

Systemic Acquired Resistance: Turning Local Infection into Global Defense

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Abstract

Systemic acquired resistance (SAR) is an induced immune mechanism in plants. Unlike vertebrate adaptive immunity, SAR is broad spectrum, with no specificity to the initial infection. An avirulent pathogen causing local programmed cell death can induce SAR through generation of mobile signals, accumulation of the defense hormone salicylic acid, and secretion of the antimicrobial PR (pathogenesis-related) proteins. Consequently, the rest of the plant is protected from secondary infection for a period of weeks to months. SAR can even be passed on to progeny through epigenetic regulation. The *Arabidopsis* NPR1 (non-expresser of *PR* genes 1) protein is a master regulator of SAR. Recent study has shown that salicylic acid directly binds to the NPR1 adaptor proteins NPR3 and NPR4, regulates their interactions with NPR1, and controls NPR1 protein stability. However, how NPR1 interacts with TGA transcription factors to activate defense gene expression is still not well understood. In addition, redox regulators, the mediator complex, WRKY transcription factors, endoplasmic reticulum–resident proteins, and DNA repair proteins play critical roles in SAR.

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INTRODUCTION

Plants are potential hosts for diverse groups of pathogens, including fungi, oomycetes, viruses, bacteria, and nematodes (1). The sessile nature of plants makes exposure to such environmental stresses inevitable. However, even in the absence of a circulatory system, plants are able to mount a defense against infection not only locally but also systemically. In fact, infection is the exception rather than the rule.

Plant cells are generally protected by several layers of physical barriers, including the waxy cuticle on the leaf surface, the cell wall, and the plasma membrane, which deny access to most microbes. Plants can also produce a wide variety of chemicals to form a chemical barrier against microbes and pests. For example,

saponins are glycosylated triterpenoids on the surfaces of many plant species. Their soap-like properties can disrupt the cell membranes of fungal pathogens (8). In addition to these non-specific defense mechanisms, different classes of pathogens (e.g., gram-positive as opposed to gram-negative bacteria) can be recognized by the cell surface-localized pattern-recognition receptors (PRRs) through highly conserved pathogen-associated molecular patterns (PAMPs) (10). Both plants and animals have independently evolved PAMP-triggered immunity (PTI) as the first layer of active defense at the cellular level, highlighting the importance of this immune mechanism in preventing potential pathogen infection (5). For instance, an important PAMP from bacterial pathogens,

Pathogen-associated molecular pattern (PAMP): a set of conserved molecules in pathogens recognized by the host immune system

PAMP-triggered immunity (PTI): defense responses triggered by the detection of PAMPs by host pattern recognition receptors

flagellin, is recognized by both the receptor kinase FLS2 in plants and TLR5 (Toll-like receptor 5) in mammals (10, 53, 54, 150) even though different regions of flagellin are targeted.

To establish a successful infection, plant pathogens can suppress PTI by injecting effectors into the host cells (62). For example, a type III effector from *Pseudomonas syringae*, AvrPtoB, functions as an E3 ligase and targets the flagellin receptor FLS2 for degradation through the 26S proteasome (52). To counter this virulence strategy, plants have evolved the so-called resistance (R) proteins, which can either directly detect the effectors or indirectly detect their activity. In plants where the activity of AvrPtoB is detected by the R protein Prf, effector-triggered immunity (ETI) is activated against the pathogen (112). AvrPtoB thus becomes a trigger for ETI, rendering the pathogen avirulent. ETI in plants is often associated with rapid, localized programmed cell death (PCD) at the infection site, a visible phenotype known as the hypersensitive response (18).

An avirulent pathogen not only triggers defense responses locally but also induces the production of signals such as salicylic acid (SA), methyl salicylic acid (MeSA), azelaic acid (AzA), glycerol-3-phosphate (G3P), and abietane diterpenoid dehydroabietinal (DA) (20, 22, 63, 84, 91, 103). These signals then lead to systemic expression of the antimicrobial *PR* (*pathogenesis-related*) genes in the uninoculated distal tissue to protect the rest of the plant from secondary infection (45). This phenomenon is called systemic acquired resistance (SAR). SAR can also be induced by exogenous application of the defense hormone SA or its synthetic analogs 2,6-dichloroisonicotinic acid (INA) and benzothiadiazole S-methyl ester (BTH) (45). SAR provides broad-spectrum resistance against pathogenic fungi, oomycetes, viruses, and bacteria. SAR-conferred immune “memory” in plants can last for weeks to months, and possibly even the whole growing season (73). In contrast to ETI, SAR is not associated with PCD, and instead promotes cell survival. The onset of SAR is associated with massive transcriptional re-

programming, which is dependent on the transcription cofactor NPR1 (nonexpresser of *PR* genes 1) and its associated transcription factors (TFs) such as TGAs (40, 104). SAR is believed to be conferred by a battery of coordinately induced antimicrobial *PR* proteins whose secretion requires significant enhancement of endoplasmic reticulum (ER) function (138, 139).

Despite intense research, there are many gaps in our knowledge of the SAR signaling pathway. It is not completely known how an avirulent pathogen induces the biosynthesis of the essential immune signal, SA, both locally and systemically. The nature of the mobile signal for SAR is still up for debate. Is there only one such signal, or multiple signals? How is the SA signal perceived? In other words, what is the identity of the SA receptor? Moreover, how does NPR1 control the transcriptional cascade, which affects approximately 10% of the transcriptome? Finally, what is the molecular basis for immune memory in plants, and can this memory be passed on to the progeny? In this review, we report on recent progress in addressing these fundamental questions.

THE INITIAL TRIGGER FOR SAR

It is well known that ETI can trigger SAR through both local and systemic synthesis of SA. Because grafting experiments using the SA-deficient *nahG* rootstock have shown that SA is required only in the systemic tissue (49), the initial signal produced at the ETI site is a molecule other than SA. This signal is unlikely to be effector specific, as different effector-R pairs can trigger SAR and studies have shown that virulence infection could also induce SAR (4, 14, 60). The reports published so far point to different compounds as the potential initial SAR signals.

Amino Acids and Derivatives

A recent report by Pajerowska-Mukhtar et al. (101) suggested that SAR signaling may be associated with changes in amino acid homeostasis induced by ETI. Pathogen infection can lead

Effector: a virulence protein injected into a host cell by a pathogen to suppress host defense and cause disease

Effector-triggered immunity (ETI): a set of defense responses triggered by specific pathogen effectors upon recognition by their cognate host resistance proteins

Hypersensitive response: the phenotypic response generated as a result of ETI, characterized by well-defined necrotic areas where infected cells have undergone programmed cell death

***PR* (*pathogenesis-related*) genes:** a group of genes induced after pathogen infection that encode small, secreted, or vacuole-targeted proteins with antimicrobial activities

System acquired resistance (SAR): a broad-spectrum plant disease resistance induced in the whole plant after a local pathogen infection

NPR1 (nonexpresser of *PR* genes 1): a protein first identified in *Arabidopsis thaliana* that is required for *PR* gene expression, local defense, SA signaling, and SAR

Mobile signal: a signal transmitted from the local infection site to the systemic tissue to induce systemic resistance

to the synthesis of a large number of phenolic compounds, which are derivatives of phenylalanine. Pajerowska-Mukhtar et al. discovered that the key TF, TBF1 (TL1-binding factor 1), which is required for the growth-to-defense transition upon pathogen challenge, is rapidly translated from its mRNA, which contains two upstream open reading frames enriched for phenylalanine. Under normal growth conditions, translation of the upstream open reading frames prevents the translation of TBF1 downstream and suppresses immune responses. However, upon ETI induction by *P. syringae* pv. *maculicola* (Psm) ES4326/AvrRpt2, a rapid increase in uncharged tRNA^{phe} leads to activation of the GCN2 (general control nonrepressed 2) kinase, which senses amino acid deficiency by binding to uncharged tRNA and in turn phosphorylates the translation initiation factor eIF2a, resulting in the translation of TBF1. Derepression of TBF1 occurs within 30 min of the pathogen challenge, suggesting that it may be one of the earliest triggering responses for SAR. Interestingly, a similar pathogen-induced translational regulatory mechanism has been found for the key *Caenorhabditis elegans* immune TF zip2 (43), suggesting that amino acid starvation may be a common early cellular signal for activation of immunity.

Characterization of the *Arabidopsis ald1* (*agd2-like defense response protein 1*) mutant also suggests that an amino acid-derived defense signal is generated upstream of SA synthesis (121). This mutant, which is defective in an aminotransferase, is compromised in SA biosynthesis and in SAR. Identification of the substrate for this enzyme may lead to the discovery of the initial signal for SAR.

Extracellular NAD(P)

NAD⁺ and NADP⁺ are major electron carriers, representing the reducing power of the cell. These pyridine nucleotides can also serve as ADP-ribose donors or acetyl group acceptors (35) or as precursors for cyclic ADP-ribose (cADPR) and NAADP, affecting Ca²⁺ transport (50, 75). In animals, extracellular

NAD(P) [eNAD(P)] acts on plasma membrane receptors and channels to control Ca²⁺ flux (113). Zhang & Mou (153) showed that in plants, the pathogen-induced hypersensitive response causes leakage of pyridine nucleotides into the intercellular fluid at concentrations sufficient to induce *PR* gene expression as well as resistance. More critically, these effects appear to be dependent on Ca²⁺ signaling and subsequent production of SA. However, whether plants have membrane receptors or ectoenzymes for these pyridine nucleotides and whether eNAD(P) is the initial trigger for SAR have not been determined.

MOBILE SIGNALS

Methyl Salicylic Acid

Even though SA has been ruled out as the mobile signal for SAR, Park et al. (103) showed that MeSA might be the signal (**Figure 1**). This idea came from a study of SABP2 (salicylic acid-binding protein 2), a methyl salicylate esterase, which converts the biologically inactive MeSA to the active SA. The authors found that after they inoculated the wild-type tobacco rootstock with tobacco mosaic virus, the *SABP2*-silenced scion failed to accumulate SA or develop SAR. They proposed that the locally synthesized SA is first converted to MeSA through the activity of SA methyltransferase and then mobilized to the systemic tissue, where it is converted back to SA by SABP2. In support of this hypothesis, silencing the SA methyltransferase in tobacco compromised SAR. A different study, however, found that the *Arabidopsis* SA methyltransferase knockout mutant (*bsmt1*) was intact in mounting SAR (4). The authors of this study also showed that although the MeSA level increased upon SAR induction, the majority of it was released into the atmosphere. These data raised questions about the validity of MeSA as a general mobile signal for SAR.

The Lipid-Transfer Protein DIR1

The *dir1* (*defective in induced resistance 1*) mutant was discovered in a labor-intensive genetic

screen designed specifically to identify SAR signals (85) (**Figure 1**). In contrast to other SAR-deficient mutants, *dir1* has a normal local defense response but is compromised in SAR (85). Even though petiole exudates collected from *dir1* lack the SAR-inducing activity, the mutant is competent in responding to induction by the petiole exudates collected from induced wild-type plants. This suggests that DIR1, which encodes a putative lipid-transfer protein, is probably involved in the synthesis or transport of a lipid molecule, which is a mobile signal for SAR (85).

Jasmonic Acid

Truman et al. (130) proposed jasmonic acid (JA) as the systemic signal for SAR. They found that JA levels increased significantly 6 h after *P. syringae* pv. *tomato* (*Pst*) DC3000/*AvrRpm1* infection and returned to normal 11 h after infection. Exogenous application of JA induced SAR. In JA-insensitive mutant *sgt1bl/jai4*, JA-biosynthesis mutant *opr3*, and JA-response mutant *jin1* plants, SAR was compromised; however, others showed that the JA-biosynthesis mutants *dde2* and *opr3*, as well as the downstream signaling mutants *coi1*, *jar1*, and *jin1*, were intact in SAR (4). Furthermore, JA was not copurified from petiole exudates with the SAR-inducing ability (21).

Azelaic Acid

Several studies have focused on the analysis of petiole exudates in the effort to identify the mobile signal for SAR. Jung et al. (63) found a significant enrichment of AzA, a C₉ dicarboxylic acid, in the petiole exudates collected from SAR-induced *Arabidopsis* leaves (**Figure 1**). When sprayed locally onto *Arabidopsis* plants, AzA accumulated not only in the petiole exudates but also in the distal tissue to induce resistance. However, free and total SA levels were not elevated in AzA-treated plants, suggesting that it does not induce defense directly but rather primes the plant for SA synthesis upon pathogen challenge. This hypothesis was supported

by a microarray analysis in which none of the proteins encoded by the 464 defense-related genes were significantly elevated in the AzA-treated plants. The authors found the lipid-transfer protein DIR1 to be required for AzA-induced resistance (**Figure 1**). They also found an AzA-induced gene, *AZI1* (*azelaic acid induced 1*), encoding a predicted secreted protease-inhibitor/seed-storage/lipid-transfer family protein, to be required for AzA signaling. The *azi1* mutant was impaired in SAR but showed normal response to local infection. Based on this finding, the authors proposed that together with DIR1, AZI1 regulates the production or translocation of a mobile SAR signal.

Glycerol-3-Phosphate

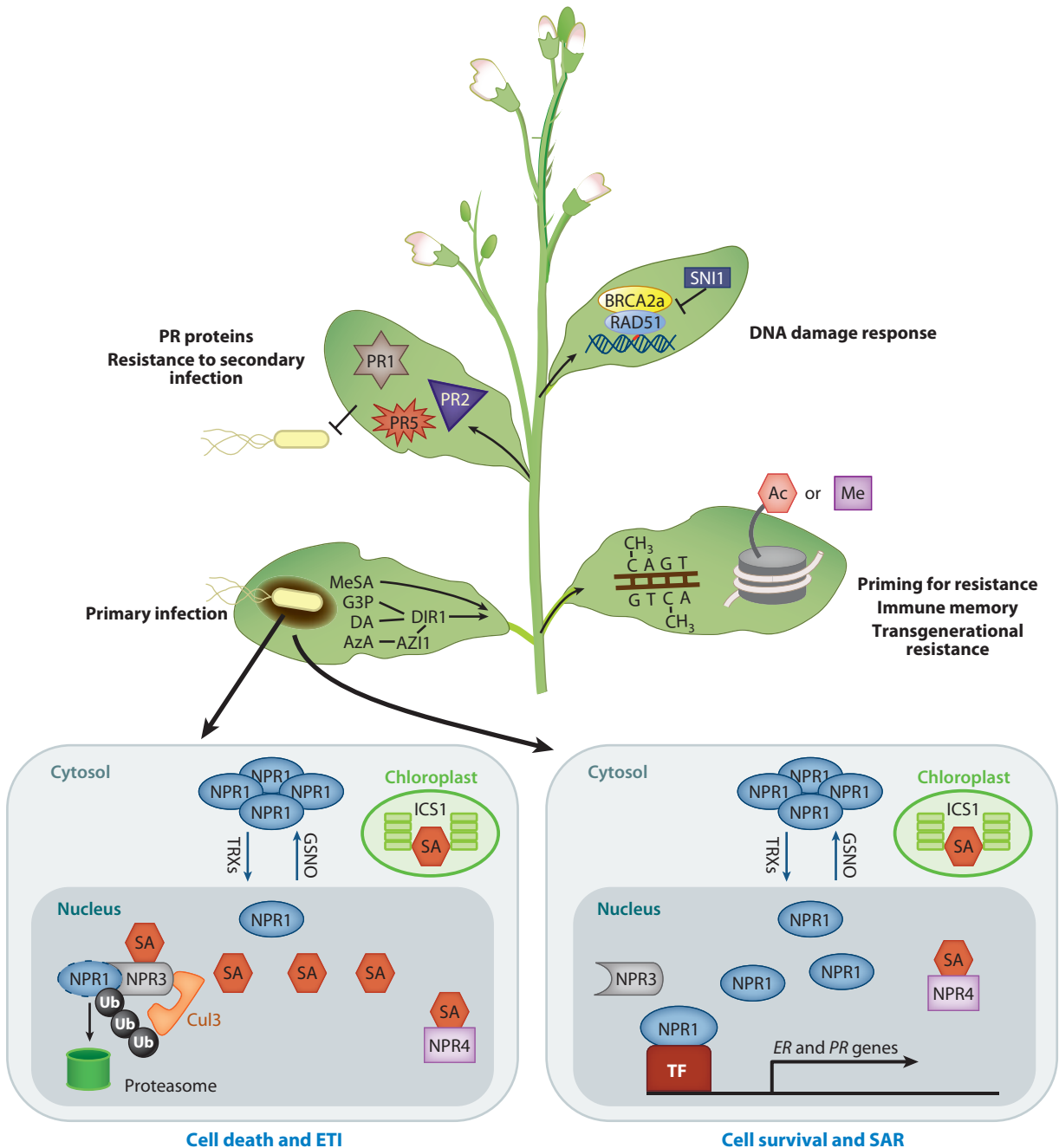
The accumulation of AzA occurs at least 24 h after pathogen inoculation, making it unlikely to be the initial mobile SAR signal. Chanda et al. (20) found that, in contrast to AzA, G3P accumulates within 6 h of pathogen challenge (**Figure 1**). G3P can be produced through the activity of the G3P dehydrogenase GLY1. GLY1 reduces dihydroxyacetone to G3P and is required for SAR (19, 88). G3P can also be synthesized in planta through phosphorylation of glycerol by glycerokinase. Glycerokinase (NHO1/GLI1) was first found to play an important role in nonhost resistance (80). The *Arabidopsis gly1* and *gli1* mutants, which are defective in G3P synthesis, were compromised in SAR, and the resistance phenotype could be restored by exogenous application of G3P. Interestingly, the *gly1* and *gli1* mutants accumulated wild-type levels of SA and AzA, and exogenous application of G3P alone did not induce SA biosynthesis or SAR. Therefore, G3P appears to be a necessary but not sufficient mobile signal for SAR. G3P translocation to distal tissue was dependent on the lipid-transfer protein DIR1; conversely, the movement of the DIR1 protein required G3P, as the DIR1-GFP protein failed to move to distal tissue in the *gly1 gli1* mutant plants, and infiltration of DIR1 protein was unable to induce SAR in the *gly1 gli1* mutant plants.

Priming: a mechanism by which plant defense is poised to respond more quickly and strongly to pathogen challenge

Abietane Diterpenoid Dehydroabietinal

In a more recent study, Chaturvedi et al. (22) purified DA as a SAR-activating compound

from petiole exudates of avirulent pathogen-treated *Arabidopsis* leaves (Figure 1). Chemically synthesized DA was effective in inducing systemic resistance against virulent strains of *P. syringae* and the fungal pathogen *Fusarium*



graminearum. Using radioactive-labeled DA, the authors showed that DA translocated to the distal untreated leaves within 15 min of application. DA-induced SAR required *NPR1*, *FMO1* (*flavin-dependent monooxygenase 1*), and *DIR1* genes. Lower doses of DA were capable of inducing SAR in wild-type plants but not in *azi1* mutant plants. When DA was applied together with AzA, the efficiency of DA in inducing SAR increased, suggesting a synergistic effect of AzA and DA in inducing SAR.

It is worth noting that AzA, G3P, and DA all require DIR1 for their functions (34) (**Figure 1**). It would be interesting to determine whether DIR1 binds to these mobile signals directly or affects them through an indirect mechanism.

BIOSYNTHESIS AND HOMEOSTASIS OF SALICYLIC ACID

SA is known to be necessary and sufficient to induce SAR because transgenic plants overexpressing the SA-degrading enzyme salicylate hydroxylase (49) and SA-synthesis mutant *ics1* (*isochorismate synthase 1*) plants (147) are defective in SAR, and exogenous application of SA induces SAR (146). SA synthesis is induced both locally and systemically upon SAR induction (84, 91).

Genetic studies have identified mutants that are compromised in SA synthesis in both local and systemic locations as well as mutants that have an SA-production defect only in systemic tissue. The first group is likely to affect the initial signaling events or the common components in the SA synthesis itself. The second group, in contrast, may affect a step that connects the mobile SAR signal to the SA synthesis in systemic tissue. The *fmo1* flavin-dependent monooxygenase mutant is an example from the second group (92). It is defective only in SA accumulation in systemic tissue and in SAR, and is normal in local SA production and ETI. Identification of the FMO1 substrate may fill this gap in the SAR signaling pathway.

Salicylic Acid Biosynthesis

Genetic studies in *Arabidopsis* have shown that SA is synthesized mainly through the pathway involving ICS1, as *ics1* (a.k.a. *eds16* and *sid2*) accumulates only 5–10% of the wild-type level of SA upon pathogen challenge (147) (**Figure 1**). Biochemically, SA can also be synthesized from cinnamate produced by phenylalanine ammonia lyase (PAL) (26), but this pathway seems to play a minor role in SAR-associated SA synthesis. The chorismate pathway has similarities to the bacterial SA-biosynthesis pathway, where SA is produced in two steps: in the first,

Figure 1

Signal transduction in SAR. A primary local infection can trigger not only effector-triggered immunity (ETI), which is often associated with programmed cell death (PCD) of the infected cells, but also production of the immune signal salicylic acid (SA) in chloroplasts through the activity of isochorismate synthase ICS1. Mobile immune signals are also produced, including azelaic acid (AzA), glycerol-3-phosphate (G3P), methyl salicylic acid (MeSA), and abietane diterpenoid dehydroabietinal (DA). AzA regulates the expression of *AZII*, which encodes a predicted secreted protease-inhibitor/seed-storage/lipid-transfer family protein, and AzA, G3P, and DA all require DIR1, a putative lipid-transfer protein, for their functions. Accumulation of SA affects the cellular redox and the NPR1 nuclear translocation through S-nitrosoglutathione (GSNO) and thioredoxins (TRXs). The nuclear NPR1 concentration is controlled by SA levels through the SA receptor proteins NPR3 and NPR4. A high concentration of SA in the local infection site promotes NPR1-NPR3 interaction and NPR1 degradation to allow PCD and ETI to occur, whereas in the neighboring cells, the intermediate level of SA disrupts NPR1-NPR4 interaction, resulting in the accumulation of NPR1. NPR1 can interact with transcription factors (TFs) to activate the expression of *ER* genes to facilitate protein secretion; the expression of antimicrobial PR proteins such as PR1, PR2, and PR5; and resistance to secondary infection. The SAR primed state is associated with acetylation (Ac) of H3K9 and methylation (Me) of H3K4 at SAR-associated gene promoters. Moreover, DNA methylation and proteins affecting chromatin architecture (e.g., SNI1) and DNA repair (e.g., RAD51 and BRCA2) may function in priming plant defense genes and protecting genome stability not only in the current generation but also in the progeny.

ICS1 converts chorismate to isochorismate; in the second, SA is generated from isochorismate catalyzed by isochorismate pyruvate lyase (IPL) (90, 116). Consistent with its proposed prokaryotic origin, ICS1 has a transit peptide at the N terminus and is located in the chloroplast. However, the plant IPL has not yet been found (26), which has significantly hindered progress in our understanding of the biosynthesis of this important defense hormone.

EDS5 (enhanced disease susceptibility 5, a.k.a. SID1), PBS3 (*avrPphB* susceptible 3, a.k.a. WIN3 for HopW1-1-interacting 3), and EPS1 (enhanced *Pseudomonas* susceptibility 1) are three proteins whose roles in SA synthesis have been proposed but not specifically confirmed. Because EDS5 encodes a multidrug and toxin extrusion (MATE) transporter family protein, it is hypothesized to be involved in transporting SA or a precursor of SA (97). PBS3 belongs to the GH3 acyl adenylase family of enzymes. The related JAR1 (GH3.11) protein is known to adenylate JA, leading to the conjugation of isoleucine to JA to form the bioactive JA-Ile (125, 126). Okrent et al. (100) found that PBS3 (GH3.12) can conjugate amino acids to 4-substituted benzoates and that SA inhibits this enzymatic activity. This result has been confirmed by a crystal-structure study in which the specific amino acid was identified as glutamate (145). Okrent et al. (100) hypothesized that 4HBA-Glu serves as a signal to prime SA synthesis. However, Chen et al. (26) proposed a more direct enzymatic role for PBS3 together with EPS1 (which encodes a member of the BAHD acyltransferase superfamily) in SA biosynthesis (160). They believe that PBS3 and EPS1 together provide the enzymatic activity that is equivalent to IPL found in bacteria.

Regulation of Salicylic Acid Synthesis

Many mutants affect events upstream of SA synthesis. For example, *eds1* (*enhanced disease susceptibility 1*), *pad4* (*phytoalexin deficient 4*), and *ndr1* (*non-race-specific disease resistance 1*) are known to affect the onset of ETI and the subsequent SA synthesis. The EDS1 protein has recently

been found to complex with both the pathogen effectors and their cognate R proteins, and partitioning of the EDS1 complex in the cytoplasm and nucleus is required for full activation of local resistance (9, 56). It will be interesting to determine whether both cytoplasmic and nuclear EDS1 are required to induce SA synthesis.

Several transcription activators and repressors have been found to regulate *ICS1* expression. Through a genetic screen, Zhang et al. (158) identified the plant-specific SARD1 (*SAR* deficient 1) and its homolog CBP60g as TFs of *ICS1*. In the *sard1 cbp60g* double mutant, ETI- and UVB-induced SA synthesis was blocked and both basal defense and SAR were compromised. SARD1 and CBP60g could both bind to the *ICS1* promoter at the sequence GAAATTTTGG. Besides these transcription activators, transcription repressors of *ICS1* include EIN3 (ethylene insensitive 3), EIL1 (EIN3-like 1), and ANAC019, ANAC055, and ANAC072 (23, 159). Interestingly, these TFs are also involved in ethylene and JA signaling (13, 149), indicating that SA synthesis is a point of regulation in crosstalk with other plant hormones.

Salicylic Acid Metabolism

Because SA is a defense hormone, its level is normally tightly regulated in plants. After pathogen infection, most of the SA is glucosylated by the SA-inducible SA glucosyltransferase (SAGT) to form the inactive SA glucoside (SAG) (32). There are two SAGTs in *Arabidopsis*; one is involved primarily in converting SA to SAG, whereas the other generates the less abundant SA derivative salicyloyl glucose ester (SGE) (136). After SA is synthesized in the chloroplast, it conjugates with glucose to form SAG through the cytoplasmic SAGT and is then stored in the vacuole (32). Upon pathogen challenge, SAG can be readily hydrolyzed to generate the bioactive free SA.

MeSA is another SA metabolite. This volatile molecule serves as a systemic signal for SAR in tobacco (103). However, determining whether signaling is the main function of this

molecule or it is just an SA metabolite will require further tests.

Crosstalk Regulation of Salicylic Acid Levels by Other Plant Hormones

Because plants do not have specialized immune cells, balancing growth and defense is critical for their survival. This balance can be achieved through crosstalk between different plant hormones. Here, we describe only the crosstalk between SA and JA, another stress hormone, with an emphasis on the biological significance of this interaction.

Both synergistic and antagonistic interactions between SA and JA have been reported, suggesting that the interaction is either concentration dependent (96) or tissue specific and dynamic. Application of low concentrations of SA and JA resulted in synergistic expression of both the SA target gene *PR1* and the JA marker genes *PDF1.2* and *Tbi1.2*. In contrast, higher concentrations of SA and JA have antagonistic effects on expression of the same genes (96). It is generally believed that this antagonism between SA and JA allows plants to prioritize defense against either biotrophic or necrotrophic pathogens. Host plants rely on SA-mediated defense against biotrophic pathogens, whereas JA-mediated signaling participates in defense against necrotrophic pathogens (51). When the plant is challenged by a biotrophic pathogen, the crosstalk leads to activation of SA defense and repression of the JA pathway. However, if such a crosstalk occurs systemically, it may have a deleterious effect on plant health, as exposure to one type of pathogen may reduce resistance to another. Spoel et al. (123) found that strong crosstalk does not occur in systemic tissue. For plants inoculated with the virulent *Psm* ES4326, the trade-off for resistance against *Alternaria brassicicola* was detected only in tissues adjacent to the infection site (123). Surprisingly, when the avirulent *Psm* ES4326/avrRpt2 was used, no crosstalk was observed even in the adjacent tissue, where high levels of SA accumulated. This indicates that during ETI, which is often associated with host cell death, an unknown

mechanism is activated to inhibit crosstalk and prevent necrotrophic pathogens from taking advantage of this immune response.

Many pathogens have evolved mechanisms to exploit the host crosstalk mechanisms to promote virulence (122). A prime example is the bacterial toxin coronatine, which is produced by many strains of *P. syringae*. Coronatine is a mimic of JA-Ile and has been shown to bind to the JA-Ile coreceptors COI1-JAZ with high affinity (47, 65). A recent study by Zheng et al. (159) revealed a signaling cascade by which coronatine stimulates stomata re-opening to allow bacterial entry into the plants and promotes bacterial growth both locally and systemically. The authors found that three homologous *NAC* TF genes—*ANAC019*, *ANAC055*, and *ANAC072*—were induced by the MYC2 TF released after coronatine binding to the COI1-JAZ coreceptors. These *NAC* TFs then repressed the SA-biosynthesis gene *ICS1* but activated the SA-metabolism genes *SAGT1* and *BSMT1* through direct binding to their gene promoters. Consequently, the overall SA concentrations were reduced, leading to enhanced bacterial virulence.

SALICYLIC ACID SIGNAL TRANSDUCTION

Multiple genetic screens performed for SA-insensitive mutants led to a single genetic locus, *npr1* (16, 17, 33, 117). This suggests that either the SA pathway is very short or there are multiple parallel signaling components or events, making them difficult to detect through genetics. It is also possible that some of the signaling components are essential. Besides inducing SAR, SA is known to inhibit the hypersensitive response during ETI (38, 152), trigger thermogenesis in plants (105, 106), and inhibit plant growth, chloroplast development, and photosynthesis (109). It is possible that distinct SA signaling pathways control these physiological responses. Biochemical screens for SA-binding proteins, spearheaded by Klessig and colleagues (25, 44, 128), resulted in the identification of multiple enzymes, such as catalase, ascorbate

Biotrophic

pathogens: pathogens whose growth relies on nutrients from the living host cells

Necrotrophic

pathogens: pathogens whose growth relies on nutrients released from dead host cells

peroxidase, the E2 subunit of α -ketoglutarate dehydrogenase, and glutathione S-transferases, and showed that their enzymatic activities are inhibited upon binding to SA. However, genetic studies do not support the possibility that these SA-binding proteins are the bona fide SA receptors. Alternatively, because these are enzymes affecting reactive oxygen species production, SA may signal through changes in cellular redox. In addition to these enzymes, recent reports show that SA binds directly to NPR1 paralogs and possibly NPR1 to regulate NPR1 stability and activity (48, 148).

Regulation of NPR1 by Cellular Redox

Mou et al. (95) discovered that exogenous application of SA could induce a biphasic (first oxidizing and then reducing) fluctuation in cellular redox, as measured by GSH/GSSG. This fluctuation can be sensed by NPR1, as it switches between oligomer and monomer reversibly both in vitro and in vivo (95, 127). The NPR1 oligomer forms through intermolecular disulfide bonds. Tada et al. (127) found that S-nitrosoglutathione, which functions as an NO donor, facilitates NPR1 oligomer formation through S-nitrosylation of cysteine residue 156 (Figure 1). Upon SA induction, the NPR1 monomer is released owing to the enzymatic activity of the cytoplasmic thioredoxins TRX-h3 and TRX-h5. Mutating either NPR1 cysteine 156, the TRXs, or the TRX reductase compromised SAR. Further supporting the notion that reducing power is required for NPR1 monomer release, Mou et al. (95) showed that inhibiting the pentose phosphate pathway, a major source of cytoplasmic NADPH, using the inhibitor 6-aminonicotinamide blocked SA-induced release of the NPR1 monomer and SAR.

Nuclear Degradation of NPR1

The SA-induced oligomer-to-monomer switch of NPR1 is a critical step in inducing SAR, as the NPR1 monomer is nuclear translocated and required for resistance (69, 95). However, the significance of forming the cytoplasmic

oligomer was not immediately evident. Spoel et al.'s (124) discovery that NPR1 is constantly degraded in the nucleus by the 26S protein revealed the underlying significance of this regulation. NPR1 is stored in the cytoplasm as an oligomer not only to prevent spurious activation of SAR in the absence of the pathogen challenge, but also to maintain NPR1 protein homeostasis during SAR induction when NPR1 monomers are transported to the nucleus.

The study of NPR1 degradation was prompted by the discovery that NPR1 has the typical structure of an adaptor protein for the Cullin 3 E3 ubiquitin ligase. Like many such adaptor proteins, NPR1 contains a BTB domain that may bind to Cullin 3 and an ankryin repeat domain that binds to the substrate. Even though the substrate for NPR1 has yet to be identified, Spoel et al. (124) found that NPR1 itself is polyubiquitinated by the Cullin 3 E3 ligase and degraded by the 26S proteasome. Surprisingly, proteasome-mediated degradation of NPR1 occurred both before and after SAR induction. Degradation of NPR1 after SAR induction appeared to be required for full induction of NPR1 target genes. The authors hypothesized that this is a mechanism to refresh the initiation complex after each round of transcription. Genetic data showed that phosphorylation at the I κ B-like site found in NPR1 (S11/15) was involved in this postactivation degradation.

NPR3 and NPR4 Are Salicylic Acid Receptors That Regulate NPR1 Stability

The result from Spoel et al. (124) implies that there are two adaptor proteins mediating NPR1 degradation: One is involved in NPR1 degradation in the absence of SA, whereas the other is involved in the presence of SA. A genetic study by Zhang et al. (155) suggested that the NPR1 paralogs NPR3 and NPR4 might be good candidates for these adaptors, as the *npr3 npr4* mutant showed enhanced disease resistance as opposed to the compromised resistance observed in *npr1*. More importantly,

this enhanced resistance was NPR1 dependent, as the *npr1 npr3 npr4* mutant showed the *npr1* phenotype. Indeed, NPR4 and NPR3 were found to directly interact with Cullin 3 and function as adaptors to mediate NPR1 degradation (48). NPR4 appears to constitutively degrade NPR1 because in the *npr4* mutant, the basal level of NPR1 was elevated; NPR3, in contrast, mediates NPR1 degradation after SA induction, as in the *npr3* mutant NPR1 accumulated faster than it did in wild type.

Based on the knowledge that plant hormones, such as JA and auxin, signal by facilitating the interactions between F-box proteins and the hormone response repressors (114), Fu et al. (48) examined the possibility that NPR1-NPR3/4 interactions are regulated by SA. Surprisingly, SA indeed facilitated NPR3 interaction with NPR1 but disrupted the interaction between NPR4 and NPR1. Moreover, SA was required for NPR3-NPR3, NPR3-NPR4, and NPR4-NPR4 interactions. Fu et al. further showed that NPR3 and NPR4 could bind [³H]-SA both directly and specifically, with IC₅₀ for NPR3 at 1,811 nM and K_d for NPR4 at 46 nM. In contrast, NPR1 did not show significant SA-binding activity in the analysis. These data show that NPR3 and NPR4 are SA receptors with different binding affinities. SA binding allows NPR3 to interact with NPR1 but disrupts NPR4 interaction with NPR1 to ultimately control NPR1 protein levels.

The biological significance of the regulation of NPR1 by NPR3 and NPR4 was revealed through a series of infection experiments (48). The *npr3* single and *npr3 npr4* double mutants were found to be insensitive to SAR induction, although the basal level of resistance in *npr3 npr4* was much higher than that in *npr1* owing to the increased accumulation of NPR1. Surprisingly, *npr3 npr4* was also significantly impaired in mounting the hypersensitive response and ETI when challenged with avirulent pathogens. This is consistent with an earlier report by Rate & Greenberg (108) showing that NPR1 is an inhibitor of ETI-triggered cell death. Together, these data show that the SA concentration gradient generated at the ETI site is

sensed by NPR3 and NPR4 to control NPR1 levels and determine cell fate (Figure 1). Without pathogen challenge, NPR1 is constantly degraded by NPR4 to prevent unnecessary activation of defense. Upon pathogen challenge, the high SA levels at the infection site allow NPR3-mediated degradation of NPR1 and the onset of the hypersensitive response and ETI. In the adjacent cells, however, SA levels are lower, insufficient to bring about NPR3-NPR1 interaction but high enough to disrupt NPR4-NPR1 interaction. Consequently, NPR1 accumulates in the neighboring cells to promote cell survival and induce SAR.

NPR1-MEDIATED TRANSCRIPTION REPROGRAMMING

Exactly how NPR1 brings about the profound changes in transcription upon SA induction is not completely understood. Maier et al. (83) and Wu et al. (148) proposed that NPR1 contains a transactivation domain at its C terminus and that this domain is exposed when NPR1 binds to SA. However, these experiments involved the use of truncated NPR1 fragments and an artificial transcriptional reporter system. Whether NPR1 binds SA is also debatable. Crystal-structure data are required to resolve this issue. Importantly, the protein domains of NPR1 suggest that it exerts its function as an adaptor for the Cullin 3 E3 ligase. The substrate for NPR1 is likely a repressor of SA signaling. NPR1 physically interacts with TGA and NIMIN (NIM1-interacting) proteins; TGAs mainly activate NPR1 target genes, whereas NIMINs repress expression. More in-depth studies of the effect of NPR1 on TGA and NIMIN stability and a search for new NPR1 targets are warranted.

TGAs

Seven of the ten TGA TFs in *Arabidopsis* have been found to interact with NPR1 in yeast two-hybrid screens (58, 156, 161). Interestingly, whereas TGA2, TGA3, TGA5, TGA6,

Mediator: a large protein complex that connects TFs and RNA polymerase II and regulates stimulus specific transcription

and TGA7 constitutively interact with NPR1, TGA1 and TGA4 interact only with NPR1 in SA-treated leaves (36, 161). Després et al. (36) found two cysteine residues that were unique to these TGAs, and only when the residues were reduced upon SA treatment were these TGAs able to interact with NPR1. This finding is consistent with the observation that NPR1 is also activated through SA-triggered reduction of its cysteine residues (95).

TGAs have been shown to directly bind to *PR* gene promoters at the *as-1* elements in gel mobility shift and chromatin immunoprecipitation assays (61, 110, 156, 161). Linker-scanning mutagenesis of the *PR1* promoter showed that some of the *as-1* elements positively affected gene expression, whereas others did so negatively (74). The binding of TGA2 and TGA3 to these *cis*-elements was enhanced by NPR1 and upon SA induction (37, 61). With the exception of TGA2, genetic data support the notion that TGA TFs play a redundant and positive role in conferring basal resistance and SAR, as *tga1*, *tga3*, *tga1 tga4*, *tga2 tga5 tga6*, and *tga2 tga3 tga5 tga6* mutants displayed different degrees of enhanced disease susceptibility and insensitivity to induction of *PR* genes and resistance (66, 157).

NIMINs

In addition to TGAs, NIMINs were identified as interactors with NPR1 [a.k.a. NIM1 (non-inducible immunity 1)] in yeast two-hybrid screens. Among the three *Arabidopsis* NIMINs, NIMIN1 and NIMIN2 interact with the C-terminal region of NPR1, whereas NIMIN3 binds to the N terminus of NPR1. A yeast three-hybrid assay suggested that NIMINs, TGAs, and NPR1 could be in the same complex (143). Transgenic plants overexpressing NIMIN1 showed reduced *PR* gene expression and compromised SAR, whereas the knockout mutant showed enhanced *PR* gene expression but normal resistance to pathogen infection. These data suggest that NIMIN1 is a negative regulator of defense and might be functionally redundant with NIMIN2 and NIMIN3

(144). Weigel et al. (143, 144) proposed that NIMIN1 inhibits gene expression not through direct promoter binding but rather through association with the NPR1-TGA complex. Like the well-studied transcription repressors ERF (ethylene-responsive element binding factor) and AUX/IAA (auxin/indole-3-acetic acid) (99, 129), NIMINs contain the transcription repression motif EAR (L/FDLNL/F(x)P). Maier et al. (83) observed that SA could disrupt NPR1-NIMIN interaction in yeast two-hybrid assays, suggesting a regulatory mechanism by which SA and NPR1 may regulate NIMIN1 activity or stability and the activation of SAR gene expression.

Mediator

Further supporting the notion that SAR induction involves transcription reprogramming are several recent findings showing that the mediator complex plays an essential role in SAR. As a large protein complex, mediator functions as a bridge between RNA polymerase II and TFs and plays an essential role in regulating activator-dependent transcription (68, 71). The mediator complex consists of 20–30 subunits, mostly conserved in all eukaryotes (6, 11, 12), which are organized into the head, middle, and tail core modules as well as the detachable kinase module. The tail module is believed to interact with TFs, whereas the head and middle modules bind to the C-terminal domain of the RNA polymerase II holoenzyme (87).

The first study of mediator's role in plant defense, however, was not in SA-induced SAR but rather in JA-mediated resistance against necrotrophic pathogens. Knocking down MED21, a subunit in the middle module, in *Arabidopsis* caused enhanced susceptibility to *Botrytis cinerea* and *A. brassicicola* (39). A similar effect was observed for the *med25/pft1* and *med8* mutants (67). Besides JA-mediated gene expression, *med25/pft1* also affected the expression of SA-responsive genes. The location of MED25 in the mediator complex is unknown; MED8 is a part of the head module in other eukaryotes.

Two independent studies have shown that MED16 is involved in both SA- and JA-mediated plant defenses. The *med16/sfr6* mutant was first identified in a genetic screen for mutants defective in cold acclimation to freezing temperature. In this first study, Wathugala et al. (142) found that *med16/sfr6* was also compromised in SA-induced PR gene expression and resistance to *P. syringae*. In the second study, Zhang et al. (154) identified *med16/ien1* as a mutant insensitive to exogenous NAD⁺ treatment, which is known to induce SAR (153). The *med16* plants had reduced NPR1 protein levels and exhibited impaired SAR. Moreover, *med16/ien1* was also defective in JA/ET-responsive genes and resistant to *B. cinerea* and *A. brassicicola*. In yet another genetic screen for insensitivity to BTH-induced growth inhibition, *med15/nrb4* (*nonrecognition of BTH 4*) was identified (15). MED15/NRB4, which is part of the mediator tail module, appeared to function downstream of NPR1. In the *med15/nrb4* mutant background, NPR1-HBD, whose nuclear translocation is controlled by the glucocorticoid receptor hormone-binding domain, failed to rescue the mutant phenotype in response to BTH even after treatment with the steroid dexamethasone.

EXECUTION OF SAR

Execution of SAR involves transcriptional reprogramming regulated by a cascade of transcriptional events initiated by NPR1. Because this cascade has feedback regulatory mechanisms, it is difficult to identify the end point of the signaling pathway. Using an innovative microarray experimental design, Wang et al. (139) were able to identify the direct transcriptional targets of NPR1. We arbitrarily consider these NPR1 direct targets to be the “outputs” for SAR, as they include those involved in the synthesis and secretion of antimicrobial PR proteins. However, the signal cascade is far from linear, as the TF controlling the NPR1-dependent ER-resident genes (TBF1) is also required for the induction of *NPR1* gene expression during plant defense. Moreover, ER

function is needed for not only SAR but also PTI (98, 111). The list of NPR1 direct targets also includes many WRKY TFs, a plant-specific group of TFs that are highly versatile owing to their large number (74 members in *Arabidopsis*) and inducibility by various stresses (132). Because some WRKY TFs are involved in feedback regulation of SA synthesis, it seems justified to put them in the SAR output category.

PR Proteins: The Executioners of SAR

The term PR proteins is a misnomer for these small (5–75-kDa) secreted or vacuole-targeted proteins with antimicrobial activities because they are more likely to contribute to resistance than to pathogenesis (115). Since their first discovery in the early 1970s in tobacco plants showing ETI against tobacco mosaic virus (134), 17 families of PR proteins have been named (115). In *Arabidopsis*, the expression of *PR1* (function unknown), *PR2* (encoding β -1,3-glucanase), and *PR5* (encoding a thaumatin-like protein) is induced by SA and used as a readout for SAR (131) (**Figure 1**). However, it is difficult to genetically test the contribution of each PR protein to pathogen resistance because these proteins are likely to work in concert (133) and are often encoded by multiple genes in gene clusters (41, 118). Because of their small sizes, PR proteins are easily missed during genome annotation. For example, 317 defensin-like sequences have recently been identified through structure alignments, 80% of which were unannotated at the *Arabidopsis* Information Resource (118).

Endoplasmic Reticulum Functions and TBF1

In a study of the direct transcriptional targets of NPR1, Wang et al. (139) observed that prior to PR gene induction, ER-resident genes were coordinately induced to aid secretion of PR proteins (**Figure 1**). NPR1 regulated induction of not only the secreted PR proteins but also the secretory machinery. However, these ER-resident genes do not share the *as-1* element

for TGAs in their promoters, but rather are enriched for a novel *cis*-element (GAAGAA-GAA) named TL1 (139). In a subsequent study, Pajerowska-Mukhtar et al. (101) found that this element binds to a heat shock factor-like TF, TBF1. Genome-wide transcriptional profiling showed that TBF1 plays a major role in the growth-to-defense transition. Upon SA treatment, TBF1 downregulates genes in chloroplast function and protein translation while inducing genes in ER activities and multiple defense responses. Consequently, the *tbf1* mutant was compromised in PTI as well as SAR. Exactly how NPR1 functions together with TBF1 to control the ER-resident gene expression remains to be further investigated. At the transcript level, these two important defense regulators appeared to regulate each other's transcription.

Some of the ER-resident genes are involved in the unfolded protein response, which is regulated by the IRE1 kinase/endoribonuclease (inositol-requiring and ER-to-nucleus signaling) (57). Moreno et al. (94) recently found that SAR induction could also bring about significant induction of the *IRE1* gene. IRE1 could then catalyze the cytoplasmic splicing of the intron sequence in the bZIP60 mRNA, leading to the translation of the active TF and an increase in ER function. Mutating either *IRE1* or *bZIP60* compromised SAR. It is not known, however, whether this IRE1/bZIP60-mediated upregulation of ER function is mechanistically linked to the TBF1-mediated induction or whether there is any interaction between these two pathways.

WRKYs

The important role of WRKY TFs in different plant defense responses has been well established despite the functional redundancy of this large group of proteins (102). Here we focus on only a few examples related to SAR. *W* boxes, the *cis*-elements for WRKYs, are overrepresented in the promoters of the SAR-related genes, including *ICS1*, *NPR1*, and *PR1* (86, 147, 151). Mutating the *W* boxes compromised

both basal and induced expression of *NPR1* (151), whereas overexpression of *WRKY28* and *WRKY46* resulted in increased expression of *ICS1* and *PBS3* in *Arabidopsis* protoplasts (135). Most of the single loss-of-function *wrky* mutants do not have detectable defense phenotypes. The *wrky18* and *wrky70* mutants are the exceptions; the former is defective in SAR (137), and the latter is more susceptible to *Erysiphe cichoracearum* (76) and *Hyaloperonospora parasitica* (70). Two other WRKY TFs, WRKY38 and WRKY62, whose expression is coupled to the degradation of NPR1, are redundantly required for SAR, as the *wrky38 wrky62* mutant is deficient in biologically induced SAR (124).

The inducible nature of the WRKY TF-encoding genes suggests that the TFs are likely auxiliary in the activation phase of a defense response and repressors in turning off defense when infection subsides. Wang et al. (137) showed that WRKY54 and WRKY70 are important suppressors of SA biosynthesis: In the *wrky54 wrky70* double mutant, *ICS1* was expressed and SA accumulated at much higher levels than it did in the wild type. Because this phenotype is similar to that of *npr1* and because *WRKY54* and *WRKY70* are target genes of NPR1, the authors hypothesized that NPR1 feedback regulates SA biosynthesis through these WRKY TFs.

SAR-ASSOCIATED IMMUNE MEMORY

It is detrimental for the host to have constitutive immune activities (55). In higher vertebrates, prior pathogen exposure leads to the generation and proliferation of long-lived memory B and T cells, which are quiescent in immunity but can respond to the second pathogen challenge much more quickly and strongly than the naive B and T cells. In the absence of such specialized cells, plants maintain immune memory through "priming." In fact, the induction of SAR is a process of priming (29–31). Once induced, SAR is known to last for weeks to months. Moreover, recent reports have suggested the existence of transgenerational immune memory (82, 107,

119). Luna et al. (82) and Slaughter et al. (119) showed that exposures to *Pst*, *Pst/avrRpt2*, and β -amino butyric acid (BABA) in the parent *Arabidopsis* plants could cause faster and stronger induction of defense genes and enhanced resistance to *Pst* as well as an unrelated pathogen, *Hyaloperonospora arabidopsidis*, in the next generation. Luna et al. (82) further showed that this response is NPR1 dependent. In a study of JA-mediated transgenerational memory of herbivory resistance, Rasmann et al. (107) showed that perception of JA by COI1 is required in the parent but not in the progeny, indicating that COI1 and probably NPR1 are involved in the establishment of the primed state. The underlying molecular basis for the immune memory has just begun to be investigated. At present, the accumulation of latent-state immune signaling components, epigenetic modifications, and changes in the chromosome architecture have been shown to be involved.

Priming Through MPK3 and MPK6

Treating plants with BTH gradually induces the expression of MPK3 and MPK6 without increasing the phosphorylation activities of these kinases. Beckers et al. (7) found that upon pathogen challenge, the pretreated plants showed enhanced MPK3 and MPK6 activities and enhanced resistance compared with naive plants. In the *mpk3* and *mpk6* mutants, both BTH-induced resistance and pathogen-induced SAR were compromised. In the *npr1* mutant, priming through MPK3 and MPK6 was inhibited, probably because transcription of these genes is NPR1 dependent. How long this primed state can last and whether it goes beyond the 72 h tested need to be further examined (7).

Epigenetic Regulation

In general, the loss of DNA methylation makes plants more resistant to bacterial infection. When rice plants were treated with 5-azadeoxycytidine to boost global demethylation, they became more resistant to infection by the bacterial pathogen *Xanthomonas oryzae*

pv. *oryzae* (2). *Arabidopsis met1-3* mutant plants defective in the maintenance of CG methylation and *ddc* (*drm1 drm2 cmt3*) mutant plants defective in the maintenance of non-CG methylation are both highly resistant to virulent *Pst* infection (42). Mutant plants defective in RNA polymerase V, which is recruited to establish the DNA methylation, are also more resistant to *Pst* (79). Using genome-wide methylome profiling, Downen et al. (42) discovered that *Pst* infection could cause both hypo- and hypermethylation in gene-rich regions, indicating that demethylation and remethylation are induced by pathogen infection to influence host gene expression (**Figure 1**). Interestingly, the authors also found that SA treatment specifically affected differential methylation of transposable elements and the biogenesis of 21-nucleotide small interfering RNAs (siRNAs). They proposed that these siRNAs might be involved in systemic priming of intact tissues for future pathogen and insect challenge and might even serve as signals for transgenerational immune memory. This hypothesis was supported by the observations that the non-CpG DNA methylation *ddc* mutant mimicked the transgenerational SAR phenotype (82) and that the siRNA biogenesis mutants *npr1* (*npr1*), *npr2* (*npr2*), *npr3* (*npr3*), *npr4* (*npr4*), *npr5* (*npr5*), *npr6* (*npr6*), *npr7* (*npr7*), *npr8* (*npr8*), *npr9* (*npr9*), *npr10* (*npr10*), *npr11* (*npr11*), *npr12* (*npr12*), *npr13* (*npr13*), *npr14* (*npr14*), *npr15* (*npr15*), *npr16* (*npr16*), *npr17* (*npr17*), *npr18* (*npr18*), *npr19* (*npr19*), *npr20* (*npr20*), *npr21* (*npr21*), *npr22* (*npr22*), *npr23* (*npr23*), *npr24* (*npr24*), *npr25* (*npr25*), *npr26* (*npr26*), *npr27* (*npr27*), *npr28* (*npr28*), *npr29* (*npr29*), *npr30* (*npr30*), *npr31* (*npr31*), *npr32* (*npr32*), *npr33* (*npr33*), *npr34* (*npr34*), *npr35* (*npr35*), *npr36* (*npr36*), *npr37* (*npr37*), *npr38* (*npr38*), *npr39* (*npr39*), *npr40* (*npr40*), *npr41* (*npr41*), *npr42* (*npr42*), *npr43* (*npr43*), *npr44* 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at the *PR1*, *WRKY6*, and *WRKY53* promoters (**Figure 1**). These studies provided evidence that chromatin modifications might function as a memory for SAR. In support of this hypothesis, Choi et al. (28) found that HDAC19, a histone deacetylase, could directly bind to the *PR1* and *PR2* promoters to repress their expression; in *bda19* mutant plants, in contrast, the basal H3 and H3K9 acetylation at the *PR1* and *PR2* promoters was increased and defense genes were upregulated. The *Arabidopsis* histone methyltransferase ATX1 (trithorax 1) was also found to positively and directly regulate *WRKY70* transcription through H3K4 trimethylation at the *WRKY70* promoter, and *atx1* mutant plants had reduced *PR1* gene expression and impaired resistance to *Pst* infection (3).

DNA Repair Machinery and Chromatin Architecture

NPR1 is required for SA-induced priming as well as transgenerational immune memory (7, 82). The molecular mechanism may lie with the SNI1 and SSN DNA repair proteins identified through mutant screens. The SNI1 protein, which has recently been found to be part of a protein complex involved in maintaining chromatin integrity (S. Yan & X. Dong, unpublished data), is a negative regulator of SAR (**Figure 1**). Genetic data placed SNI1 downstream from or parallel to NPR1 in the signaling pathway, as mutations in *SNI1* restored SAR in the *npr1* mutant background (77). The *sni1* single mutant had elevated basal expression of *PR* genes and, consequently, visibly retarded growth. This phenotype was then used to identify suppressors of *sni1*. Interestingly, all of the SSN genes cloned so far encode proteins involved in DNA repair, from a DNA damage sensor (S. Yan & X. Dong, unpublished data) and a regulator, BRCA2 (SSN3) (140), to the downstream RAD51D (46), RAD51 (140), and a SWIM (SWI2/SNF2 and MuDR) domain-containing protein (SSN2) (120). The direct involvement of these DNA repair proteins in plant defense has been established

by the enhanced disease susceptibility observed in the *sn* mutants. The most surprising finding from these studies, however, was the specific association of SNI1, SSN2, RAD51, and BRCA2 with the *PR* gene promoters (120, 140). Wang et al. (140) found that RAD51, which is normally delivered to the site of DNA repair by BRCA2, became associated with the *PR* gene promoters only after SA treatment and only in the presence of BRCA2a, not its close homolog BRCA2b (**Figure 1**). How SSNs, which are normally not sequence specific, become specifically associated with *PR* promoters is still unknown. Song et al. (120) proposed that this likely involves NPR1 and its associated TFs.

The deeper question with regard to the involvement of DNA repair machinery in plant immunity is its biological significance. It is not difficult to envision that these DNA repair proteins remodel the chromatin and even change the overall chromosomal architecture to facilitate immune-associated transcriptional reprogramming. A recent study by Moissiard et al. (93) showed that mutations in the ATPase-encoding *Arabidopsis* MORC (*Microorchidia*) family members *AtMORC1* and *AtMORC6* could cause derepression of methylated genes and transposable elements without altering the DNA and histone methylation status of the targets. Using Hi-C analysis, Moissiard et al. found that *AtMORC1* and *AtMORC6* affect the chromosomal superstructure, resulting in heterochromatin condensation and gene silencing. Interestingly, *atmorc1* (a.k.a. *crt1* and mutant 10) was previously isolated for its impaired ETI to various pathogens (64, 141). It will be interesting to determine whether SNI1 and SSN proteins also affect chromatin superstructure and whether the chromosome architecture is different during ETI in which cells are destined to undergo PCD from the architecture during SAR.

The more significant role of DNA repair machinery in plant immunity may be the maintenance of genome stability. That both biotic and abiotic stresses can induce genome instability has been known for a long time (89). Using a reporter system, Lucht et al. (81) and

Kovalchuk et al. (72) showed that induction of SAR could result in systemic increase in somatic homologous DNA recombination. SNI1 and the SSNs are known to be involved in this response because the *smi1* mutant showed a higher recombination rate than the wild type even without pathogen challenge, and this increase could be blocked in the *ssn* mutant backgrounds (46, 120, 140). It remains to be tested whether the defense-related genes, such as *PR* genes, are especially prone to DNA damage owing to active transcription during plant defense, when toxic molecules such as reactive oxygen species are produced, and whether the association of SSNs to these gene promoters is to safeguard them from damage.

FUTURE DIRECTIONS

Studies of SAR have generated a wealth of knowledge in many areas of plant biology at both the molecular and organismal levels. However, there are still gaps in our knowledge of the signaling pathway. We have yet to identify the initial triggering molecule for SAR. Such a signal must be common to all ETI responses. Even though several mobile signals have been reported as able to induce resistance in systemic tissue, whether they function in the same pathway or represent specific induction conditions or plant species will need further investigation. Without definitive knowledge of the mobile signals, we cannot begin to understand how such signals are perceived in the systemic tissue, leading to the accumulation of SA. Further impeding progress is our incomplete knowledge of the SA-biosynthesis pathway. Recent identification of NPR3 and NPR4 as the SA receptors explained how the SA concentration gradient generated at the

infection site is perceived by these receptors to control nuclear NPR1 levels in local and distal tissues and to determine cell death and survival. However, whether other SA-binding proteins play a role in SAR needs further study. Does NPR3 and NPR4 interaction with NPR1 also trigger its oligomer-to-monomer switch? Or is this achieved indirectly through the effect of SA binding on those other SA-binding proteins identified by Klessig and colleagues (25, 44, 128)? How does NPR1 regulate transcription? Does it regulate transcription through direct binding to SA, which exposes its transactivation domain, as proposed by Wu et al. (148), or through degradation of a repressor similar to other hormones, such as JA and auxin? Structural studies of NPRs may help us answer these questions. Another interesting area for exploration is to elucidate how NPR1 establishes immune memory and to identify the signal for transgenerational immunity. CRT1, SNI1, and SSNs in the DNA repair machinery may have a role in this intriguing phenomenon.

The study of SAR will ultimately benefit agriculture and even medicine. Besides the commercialization of BTH in crop protection, the *NPR1* gene has been introduced into various plants by transformation (24, 27, 78) and shown to confer resistance to various pathogens. However, more knowledge of the molecular function of NPR1 is required to reduce the adverse effect of overexpression of this immune regulator. The study of SA perception and signaling in plants may provide valuable information for understanding the multiple medicinal effects of SA and SA derivatives, such as aspirin. Besides pain relief, these compounds are being used for the treatment and prevention of cardiovascular diseases, cancer, and diabetes. The field of SAR study clearly holds much promise.

SUMMARY POINTS

1. Methyl salicylic acid, azelaic acid, glycerol-3-phosphate, and abietane diterpenoid dehydroabietinal have been identified as mobile signals for SAR. Azelaic acid, glycerol-3-phosphate, and abietane diterpenoid dehydroabietinal all require DIR1, a lipid transport protein, for their functions.

2. ICS1 is responsible for approximately 90% of SA production during pathogen infection.
3. NPR1, as a transcription coactivator, is a master regulator of plant defense required for *ER* and *PR* gene induction, local defense, and SAR.
4. NPR3 and NPR4 function as SA receptors, and their interactions with NPR1 are regulated by SA. They serve as adaptors for the Cullin 3 E3 ligase, regulating NPR1 degradation by the 26S proteasome.
5. Epigenetic regulations serve as markers for immune memories and transgenerational SAR.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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