it is unclear whether these mutants directly affect SA synthesis, or whether SA levels are elevated as an indirect effect of cell death or disruption of cellular homeostasis. It has recently been shown that two mutants with elevated SA levels, *ssi4* and *snc1*, have mutations in *R* genes that result in constitutive activation of a local defense response and therefore affect a step upstream of SA synthesis (95, 122). Interestingly, *snc1* plants do not form spontaneous lesions as observed in *ssi4*, suggesting that HR may not be required for activating SA biosynthesis.

SA synthesis induced by another *R* gene, *RPS4*, requires *EDS1* and *PAD4* (31, 125). The *eds1* and *pad4* mutants also block SA synthesis triggered by infection with virulent *P. syringae*. In *eds1* and *pad4*, induction of *EDS5*, after infection with either virulent or avirulent *P. syringae* is blocked, places EDS1 and PAD4 upstream of EDS5 in the regulation of SA synthesis (76). Since EDS1 and PAD4 are required for resistance conferred by the same subset of *R* genes (TIR-NB-LRR) and have been shown to physically interact in planta, they are likely to function in the same pathway (31). However, the *eds1* mutation significantly impedes the onset of HR and confers full susceptibility, whereas *pad4* plants retain HR and show only intermediate susceptibility. This leads to the hypothesis that EDS1 contributes to initial SA accumulation and development of the HR downstream of TIR-NB-LRR type *R* genes, and then recruits PAD4 to drive amplification of the defense response by further increasing SA levels. Consistent with this hypothesis, EDS1 and PAD4 influence the expression of each other, with *PAD4* expression decreased more strongly in *eds1* than *EDS1* expression in *pad4* (31). This suggests that EDS1 and PAD4 function in a positive feedback loop that amplifies their own expression and increases production of SA after infection. A role for a positive feedback loop in SA signaling is also supported by SA-mediated *EDS1*, *PAD4*, and *EDS5* expression (28, 47, 76). The similarity of EDS1 and PAD4 to lipases (28, 47) suggests that lipid metabolites may be

involved in regulating the synthesis and/or accumulation of SA in local and systemic tissues.

Enhancement of the SA signal also occurs through a signal amplification loop involving ROS (96). The observation that SA binds the H_2O_2 scavenging enzymes catalase and ascorbate peroxidase (APX) and inhibits their activity led to the proposal that increases in H_2O_2 were responsible for signal transduction leading to *PR* gene induction and resistance (11, 27). However, the concentrations of SA required for inhibition of catalase and APX are higher than those seen in systemic tissues after infection. Later studies suggested that H_2O_2 functions upstream of SA. Treatment of tobacco with high concentrations (>300 mM) of H_2O_2 leads to a dose-dependent accumulation of SA and *PR-1* expression, which was suppressed in plants expressing *nahG* (58, 78). Low concentrations of SA have also been shown to potentiate the production of ROS and HR cell death. In soybean cells inoculated with *P. syringae*, the addition of SA dramatically enhances the oxidative burst and cell death (96, 103). It is hypothesized that in systemic tissues, the accumulation of low levels of SA together with the development of microbursts of ROS could amplify responses to secondary infections and contribute to SAR (25, 96).

In addition to the signal amplification loops described above, there is evidence for negative feedback of SA synthesis. In the SA-insensitive *npr1* mutant, levels of *ICS1* mRNA and SA are both elevated after infection compared to wild type (16, 94, 117). Furthermore, *npr1* mutants show reduced tolerance to exogenous SA (0.5 mM), failing to develop beyond the cotyledon stage (9, 52). The biological significance of such a feedback mechanism has yet to be determined; however, it might be utilized to shut off SAR once the pathogen challenge subsides. Many mutants with constitutively high levels of SA are dwarfs (42), and continuous spraying of wild-type plants with BTH also results in growth retardation (N. Weaver & X. Dong, unpublished observations), suggesting that accumulation of SA is detrimental to the plant's growth and development.

NPR1-DEPENDENT SA SIGNALING

To identify components involved in SA signal transduction, a number of mutant screens were performed that identified multiple alleles of a single gene, *NPR1/NIM1* (8, 16, 37, 94). Further characterization showed that the role of NPR1 is not limited to SAR. The *npr1* mutant also displays enhanced disease symptoms when infected with virulent pathogens and is impaired in some *R* gene-mediated resistance, suggesting that NPR1 is important for restricting the growth of pathogens at the site of infection (8, 16, 37, 94). NPR1 is required for another induced resistance response, known as induced systemic resistance (ISR), which is triggered by nonpathogenic root-colonizing bacteria and confers resistance to bacteria and fungi in aerial parts of the plant (82, 83). NPR1 also mediates cross-talk between the SA signaling pathway and the jasmonic acid (JA) and ethylene (C_2H_4) signaling pathways that confer resistance to insects and some necrotrophic pathogens (101). As discussed earlier, *npr1* has reduced tolerance to SA toxicity and accumulates

high endogenous levels of SA, suggesting a role for NPR1 in both detoxification of SA and feedback regulation of SA biosynthesis (9, 52). In addition, NPR1 has functions that are not directly related to resistance, including the regulation of cell division and/or endoreduplication (111).

NPR1 is expressed throughout the plant at low levels and its mRNA levels rise two- to threefold after pathogen infection or treatment with SA (9, 90). *NPR1* expression is likely mediated by WRKY transcription factors as mutation of the WRKY binding sites (W-boxes) in the *NPR1* promoter abolished its expression (119). Overexpression of *NPR1* in *Arabidopsis* enhances resistance to *P. parasitica*, *P. syringae*, and *Erysiphe cichoracearum* with no apparent detrimental effects on the plant (10, 33). Unlike many mutants with constitutive resistance, the *NPR1* overexpressing lines do not constitutively express *PR* genes. The enhancement of resistance is probably caused by the more rapid or higher induction of *PR* genes observed in these overexpressing lines (10, 33). This indicates that, even when expressed at higher levels, the NPR1 protein must be activated to induce SAR.

The NPR1 protein has two protein-protein interaction domains, an ankyrin-repeat and a BTB/POZ (*Broad-Complex*, *Tramtrack*, *Bric-a-brac*/Poxvirus, Zinc finger) domain, as well as a putative nuclear localization signal and phosphorylation sites (9, 90). Functional studies have shown that accumulation of NPR1 in the nucleus after treatment with SAR inducers is essential for *PR* gene induction (52).

NPR1 homologues have been identified in rice, tobacco, tomato, apple, and orange (12, 61; S.-Y. He, personal communication; M. Kinkema, J.-Y. Yang & X. Dong, unpublished observations), suggesting that NPR1 function is conserved across plant species. This is supported by the demonstration that overexpression of *Arabidopsis NPR1* in rice confers resistance to *Xanthomonas oryzae* pv. *oryzae* (12).

TGA Transcription Factors

The absence of any obvious DNA-binding domain and the presence of protein-protein interaction domains in NPR1 prompted several laboratories to carry out yeast two-hybrid screens for NPR1-interacting proteins. In one of these screens, three small structurally similar proteins named NIMIN1, NIMIN2, and NIMIN3 (NIM interactor) were identified. NIMIN1 and NIMIN2 interact with the C terminus of NPR1, while NIMIN3 interacts with the N terminus (115). NIMINs contain stretches of acidic amino acids and are hypothesized to be transcription factors; however, more experiments are required to demonstrate their biological activity.

The predominant NPR1 interactors found in the yeast two-hybrid screens were members of the TGA family of basic leucine zipper transcription factors. NPR1 interacts with the *Arabidopsis* TGA factors, TGA2, TGA3, TGA5, TGA6, and TGA7 but only weakly or not at all with TGA1 and TGA4 (20, 51, 121, 124). NPR1 also interacts with TGA factors from tobacco and rice (12, 80). Using truncated or mutant forms of NPR1, the ankyrin-repeat domain in the middle of the protein

was shown to be essential for binding TGA factors, while the N-terminal region appears to enhance binding (20, 121, 124).

TGA factors bind to activator sequence-1 (*as-1*) or *as-1*-like promoter elements (49), which have been found in several plant promoters activated during defense, including *Arabidopsis PR-1* (56). Linker scanning mutagenesis of the *PR-1* promoter identified two *as-1*-like elements, *LS7* and *LS5*. *LS7* is a positive regulatory element required for induction by INA, whereas *LS5* is a weak negative regulatory element (56). Després et al. used these *cis*-elements as probes for electrophoretic mobility shift assays (EMSA) and showed that both TGA2 and TGA4 could bind to *LS7*, whereas only TGA2 could bind to *LS5* (20). Furthermore, binding of TGA2 but not TGA4 was enhanced by the addition of NPR1, consistent with the yeast two-hybrid interaction data.

Although NPR1 is clearly a positive regulator of *PR* genes, it may exert its function by either enhancing a transcriptional activator or inhibiting a transcriptional repressor. The presence of multiple *as-1*-like elements in the *PR-1* promoter and the differential binding affinities of each TGA factor to these elements as well as to NPR1 highlight the complexity of the regulatory mechanism. Indeed, in an EMSA performed by Després et al., binding to the *as-1* element from the *35S* promoter was significantly enhanced in protein extracts from SA-treated plants (20). However, extracts from untreated *npr1* plants also contained strong *as-1*-binding activity and this was not changed by SA treatment. This result can be reconciled if different TGA factors are responsible for the observed *as-1*-binding in wild type and *npr1*. Consistent with this hypothesis, when EMSA was performed using the *LS7* element from the *PR-1* promoter, Johnson et al. found that SA enhanced the binding activity in wild-type plants and this binding was abolished in *npr1* plants (48). This result was confirmed by chromatin immunoprecipitation (ChIP) experiments (48). Recruitment of TGA2 or TGA3 to a 1kb fragment of the *PR-1* promoter was observed only after treatment with SA and not in untreated wild-type plants or SA-treated *npr1* plants. Unfortunately, ChIP is unable to resolve the adjacent binding sites *LS7* and *LS5*, which are within 30 bp of each other.

Another approach to study the role of TGA factors in vivo is to examine the phenotypes of mutant plants. As there are 10 TGA factors in *Arabidopsis* (45), functional redundancy may prevent observation of a mutant phenotype. Indeed, analysis of single knockout mutants of TGA2 and TGA3 revealed little phenotype (M. Kesarwani & X. Dong, unpublished observations). Consistent with this, overexpression or silencing of TGA2 did not alter resistance to a virulent strain of *P. parasitica* (51). However, overexpression of TGA5 enhanced resistance to *P. parasitica*, but this was not dependent on SA or NPR1 and did not correlate with *PR* gene expression. Using a reverse genetics approach, Li et al. isolated a knockout of the adjacent *TGA2* and *TGA5* genes (59). This was crossed to a knockout of *TGA6* to create the *tga2 tga5 tga6* triple mutant (123), thus deleting all members of one of three subclasses of TGA factors (118). The *tga2 tga5 tga6* triple mutant has phenotypes similar to *npr1*, showing compromised SAR and decreased tolerance to high concentrations of SA. All three genes must be deleted to

observe this phenotype, leading to the conclusion that TGA2, TGA5, and TGA6 are essential for and play redundant roles in the induction of SAR. Interestingly, the triple knockout and also the *tga2 tga5* double mutant have increased *PR-1* expression in the absence of SAR induction, suggesting that TGA factors also play a role in the repression of basal *PR-1* expression. This might be through interaction with the negative *LS5* element in the *PR-1* promoter (56). If knocking out *TGA2*, *TGA5*, and *TGA6* is sufficient to abolish SAR, then what is the role of the other TGA factors? Despite compromised SAR, the *tga2 tga5 tga6* triple mutant does not show enhanced susceptibility to a virulent strain of *P. syringae*, suggesting that other TGA factors may be involved in basal resistance. It is also possible that the different subgroups of TGA factors regulate different sets of defense genes and that loss of induction of one set would be sufficient to impede SAR. This question can best be addressed by deleting all members of the other subgroups of TGA factors.

As an alternative to mutant analysis, dominant-negative versions of TGA factors that can no longer bind to DNA were expressed in tobacco and *Arabidopsis*. In tobacco, overexpression of a dominant-negative *TGA2.2* decreased *as-1*-binding activity and *PR* gene induction (79). In another study, a dominant-negative version of *Arabidopsis* TGA2 was expressed in tobacco (84). In this case, *as-1*-binding activity was completely abolished in untreated plants but in contrast to the previous study, induction of *PR* genes and pathogen resistance were both enhanced. The discrepancy between these experiments is difficult to explain because the dominant-negative TGA factors used in these studies could bind endogenous TGA factors as well as NPR1. However, these studies do support the idea that TGA factors can play both positive and negative roles in *PR* gene regulation.

To observe activity of specific TGA factors in vivo, chimeric transcription factors have been constructed in which TGA2 or TGA3 were fused to the yeast GAL4 DNA-binding domain. Fan & Dong showed that replacing the bZIP domain of TGA2 with the GAL4 DNA-binding domain produced a transcription factor that activated the expression of a UAS^{GAL4}*::GUS* reporter construct in response to INA or SA (29). This reporter gene activation was abolished in the *npr1* mutant. EMSA showed that TGA2-GAL4 binding to UAS^{GAL4} was enhanced by INA treatment and is dependent on NPR1. This is consistent with the findings that NPR1 enhances binding of TGA2 to the *LS7* element (20). Johnson et al. used a similar heterologous system to show that TGA3 is also a transcriptional activator (48).

Redox Signaling

The in vivo interaction of NPR1 with TGA factors requires induction with SA, even though both proteins are constitutively expressed. Until recently, the controlling mechanisms for NPR1 nuclear localization and activation of TGA factors were unclear. Two exciting new papers have revealed that changes in the redox status of the cell after SA treatment play an important role in this regulation (19, 74).

The observation that NPR1-like proteins from different species contain ten conserved cysteines suggested that NPR1 might be under redox-regulation. Mou et al. tested this hypothesis by examining NPR1 under different redox conditions (74). When proteins were extracted in the absence of the reducing agent DTT, monomeric NPR1 could only be detected in INA-treated samples, whereas in the presence of DTT equal amounts of monomeric NPR1 were detected with or without INA treatment. This suggests that before and after SAR induction NPR1 is present in two different conformations. As antibodies developed against the endogenous NPR1 only recognize the reduced form, further analyses used GFP-tagged NPR1. In extracts from untreated plants, NPR1-GFP was found in a high MW (>250,000) protein complex. Addition of DTT to the sample reduced all the NPR1-GFP to its monomeric form, suggesting that the high MW complex is formed through intermolecular disulfide bridges. Interestingly, this complex is partially reduced as a result of INA treatment. This pattern of conformational changes was also observed after pathogen infection in both inoculated and distal tissues and precedes *PR* gene induction. Measurements of cellular glutathione pools showed that a biphasic change in redox occurs after SAR induction, first oxidizing and then reducing. Lowering NADPH levels diminished both NPR1-GFP reduction and *PR-1* expression after INA treatment. Mutation of cysteine residues C82 or C216 in NPR1 resulted in constitutive monomerization, nuclear accumulation of mutant proteins and expression of *PR-1*. These data demonstrate that the monomer is the active form of NPR1 for *PR-1* induction and provide a model for the activation of NPR1 by SA: SA accumulation triggers conversion of NPR1 from an oligomer to a monomer through changes in cellular redox status favoring reduction. This monomeric form of NPR1 is then able to move to the nucleus where it interacts with TGA factors to induce *PR* gene expression.

As discussed earlier, in yeast two-hybrid studies NPR1 interacts strongly with TGA2 and TGA3 but very weakly or not at all with TGA1 and TGA4 (20, 124). Using a plant two-hybrid assay in *Arabidopsis*, Després et al. demonstrated a physical interaction between NPR1 and TGA1 (19). Using domain swapping between TGA1 and TGA2, the plant-specific regulatory region was defined to a 30 aa region containing two cysteine residues in TGA1 (and TGA4) that are not found in TGA2 or other TGA factors. Mutation of these residues in TGA1 allowed interaction with NPR1 in yeast and in untreated leaves. A clever labeling experiment designed to distinguish between reduced and oxidized cysteine residues showed that TGA1 (and/or TGA4) exists in both oxidized and reduced forms in untreated leaves. After SA treatment, only the reduced form was detected (19). This indicates that SA controls the redox status of TGA1 (and/or TGA4) and only the reduced form can bind NPR1. Evidently, redox changes do not increase TGA1 DNA-binding activity directly; instead, this is achieved through enhancement of its interaction with NPR1. These experiments add TGA1 and TGA4 to the spectrum of TGA factors that interact with NPR1, although their role in SAR has yet to be established. These results are consistent with the finding by Mou et al. that the SA signal is transduced through changes in cellular reduction potential that lead to

monomerization of NPR1 (74). We are just beginning to realize the significance of such redox changes during SAR. In the past, research has mainly focused on the initial oxidative burst during *R* gene-mediated defense. These two studies highlight the importance of the reducing state that usually appears following the oxidative stress.

OTHER REGULATORY COMPONENTS IN SAR SIGNALING

To identify other components of SAR signaling, several genetic screens have been conducted looking for suppressors of *npr1*. The recessive *sni1* (*suppressor of npr1 inducible*) mutant restores SA-inducible *PR* gene expression and pathogen resistance in the *npr1* background (60). The *sni1* mutant has wild-type levels of SA and only slightly elevated expression of *PR* genes in the absence of an SAR inducer, indicating that *sni1* is likely downstream of *npr*. The *sni1* phenotype suggests that SNI1 is a negative regulator of *PR* gene expression and SAR, whose repression is relieved by NPR1 after induction. The low basal levels of *PR* gene expression and restored induction in the *sni1 npr1* double mutant indicate that, in addition to NPR1-mediated inactivation of SNI1, an SA-dependent but NPR1-independent regulatory step is also required for SAR gene induction. Consistent with the hypothesis that SNI1 is a repressor of *PR* genes, SNI1-GFP has been observed in the nucleus when bombarded into onion epidermal cells (60). Moreover, when fused to the GAL4 DNA-binding domain and expressed in yeast, SNI1 repressed transcription of a reporter carrying UAS^{GAL4} upstream of a constitutive promoter (R. Mosher & X. Dong, unpublished observations). This result suggests that SNI1 may repress a general transcriptional mechanism that is conserved between yeast and plants.

SNI1 is a novel plant-specific protein with no similarity to proteins of known function. However, putative homologues have been found in many plant species including barley, *Medicago truncatula*, potato, rice, soybean, and sugar cane, indicating that SNI1 function may be conserved (R. Mosher & X. Dong, unpublished observations). SNI1 contains no obvious DNA-binding domain, suggesting that it represses transcription through interaction with other factors rather than binding directly to the promoter. Linker scanning mutagenesis of the *PR-1* promoter identified the negative regulatory *cis*-element, *LS4*, which has a W-box consensus sequence (56). Mutation of *LS4* resulted in elevated basal expression and stronger induction in response to INA treatment, a pattern similar to that of *PR-1* in *sni1*. This suggests that SNI1 might be recruited to the *PR-1* promoter through interaction with a WRKY factor.

As an alternative approach to investigate the function of SNI1, a screen for suppressors of *sni1* (*ssn*) was performed. Three mutants were identified, *ssn1*, *ssn2*, and *ssn3*, which alleviate both the dwarf morphology and the background *PR* gene expression of *sni1* (W. Durrant & X. Dong, unpublished observations). In the *sni1 ssn* double mutants, the pattern of *PR* gene expression is the same

as wild-type, whereas in the *sni1 npr1 ssn* triple mutants induction of *PR* gene expression by SA is blocked, similar to *npr1*. These results indicate that the wild-type *SSN* genes are involved in controlling both basal and SA-inducible *PR* gene expression observed in *sni1 npr1*. In other words, the same transcription factor(s) is probably responsible for the background and SA-inducible NPR1-independent *PR* gene expression.

Likely candidates for regulators of NPR1-independent *PR* gene expression and resistance are the Whirly (Why) family of transcription factors, named after the whirligig appearance of their crystal structure (21). Potato StWhy1 specifically binds the single-stranded form of a *cis*-element in the *PR10a* promoter. *Arabidopsis* has three genes encoding Whirly proteins, of which AtWhy1 is the most similar to StWhy1 (21a). SA treatment induced AtWhy1 DNA-binding activity in both wild-type and *npr1* plants, indicating that AtWhy1 activation is independent of NPR1. Knockout mutants of *AtWhy1* were lethal. However, two lines with missense mutations in the ssDNA-binding domain (*a*twhy1.1) or the central α-helical region (*a*twhy1.2) were viable and showed reduced DNA-binding activity, SA-induced *PR-1* transcript accumulation, and resistance to *P. parasitica*. The NPR1-independent activation of AtWhy1 and the decrease in *PR-1* expression observed in the *atwhy1* mutants suggest that AtWhy1 is important for NPR1-independent *PR* gene expression. It would be interesting to test whether *atwhy1* mutants can block the NPR1-independent *PR* gene expression observed in *sni1 npr1*.

Other possible SAR regulatory components include DTH9 (DETACHMENT 9). The *dth9* mutant has increased susceptibility to virulent pathogens, accumulates elevated levels of SA, and fails to develop SAR in response to pathogen infection or SA treatment (67). These phenotypes are reminiscent of *npr1*; however, *dth9* differs from *npr1* in that its *PR-1* and *PR-2* expression in response to infection or SA treatment is unaltered. Since SA treatment did not reverse the disease susceptibility observed in the mutant, DTH9 should be placed downstream of SA in a pathway parallel to NPR1 that contributes to SAR. Interestingly, *dth9* is also insensitive to auxin treatment, indicating that auxin signaling may play a role in plant defense.

GENE EXPRESSION CHANGES DURING SAR

There is ample evidence indicating that SAR is conferred by expression of a collection of genes. The phenotype of *dth9* is a good example, showing that SAR can be blocked without affecting the induction of *PR-1* and *PR-2*. The sequencing of the *Arabidopsis* genome has allowed global analyses of gene expression changes during SAR to be conducted using DNA microarray technology. Maleck et al. surveyed 25–30% of *Arabidopsis* genes under 14 SAR-inducing or repressing conditions, identifying 413 ESTs (about 300 genes) that show differential expression during SAR (65). Cluster analysis was used to identify a group of 31 genes with a similar transcription pattern to that of *PR-1*. The genes in this *PR-1* regulon are strongly

induced in systemic tissue during SAR and this induction is NPR1-dependent. They are also induced by infection with virulent *P. parasitica*, suggesting that activation of SAR-related genes in local tissue can limit infection by compatible pathogens. This is consistent with the enhanced susceptibility to virulent pathogens observed in *npr1* mutants. Interestingly, only 17 of 26 *PR-1* regulon genes have an *as-1* element in their promoter, whereas W-boxes were overrepresented, occurring an average of 4.3 times in every promoter. This suggests that WRKY factors rather than TGA factors are important for coregulation of *PR-1* regulon genes. The *LS4* W-box in the *PR-1* promoter acts as a strong negative *cis*-element (56), leading Maleck et al. to propose that WRKY factors repress the expression of *PR-1* regulon genes (65). Upon activation of SAR, NPR1-dependent derepression would occur, possibly through the inactivation of SNI1.

Promoter analysis was also performed in another study on 1058 genes that were induced by pathogen infection, SA, MeJA, or ozone (62). This revealed that *as-1* elements, W-boxes, abscisic acid response elements, and G-boxes were overrepresented across all treatments, whereas the Myc motif was overrepresented only in the SA-induced genes. This suggests a role for these *cis*-elements in stress responses but does not identify which are important during SAR.

A different use of microarray analysis is to identify the global expression phenotype of mutants impaired in disease resistance (36). This allowed the placement of three mutants with previously undefined roles into known signal pathways: *pad1* and *eds8* in the JA/C_2H_4 pathway and *eds3* in the SA pathway. This result was confirmed by the demonstration that *pad1* and *eds8* are impaired in JA-induced anthocyanin production and *eds3* has greatly reduced SA production after infection with a virulent strain of *P. syringae*. This study also revealed that two mutant alleles of *NPR1* have different effects on pathogen-induced gene expression. The *npr1-3* mutant appears to affect only expression of SA-regulated genes, whereas *npr1-1* also affects expression of genes that require JA and C_2H_4 for induction. This may indicate that the C-terminal 194 aa of NPR1, which are missing in *npr1-3* (9), are not required for JA/C_2H_4-induced gene expression. It will be interesting to test whether *npr1-3* is impaired in ISR, which involves JA/C_2H_4-signaling instead of SA signaling. The mutation in *npr1-1* changes a structurally important residue in the ankyrin-repeat domain and likely results in a misfolded, nonfunctional protein. In *npr1-1* both SAR and ISR are blocked (8, 83).

A potential difficulty in interpreting microarray data is the lack of hierarchical information on the transcriptional events that occur during SAR. The SAR-induced genes include effector genes that confer resistance as well as regulatory genes such as transcription factors. To overcome this problem, a strategy was devised to focus on only a single transcriptional level (D. Wang & X. Dong, unpublished data). Fusion of NPR1 to the hormone-binding domain of the rat glucocorticoid receptor (GR) placed its nuclear localization under the control of the steroid hormone dexamethasone (52). Treating an *NPR1-GR* transgenic line (in *npr1* background) with SA will activate expression of SA-mediated NPR1-independent genes. Addition of dexamethasone after SA treatment will allow NPR1-GR to move to the nucleus and induce NPR1-mediated genes. To focus on the direct transcriptional targets

of NPR1, cycloheximide can be added to inhibit de novo protein synthesis and secondary transcriptional events.

INTERACTION BETWEEN SAR AND OTHER DEFENSE PATHWAYS

It is impossible to understand SAR fully without studying its interaction with other biological processes. It is hypothesized that plant defense pathways interact synergistically or antagonistically to fine-tune responses according to the challenging organism(s). Different responses may confer resistance to the same pathogen. On the other hand, activation of one pathway may lead to cross-talk inhibition of another that is less effective against the pathogen. Cross-talk between different defense pathways is reviewed elsewhere (5). Here, we focus on interactions involving components of SAR.

As mentioned earlier, NPR1 is required for other induced resistance pathways, including ISR induced by the nonpathogenic bacterium *P. fluorescens* (83, 107). Like SAR, ISR protects plants against a range of pathogens (106), but it is independent of SA and *PR* gene induction (82). ISR is blocked in the *jar1* (*jasmonic acid resistant 1*) and *etr1* (*ethylene resistant 1*) mutants, indicating a requirement for JA and C_2H_4 signaling components (83). The *Arabidopsis* ecotypes RLD and Ws, which fail to develop ISR, carry a recessive mutation that causes C_2H_4-insensitivity (104). Two previously identified mutants, *eds4* and *eds8*, which are insensitive to C_2H_4 and JA, respectively, are also impaired in ISR (105). However, a third *eds* mutant, *eds10*, responds normally to both hormones and develops normal SAR but is blocked for ISR, suggesting that *EDS10* is a novel component of ISR. ISR requires NPR1 at a point downstream of JAR1 and ETR1 (83). NPR1 is therefore an important regulator of induced defense responses downstream of either SA or JA/C_2H_4 and may differentially regulate these responses according to upstream signals. Furthermore, simultaneous induction of SAR and ISR has an additive effect on the level of induced resistance against *P. syringae* (110). Therefore, NPR1 is able to function in both of these pathways simultaneously.

There are also examples of cross-resistance where insect feeding can induce aspects of SAR (43). This has been observed in response to aphids and whiteflies, which are sucking insects and therefore do minimal damage to the tissue. The idea that plants perceive some insects as pathogens rather than herbivores is supported by the identification of an *R* gene that confers resistance to aphids and nematodes (72, 88). It makes sense for the plant to activate SAR when attacked by such insects if they act as vectors for pathogens. Evidence for coregulation by SA and JA signaling also comes from a gene expression profiling study in which 55 genes were induced by treatment with either SA or JA (92).

Besides synergy described above, there is increasing evidence for antagonism between the SA and JA/C_2H_4 pathways (43, 54). For example, tobacco plants with enhanced SAR have decreased systemic resistance to the chewing insect *Heliothis virescens* after SAR induction, whereas plants with reduced SAR show

more effective resistance (30). The induction of SAR therefore has a negative effect on the JA/C_2H_4 pathways, which are normally induced by chewing insects and wounding. SA accumulation has been associated with inhibition of JA biosynthesis and decreased expression of JA-responsive genes (43). A large-scale analysis of gene expression in wild-type and mutants defective in SA, JA or C_2H_4 signaling revealed that, although JA/C_2H_4 signaling can sometimes inhibit SA signaling, repression of JA signaling by SA signaling is more prevalent (36). Treatment of *Arabidopsis* with SA and JA simultaneously prevents the expression of JA-responsive genes (101). Studies with *npr1* plants showed that this antagonistic effect of SA on JA signaling requires NPR1. Unlike the activation of SAR, nuclear localization of NPR1 was not required for suppression of JA signaling. Thus, NPR1 is a central regulator of plant defense responses including SAR, ISR, and SA/JA cross-talk. A challenge for the future will be to understand how NPR1 coordinates these different responses and to unravel the signaling network downstream of NPR1 in each case.

FITNESS COSTS OF SAR

It has often been suggested that disease resistance is associated with fitness costs and that plants have evolved inducible defense mechanisms because it is too costly to have defense responses switched on all the time (6, 41, 42). The phenotypes of many mutants that show constitutive *PR* gene expression, accumulation of SA, and resistance to pathogens support this idea. These mutants often have reduced plant size, loss of apical dominance, curly leaves, and decreased fertility, all traits associated with decreased plant fitness (reviewed in 42). Consistent with this view, overexpression of NPR1 in rice triggers lesion development and chlorosis under certain environmental conditions, correlating with expression of defense genes (32). Although only a few studies have specifically addressed the fitness costs of SAR, they all conclude that constitutive expression of SAR in uninfected plants is detrimental.

The SA analogue BTH, which has been developed commercially as a plant activator, induces SAR in wheat and confers systemic protection against powdery mildew (38). Heil et al. have therefore studied the fitness costs associated with the use of BTH in the absence of pathogens (44). Plants grown hydroponically in the absence of pathogens or in the field showed a reduction in biomass and the number of ears and grains if treated with BTH. These effects were stronger when combined with limited nitrogen availability. Similarly, treatment of *Arabidopsis* with SA decreases seed yield (13). These experiments, although not representative of natural conditions, are useful when considering the costs and benefits of treating crop plants with such compounds.

An alternative to exogenous chemical treatment is to examine the fitness of mutants with constitutive SAR or mutants impaired in SAR. Two studies have shown that gain-of-resistance mutants such as *cpr1*, *cpr5*, *cpr6*, and *cep1* [*constitutive expression of PR-1*; (99)] have decreased fitness, demonstrated by low seed yield and small rosette diameter (13; A. Heidel, J. Antonovics & X. Dong, unpublished

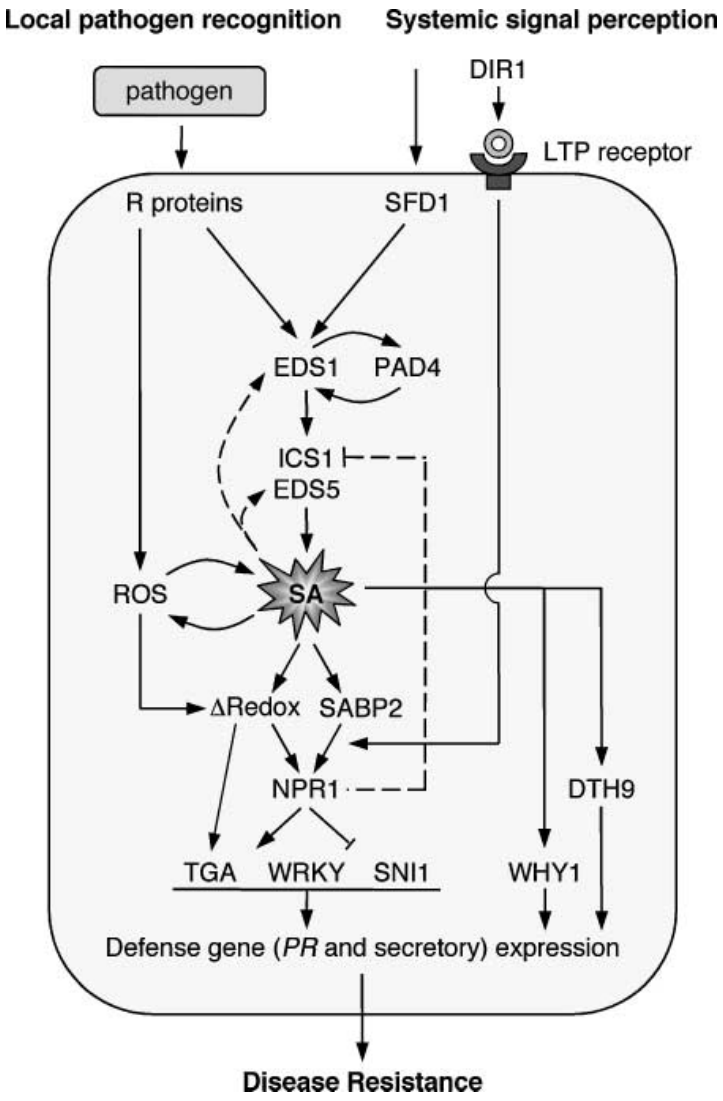

Figure 1 The sequence of events from pathogen recognition to defense gene induction.

observations). The cost of resistance observed here could be due to the allocation of the plant's resources to constitutive PR protein production. As well as a cost of constitutive SAR, there is a fitness cost associated with the inability to induce SAR. One study showed that *nahG* and *nim1* plants grown in a growth chamber have high seed production in the absence of SAR induction (13). However, in a field experiment, the *npr1* mutant and the *NPR1-L* transgenic line, in which *NPR1* is silenced (10), showed a reduction of fitness (A. Heidel, J. Antonovics & X. Dong, unpublished observations). Although there was no visible sign of disease on these plants, they might have had a low level of infection that was detrimental to plant growth. It is also possible that soil bacteria could have induced ISR in the wild-type plants, but not in *npr1* or the *NPR1-L* line, to protect them from microbial pathogens. This study shows that SAR has fitness benefits and fitness costs consistent with the inducible nature of this defense response. Such results

have important implications for development of crop protection strategies through manipulation of SAR.

CONCLUSIONS

Our understanding of SAR has increased considerably over recent years as we have begun to elucidate the molecular mechanisms underlying this response. In Figure 1, we present a summary of the data discussed in this review. Many of the processes contributing to SAR are clearly required in both local and systemic tissues and contribute to basal disease resistance. These include the synthesis of SA, changes in redox status, and the induction of defense gene expression. In local tissue, the trigger for these changes is the recognition of the invading pathogen, whereas in systemic tissue they are induced by perception of a systemic signal. There is evidence for negative and positive feedback of SA signaling and cross-talk between different signaling pathways, adding to the complexity of the defense response. As well as the central role played by NPR1-mediated signaling, there is growing evidence for an NPR1-independent pathway(s) that contributes to defense gene induction. Challenges for the future include identification of the mobile signal for SAR, to which we are one step closer after the identification of DIR1. Induction of SAR to control infection of crop plants is already being used in the field by application of BTH and it has been suggested that NPR1 overexpression is another viable strategy. Better understanding of the SAR signaling pathway will certainly lead to new environmentally friendly methods of crop protection.

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CONTENTS