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Pandemonium Breaks Out: Disruption of Salicylic Acid-Mediated Defense by Plant Pathogens

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ABSTRACT

Salicylic acid (SA) or 2-hydroxybenoic acid is a phenolic plant hormone that plays an essential role in plant defense against biotrophic and semi-biotrophic pathogens. In *Arabidopsis*, SA is synthesized from chorismate in the chloroplast through the ICS1 (isochorismate synthase I) pathway during pathogen infection. The transcription co-activator NPR1 (Non-Expresser of Pathogenesis-Related Gene 1), as the master regulator of SA signaling, interacts with transcription factors to induce the expression of anti-microbial *PR* (*Pathogenesis-Related*) genes. To establish successful infections, plant bacterial, oomycete, fungal, and viral pathogens have evolved at least three major strategies to disrupt SA-mediated defense. The first strategy is to reduce SA accumulation directly by converting SA into its inactive derivatives. The second strategy is to interrupt SA biosynthesis by targeting the ICS1 pathway. In the third major strategy, plant pathogens deploy different mechanisms to interfere with SA downstream signaling. The wide array of strategies deployed by plant pathogens highlights the crucial role of disruption of SA-mediated plant defense in plant pathogenesis. A deeper understanding of this topic will greatly expand our knowledge of how plant pathogens cause diseases and consequently pave the way for the development of more effective ways to control these diseases.

Key words: salicylic acid, NPR1, PR proteins, effectors, toxin, VIGS

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INTRODUCTION

Plants, as sessile organisms, are prone to an onslaught of pathogens including bacteria, fungi, oomycetes, viruses, and the like, not to mention the risk of being consumed by ectoparasites such as insects and other pests. Due to this immobility or inability to move away from incoming invaders, it is essential that plants retain very robust and effective defense mechanisms (Agrios, 2005). The front line of defense includes structural shields such as cuticle wax, which provide armor to the leaf, and the cell wall, which acts as a secondary layer of protection for each individual cell within the plant (Szabo and Bushnell, 2001; Underwood, 2012). If invaders penetrate these primary structural defenses, the next level of resistance employed by the plant against pathogens is a sophasticated multi-level mechanism: protecting the plant by activating basal resistance and systemic acquired resistance (Fu and Dong, 2013; Henry et al., 2013; Muthamilarasan and Prasad, 2013).

When structural resistance fails to debar pathogens, induced resistance is the next active defense mechanism in the plant's arsenal. This basal resistance involves the perception of conserved molecules in microbes called microbe-associated molecular patterns (MAMPs), which prompts the plant to activate MAMP-triggered immunity (MTI) to appropriately respond to the invader (Boller and Felix, 2009). In MTI, plant pattern recognition receptors located on the cell surface recognize specific MAMPs and induce immunity against pathogen invasion. However, diverse plant pathogens have evolved mechanisms to override MTI by delivering immunity-suppressing effectors into host cells (Ochman et al., 1996; Badel et al., 2006; Block et al., 2008). During evolution, plants have acquired R (resistance) proteins, which detect the

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pathogen effectors directly or the activity of the effectors indirectly (Jones and Dangl, 2006). When a pathogen effector is recognized by a plant R protein, this effector is also called an avirulence or Avr protein. Recognition of the Avr protein by an R protein triggers rapid programmed cell death (PCD) at the site of infection, which often results in a visible phenotype called the hypersensitive response (HR). This second layer of defense is called effector-triggered immunity (ETI) (Wu et al., 2014a). In general, ETI is more intense than MTI because ETI is associated with rapid cell death, while the responses in MTI are milder. Upon primary pathogen infection, plants not only turn on MTI and ETI at the local infection site but also systemically activate broad-spectrum resistance against secondary infection by a wide variety of pathogens, including bacteria, fungi, oomycetes, and viruses (Durrant and Dong, 2004). This phenomenon is called systemic acquired resistance (SAR).

A Pivotal Role of Salicylic Acid in Plant Immunity

During MTI or ETI, the level of the plant hormone salicylic acid (SA) is elevated (Iwai et al., 2007; Nobuta et al., 2007; Garcion et al., 2008; Palmer et al., 2017). In fact, studies have shown that SA is both required and sufficient to activate plant defense against biotrophic and semi-biotrophic pathogens. In SA biosynthesis mutants lacking SA accumulation, the plant is severely limited in its ability to withstand infection by biotrophic and semi-biotrophic pathogens (Fu and Dong, 2013). Exogenous application of SA or one of its active analogs is sufficient to upregulate plant defense against biotrophic and semi-biotrophic pathogens (Lu, 2009). Besides functioning in SAR, SA has also been shown to interfere with quorum sensing of bacterial pathogens (Joshi et al., 2016). In addition, SA reduces the production of virulence factors and inhibits the type III secretion system. For example, SA can significantly inhibit three known virulence factors in *Pseudomonas aeruginosa*: pyocyanin, proteases, and elastase (Prithiviraj et al., 2005; Bandara et al., 2006). SA and its derivatives were also found to inhibit the expression of the type III secretion system in *Erwinia amylovora* and *Chlamydia pneumoniae* (Bailey et al., 2007; Felise et al., 2008). The promoter activity of the *E. amylovora hrpA* gene, which encodes a type III pilus, could be severely inhibited by SA *in vitro* (Khokhani et al., 2013).

SA Biosynthesis and Transport

SA biosynthesis in plants occurs through two pathways: the phenylalanine pathway and the ICS1 (isochorismate synthase 1) pathway. The ICS1 pathway is the main pathway for SA biosynthesis after pathogen infection in *Arabidopsis* plants (Wildermuth et al., 2001). The ICS1 chorismate pathway begins with the conversion of chorismate to isochorismate catalyzed by ICS1, with isochorismate being subsequently converted to SA by a putative isochorismate pyruvate lyase (IPL) (Strawn et al., 2007; Mustafa et al., 2009). In *Arabidopsis*, this pathway also relies on the proper functioning of several other important players, i.e., EDS1 (enhanced disease susceptibility 1) and PAD4 (phytoalexin deficiency 4), NDR1 (non-race-specific disease resistance 1), EDS5 (enhanced disease susceptibility 5), PBS3 (avrPphB susceptibility 3), ACD6 (accelerated cell death 6), and EPS1 (enhanced pseudomonas susceptibility 1) (Rogers and Ausubel, 1997; Rate et al., 1999; Feys et al., 2001; Nawrath et al., 2002; Lu et al., 2003; Coppinger et al., 2004; Okrent et al., 2009; Vlot et al., 2009; Wu et al., 2014b). In addition, several transcription factors (TFs) including SARD1 (SAR Deficient 1), CBP60g (Calmodulin Binding Protein 60g), NTL9 (NTM1-like 9), CHE (CCA1 hiking expedition), and TCP (TEOSINTE BRANCHED 1, CYCLOIDEA, PCF1) family TFs TCP8 and TCP9 facilitate the expression of *ICS1* during plant defense to positively regulate SA biosynthesis (Zhang et al., 2010b; Wang et al., 2015; Zheng et al., 2015). Among these TFs, NTL9 plays an essential role in the induction of the *ICS1*, *PAD4*, and *EDS1* genes in guard cells to positively regulate stomata closure to prevent pathogen entry (Zheng et al., 2015). It has also been shown that the TGA TFs TGA1 and TGA4 are required for full induction of *SARD1* and *CBP60g* in plant defense, and CHE positively regulates the expression of *SARD1* and *CBP60g* in systemic tissues during SAR (Zheng et al., 2015; Sun et al., 2018).

It turns out that several important regulators of SA biosynthesis are connected with cell death. Studies have shown that *acd6-1* (*accelerated cell death 6-1*), the dominant gain-of-function mutant of ACD6, shows increased resistance to *P. syringae*, which is accompanied by elevation of the SA level, spontaneous cell death, and constitutive defense responses (Rate et al., 1999; Lu et al., 2003). *ACD6* encodes a membrane protein with several putative ankyrin repeats and belongs to one of the largest uncharacterized gene families in higher plants (Lu et al., 2003). ACD6 is necessary for activating the defense response against *P. syringae* in a dose-dependent manner and can activate SA-dependent cell death. In addition to ACD6, which is related to cell death in the absence of a pathogen challenge, EDS1, PAD4, NDR1, PBS3, and EPS1 are required for effector-triggered R protein-dependent cell death. EDS1 functions as an essential component in innate immunity and ETI mediated by the TIR-NB-LRR (Toll-Interleukin1 receptor-Nucleotide Binding site-Leucine Rich Repeat) class of R proteins. EDS1 interacts with PAD4 and SAG101 (senescence-associated gene 101). These three signaling partners form an indispensable regulatory node in plant immune response pathways. EDS1-dependent immunity, which functions downstream of the TIR-NB-LRR class of R proteins but upstream of SA synthesis and PCD, can be SA dependent or SA independent (Feys et al., 2001; Vlot et al., 2009). EDS1 and PAD4 stimulate SA production through upregulation of *ICS1*, while the expression of *EDS1* and *PAD4* can also be induced by SA, which creates a positive feedback loop both locally and systemically. In addition, EDS1 and PAD4 are crucial for the development of SAR (Gruner et al., 2013). The EDS1 and PAD4 protein complex suppresses the function of the master regulator of jasmonic acid (JA) signaling, the TF MYC2, to bolster SA-mediated plant defense (Cui et al., 2018). Overexpression of EDS1 and PAD4 activates the expression of both SA-dependent and SA-independent genes. Both the SA-dependent and SA-independent functions of EDS1 and PAD4 contribute to plant basal immunity and ETI (Cui et al., 2017). Even though EDS1, PAD4, and SAG101 show homology to a group of α/β hydrolase fold lipases, the catalytic residues of EDS1 and PAD4 are not required for their immune function, indicating a non-catalytic defense mechanism (Wagner et al., 2013). These data also suggest that EDS1 and PAD4 function as scaffold or adaptor proteins for other important plant immune regulators instead of being active enzymes (Feys et al., 2005).

NDR1 encodes a GPI-anchored and N-glycosylated membrane protein that plays an important role in ETI by interacting with the CC-NB-LRR (coiled-coil-nucleotide binding-leucine-rich repeat) class of R proteins (Coppinger et al., 2004). NDR1 was determined to be associated with RIN4 (Day et al., 2006), which is critical for the regulation of CC-NB-LRR type R protein-mediated resistance (Day et al., 2005; Chisholm et al., 2006). NDR1 is involved in the regulation of SA accumulation, and disruption of NDR1 causes a reduction of SA content in plants upon pathogen infection (Shapiro and Zhang, 2001).

PBS3, also called *WIN3* (*HOPW1-1-INTERACTING3*) and *GDG1* (Jagadeeswaran et al., 2007; Nobuta et al., 2007; Wang et al., 2011), encodes a GH3 acyl-adenylate/thioester-forming enzyme that plays an essential role in pathogen-induced SA metabolism. PBS3 was first identified from a screen of mutants that suppressed *RPS5*-mediated resistance in *Arabidopsis* (Warren et al., 1999). RPS5, which confers resistance to an avirulent strain of *Pseudomonas syringae* pv *tomato* DC3000 carrying *avrPphB* (Pst DC3000 [*avrPphB*]), is an NB-LRR R protein (Simonich and Innes, 1995). The mutant of *PBS3*, *pbs3*, shows enhanced susceptibility to both virulent and avirulent *Pst* DC3000 strains, i.e., DC3000 (*avrPphB*), DC3000 (*avrB*), DC3000 (*avrRps4*), and DC3000 (*avrRpt2*) (Warren et al., 1999). Expression of *PBS3* is pathogen-induced and is highly correlated with *ICS1* expression, and disruption of *PBS3* drastically decreases the level of SA-glucoside, a storage form of SA (Nobuta et al., 2007). PBS3 has been found to catalyze the conjugation of specific amino acids to 4-substituted benzoates *in vitro*; however, surprisingly, SA was found to be a poor substrate of PBS3 and acted as an inhibitor (Okrent et al., 2009).

The EPS1 protein is a member of the BAHD acyltransferase superfamily that catalyzes CoA-dependent acylation (Zheng et al., 2009). *Arabidopsis eps1* mutants exhibit compromised resistance to both virulent and avirulent strains of *P. syringae*, including DC3000 (*avrRpm1*), DC3000 (*avrB*), DC3000 (*avrRps4*), and DC3000 (*avrRpt2*), and reduced pathogen-induced expression of *PR* genes and reduced accumulation of total SA. EPS1, together with PBS3, is hypothesized to be involved in the ICS pathway with a function equivalent to that of IPL found in bacteria (Zheng et al., 2009). It remains to be determined whether PBS3 and EPS1 interact with R proteins and how the enzymatic activities of PBS3 and EPS1 contribute to plant basal defense, ETI, and SA biosynthesis.

Different from the above-mentioned positive regulators of SA biosynthesis, *EDS5,* also named *SID1*, encodes a protein belonging to the multidrug and toxin extrusion (MATE) transporter family that is required for SA accumulation, exporting SA synthesized in the chloroplast through the ICS1 pathway (Nawrath et al., 2002; Serrano et al., 2013). The *eds5* mutant shows compromised pathogen resistance and reduced expression of *PR* genes systemically, as well as failure to develop SAR (Pallas et al., 1996; Nawrath and Metraux, 1999; Blanc et al., 2018). More recently, it has been shown that the *Arabidopsis* atypical E2F transcription repressor DEL1 functions at the intersection of plant growth and immunity by promoting cell proliferation and reducing SA accumulation through suppression of *EDS5* expression (Chandran et al., 2014). JA induces the expression of *EDS5* while repressing the expression of *PAD4*, which is a positive regulator of *EDS5.* Under normal conditions, JA inhibits SA accumulation by reducing the expression of *PAD4*. However, in the absence of PAD4, JA promotes SA accumulation through the positive regulation of *EDS5* (Mine et al., 2017). Therefore, JA negatively regulates the SA pathway in the presence of an intact network but induces the SA pathway under PAD4 perturbation to provide a robust SA-mediated defense response and minimize SA-induced fitness costs.

SA Signaling in Plant Defense

One of the major effects of SA in plant defense is to induce the expression of *PR* (*Pathogenesis-Related*) genes, which encode proteins with anti-microbial activities. So far, 17 families of PR proteins have been identified (Stintzi et al., 1993; Hoffmann-Sommergruber, 2000). Among *PR* genes, *PR1*, *PR2*, and *PR5* are strongly induced upon infection by biotrophic and semi-biotrophic pathogens. The expression of *PR1*, *PR2*, and *PR5* is dependent on SA (Leah et al., 1991; Selitrennikoff, 2001; Zhang et al., 2010a), and these genes are often used as markers of the SA pathway. The biochemical function of PR1 is currently unknown, although a recent study showed that PR1 has sterol binding activity, which inhibits pathogen growth by sequestrating sterol from pathogens (Gamir et al., 2017). *PR2* encodes β-1,3-glucanase, while *PR5* encodes a thaumatin-like protein (Leah et al., 1991; Selitrennikoff, 2001).

Through genetic screens for *Arabidopsis* mutants with abolished *PR* gene expression, a locus called *NPR1* (non-expresser of PR genes 1) was identified (Cao et al., 1997; Ryals et al., 1997; Shah et al., 1997). Later, *NPR1* was found to be a master regulator of SA-mediated plant defense. The expression of over 98% of SA-regulated genes is dependent on *NPR1* (Wang et al., 2006). Importantly, SA controls the relocation of NPR1 protein from the cytosol to the nucleus through specific redox changes (Mou et al., 2003). Before pathogen infection, NPR1 remains in the cytoplasm as oligomers formed through intermolecular disulfide bonds; upon infection or SA treatment, these bonds break down, which releases the NPR1 monomers to translocate into the nucleus where they induce the expression of defense-related genes.

Since NPR1 lacks a DNA-binding domain, it has been proposed that NPR1 regulates *PR* gene expression during plant defense by acting as a co-factor to the TGA TFs (Zhang et al., 1999; Kesarwani et al., 2007). TGA TFs are a conserved family of basic-leucine-zipper proteins found in plants. TGA2, 3, 5, 6, and 7 have been shown to interact with NPR1 in *Arabidopsis*, while TGA1 interacts with NPR1 only in SA-treated leaves (Despres et al., 2003). NPR1 promotes the binding of TGA TFs to the *as-1* element in the promoter region of the *PR1* gene to induce *PR1* expression (Despres et al., 2000; Johnson et al., 2003).

In contrast to NPR1, which is essential for SA signaling, NPR3 and NPR4 function as negative regulators of plant defense (Zhang et al., 2006b). Both NPR3 and NPR4 are able to bind SA and have been identified as SA receptors (Fu et al., 2012). NPR1 was also found to bind SA (Wu et al., 2012; Manohar et al.,

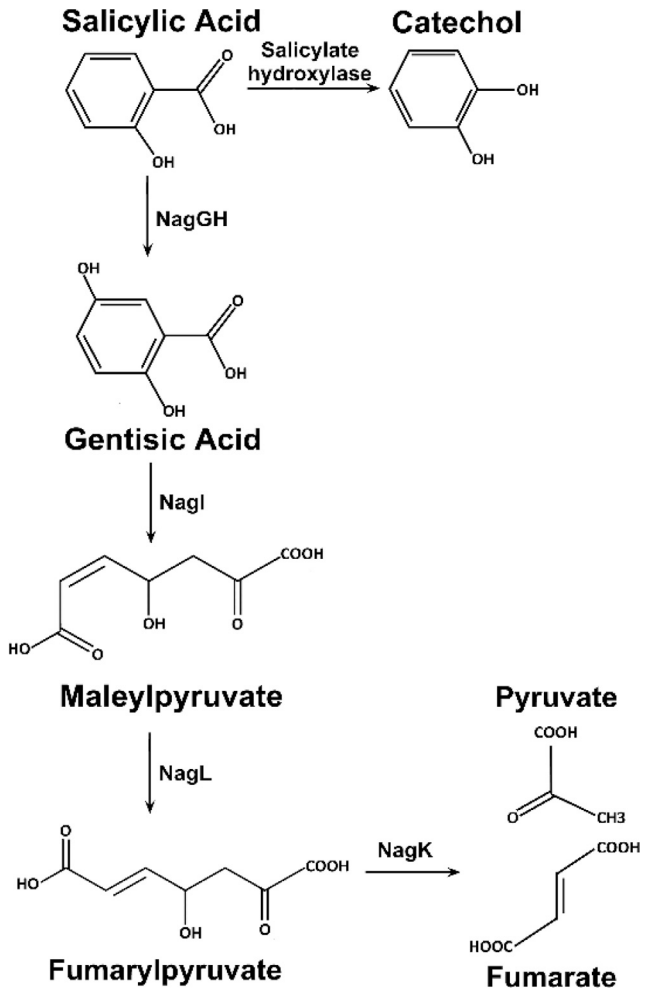

Figure 1. Degradation of the Plant Hormone Salicylic Acid (SA) by Salicylate Hydroxylase and the Nag Pathway.
Salicylate hydroxylase converts SA into catechol, which is incapable of activating plant defense. The Nag pathway degrades SA to the phenolic intermediate gentisic acid, then to maleylpyruvate, fumarylpyruvate, and finally into pyruvate and fumarate, all of which are inactive for plant defense signal transduction and not toxic or only slightly toxic to the plant bacterial pathogen *Ralstonia solanacearum*.

2014; Ding et al., 2018) and function as an SA receptor (Wu et al., 2012; Ding et al., 2018). Fu et al. (2012) found that NPR3 and NPR4, which are BTB domain-containing proteins, function as adaptors for cullin3 E3 ligase and mediate the degradation of NPR1 in order to maintain the optimal level of NPR1 during plant defense, while Ding et al. claimed that NPR3 and NPR4 function independently of NPR1 to regulate SA-induced immune responses (Fu et al., 2012; Ding et al., 2018). Ding et al. proposed that instead of controlling NPR1 stability as proposed by Fu et al. (2012), SA inhibits the repression activity of NPR3 and NPR4 by blocking their C-terminal repression domains (Ding et al., 2018). However, the disease phenotype of *npr34* double mutant appears dependent on NPR1, because two independent studies have shown that the bacterial growth on *npr134* triple mutant plants is at least 10-fold higher than that on *npr34* double mutant plants (Zhang et al., 2006b; Fu et al., 2012). In addition, it has also been found that NPR3 and NPR4 function as cullin3 adaptors to facilitate the degradation of JAZs in an SA-dependent manner to promote ETI (Liu et al., 2016).

The Mediator subunits constitute an evolutionarily conserved component of the transcriptional machinery in all eukaryotic cells that relays regulatory signals to the transcriptional machinery by connecting TFs and RNA polymerase II. The Mediator complex is composed of 25–30 subunits, which are organized into three core modules, named the head, middle, and tail (Guglielmi et al., 2004; Chadick and Asturias, 2005). The Mediator complex fine-tunes transcription through transcriptional activation or repression, depending on its interacting protein components (Conaway and Conaway, 2011). The MED14/SWP mediator subunit was initially found to control cell proliferation (Autran et al., 2002), but has recently been shown to be involved in SA-mediated resistance against *Pst* DC3000 through regulating the expression of *NPR1*, *EDS1*, *PAD4*, *ICS1*, *EDS5*, *NIMIN2*, *WRKY38*, *WRKY62,* as well as several other SAR genes (Zhang et al., 2013). The MED16/SFR16 subunit plays an essential role in SAR, serving as a positive regulator of both SA-induced plant immunity against the biotrophic bacterial pathogen *P. syringae* and JA-mediated plant defense against the necrotrophic fungal pathogens *Botrytis cinerea* and *Alternaria brassicicola* (Zhang et al., 2012, 2013). MED15/NRB4 is involved in the SA-mediated response and functions downstream of NPR1 (Canet et al., 2012).

PLANT PATHOGENS EVOLVED THREE MAJOR STRATEGIES FOR DISRUPTING SA-MEDIATED DEFENSE

SA-mediated defense is not infallible. There are many ways plant pathogens overcome this robust defense mechanism. The SAR disrupting tactics deployed by the pathogens studied so far can be categorized into three main strategies: (1) to directly lower SA accumulation by converting SA to inactive derivatives, (2) to interrupt SA biosynthesis by targeting specific pathways, and (3) to interfere with SA signaling.

Reducing SA Accumulation

Degradation of SA by SA Hydroxylase

SA hydroxylase degrades SA into catechol, which is not capable of activating plant defense (Figure 1). Several plant pathogens have been found to carry an SA hydroxylase. For example, the biotrophic tumor-inducing fungus *Ustilago maydis* carries three putative SA hydroxylase genes, *um05230*, *um03408*, and *um05967*, which are induced during pathogenic development (Rabe et al., 2013). One of the three proteins, Um05230, has been shown to be an active SA hydroxylase, and is required for the growth of *U. maydis* on SA-containing plates. Huanglongbing (HLB), otherwise known as citrus greening disease, causes widespread devastation of citrus crops. The citrus greening bacterial pathogen *Candidatus* Liberibacter asiaticus may suppress plant defense by employing an active salicylate hydroxylase, thus halting SA accumulation and HR and allowing the pathogen to overcome the host defense (Li et al., 2017). The *NahG* gene, encoding an SA hydrolase from the soil bacterium *Pseudomonas putida*, has been ectopically expressed in *Arabidopsis* and tobacco plants, and the resulting transgenic plants have a dramatically reduced SA level and are

highly susceptible to biotrophic and semi-biotrophic pathogens (Gaffney et al., 1993; Delaney et al., 1994).

Degradation of SA by Ralstonia solanacearum *through the Nag Pathway*

The bacterial pathogen *Ralstonia solanacearum*, which causes tomato wilt disease, is able to degrade SA into gentisic acid via the Nag pathway (Lowe-Power et al., 2016) (Figure 1). This process involves the activation of the *NagGH* and *NagAaAb* genes by SA. Gentisic acid was found to be 10 times less toxic to *R. solanacearum* compared with SA, thus allowing the pathogen to infect and spread in the host plant. The Nag pathway continues to break down SA further into maleylpyruvate, then fumarylpyruvate, and lastly into pyruvate and fumarate, all of which are inactive for plant defense signal transduction and not toxic or only slightly toxic to *R. solanacearum* (Lowe-Power et al., 2016). Thus, degradation of SA by the Nag pathway contributes to the fitness and pathogenicity of *R. solanacearum* in infected tomato plants.

Besides SA hydroxylases and the Nag pathway, it is possible that plant pathogens have evolved other unknown mechanisms to degrade SA. A deeper understanding of the mode of action of SA hydroxylase and the Nag pathway may help with the design of potent inhibitors that may prevent the degradation of SA by plant pathogens and potentially be used to control plant diseases.

Disruption of SA Biosynthesis

Disruption of SA Biosynthesis by Fungal and Oomycete Isochorismatases

As introduced above, isochorismate functions as a necessary intermediate in SA biosynthesis. Several fungal and oomycete pathogens have evolved the ability to secrete isochorismatases (ISCs) into host cells; these ISCs convert isochorismate into 2,3-dihydro-2,3-dihydroxybenzoate, thus decreasing SA accumulation (Figure 2). For example, the Pslsc1 effector secreted by the soybean oomycete pathogen *Phytophthora sojae* and the VdIsc1 effector secreted by the cotton vascular wilt fungus *Verticillium dahlia* show similarities to known ISC enzymes in their primary and secondary structures (Liu et al., 2014). Up- or downregulation of the expression of these effectors can substantially increase or decrease the virulence of fungal and oomycete pathogens. Overexpression of these genes in plants reduces the SA level, and purified proteins from *Nicotiana benthamiana* leaves catalyze the hydrolysis of isochorismate *in vitro*. These data strongly support the idea that these isochorismatase effectors are essential for virulence of fungal and oomycete pathogens because they destroy the SA precursor isochorismate and prevent SA accumulation in host cells, thereby disrupting plant defense and enhancing pathogen growth.

Interruption of SA Biosynthesis by Fungal Chorismate Mutase Cmu1

Chorismate mutase 1 (Cmu1) is an enzyme secreted by *U. maydis* during its infection of maize. Secreted Cmu1 competes with host plants for the substrate chorismate in the cytosol, and degrades it into prephenate, thus limiting the biosynthesis and accumulation of SA and subsequent SA signaling (Figure 2) (Rabe et al., 2013). *U. maydis* also produces an SA hydroxylase, which breaks down SA, with the resultant metabolites used as a carbon source (Rabe et al., 2013). Clearly, *U. maydis* uses different and complementary strategies to manipulate the host cell SA level to not only disable SAR but also gain essential nutrients for its growth.

Suppression of SA Biosynthesis in the Chloroplast by a Bacterial Type III Effector

The plant bacterial pathogen *P. syringae* pv. *maculicola* ES436 secretes the type III effector HopI1 through the type III secretion system (T3SS). Once it is delivered into plant cells, HopI1 enters the chloroplast, where SA is synthesized upon pathogen infection (Jelenska et al., 2007, 2010) (Figure 2). All pathogenic *P. syringae* strains have a HopI1 allele. Transgenic expression of *HopI1* in plants decreases the level of SA-inducible *PR1* gene expression and total SA level (Jelenska et al., 2007, 2010). HopI1 has a J domain in the C terminus, which is necessary for HopI1-mediated remodeling of the chloroplast thylakoid structure, and HopI1 binds to the host protein Hsp70 and alters its function. Because Hsp70 has multiple roles in folding newly synthesized proteins (Kelley, 1998; Hohfeld et al., 2001; Riordan et al., 2005), repairing improperly folded proteins, and degrading damaged proteins, it has been hypothesized that binding of Hsp70 by HopI1 in the chloroplast may disrupt the correct folding of important defense factors, including the enzymes involved in SA biosynthesis (Jelenska et al., 2007, 2010). Structural and further biochemical studies will likely help unravel the underlying molecular mechanism.

Interference with SA Signaling

In addition to reducing SA accumulation and inhibiting SA biosynthesis, plant pathogens also release toxins and effectors that interfere with SA signaling in order to suppress SA-mediated plant defense.

Disruption of SA Signaling by Coronatine

Not only do plants effectively respond to biotrophic and semi-biotrophic pathogens through the SA pathway, they also employ transcriptional reprogramming through the JA pathway when they are challenged with necrotrophic pathogens, herbivores, or parasites (Lorenzo and Solano, 2005; Birkenbihl and Somssich, 2011). JAZ proteins are considered as the on/off switch for the JA pathway (Lorenzo and Solano, 2005; Pieterse et al., 2012). In the absence of stress, there is an absence of JA in the plant, which allows JAZ proteins to bind to and inhibit the MYC2 TF; however, when plants experience stress from necrotrophic pathogens, herbivores, or parasites, the JA level rises in response. Isoleucine JA, which is the active form of JA, functions as a molecular glue promoting the interaction between JAZ proteins and the JA receptor COI1. COI1, an F-box protein and an adaptor for Cullin1 E3 ligase, then targets JAZ proteins to cullin3 E3 ligase for poly-ubiquitination and the 26S proteasome for subsequent degradation, which allows MYC2 to carry out downstream transcriptional reprogramming to initiate the stress response (Turner et al., 2002). However, studies have shown that activation of the JA pathway antagonizes SA signaling and function (Grant; Lamb, 2006).

The bacterial pathogen *P. syringae* produces a toxin called coronatine (COR), which can mimic the function of JA, thereby disrupting SA signaling (Zheng et al., 2012). COR attaches to the COI1/JAZ co-receptor complex, which then triggers JAZ ubiquitination and degradation, stimulates the transcription of JA-dependent genes, and consequently represses SA-dependent genes (Wasternack and Hause, 2013). COR specifically

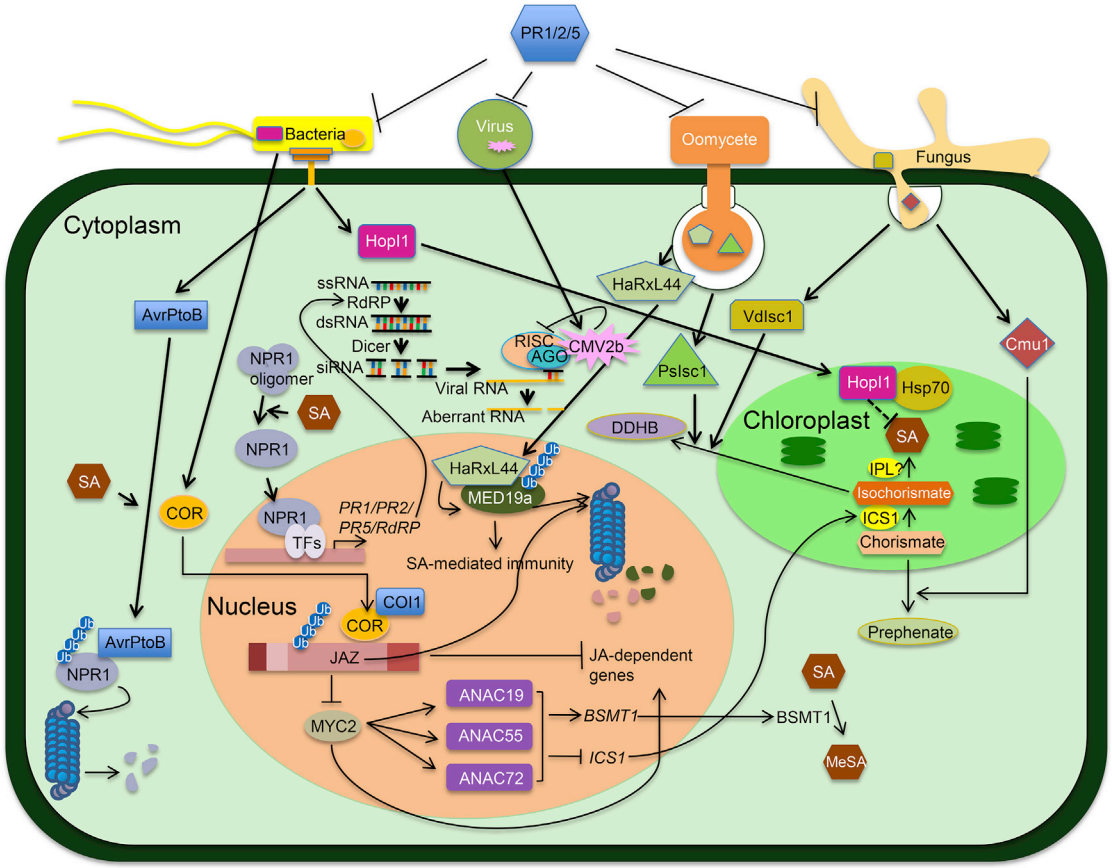

Figure 2. Disruption of Salicylic Acid (SA) Biosynthesis and Signaling by Plant Pathogens.
Upon pathogen infection, high levels of SA are produced in the chloroplast by the ICS1 (isochorismate synthesis 1) pathway in which chorismate is converted into isochorismate via ICS1. Then, SA is presumably made from isochorismate by an unidentified IPL (isochorismate pyruvate lyase). A high level of SA facilitates the reduction of oligomeric NPR1 proteins into monomers, which enter the nucleus and interact with transcription factors to facilitate the expression of *PR* (*Pathogenesis-related*) and *RdRP* (RNA-dependent RNA polymerases) genes. The PR proteins PR1, PR2, and PR5 specifically contribute to plant defense against biotrophic and semi-biotrophic pathogens. RdRPs synthesize double-stranded RNAs (dsRNAs) that are cleaved by the enzyme Dicer to produce small interfering RNAs (siRNAs), which are then assembled into the AGO (Argonaute)-containing RISC protein complex and guide the complex to viral RNA targets with complementary sequence through base-pairing interactions for destruction. Plant fungal pathogen *Verticillium dahlia* and oomycete pathogen *Phytophthora sojae* deliver the ISC (isochorismatase) effectors VdIsc1 and PsIsc1, respectively, into plant cells; these effectors decrease SA levels by directly hydrolyzing isochorismate. Cmu1, which is secreted by *Ustilago maydis*, functions as a chorismate mutase that degrades chorismate into prephenate in order to inhibit SA biosynthesis. The *Pseudomonas syringae* type III effector HopI1 is localized in the chloroplast. HopI1 interacts with Hsp70 and recruits cytoplasmic Hsp70 to the chloroplast to inhibit SA accumulation. The nuclear-localized downy mildew effector HaRxL44 interacts with and degrades the Mediator subunit 19a via the 26S proteasome to suppress SA-mediated plant defense. The viral effector CMV2b suppresses SA-induced gene silencing by interacting with AGO1 and AGO4 and inhibiting their cleavage activities in the RISC protein complex. Plant bacterial pathogen *P. syringae* pv tomato produces the coronatine (COR) toxin, which mimics the plant hormone JA, in order to promote stomatal opening and disease symptoms. COR facilitates the interaction of COI1 and JAZ, and this interaction leads to the degradation of JAZ and activation of the MYC2 transcription factor. MYC2 subsequently activates ANAC019, ANAC055, and ANAC072, which in turn repress the expression of *ICS1* and activate the expression of *BSMT1* to inhibit SA accumulation. NPR1 is the master regulator of SA-mediated local and systemic plant defense. SA promotes the interaction between the *P. syringae* type III effector AvrPtoB and NPR1. In the presence of SA, AvrPtoB, facilitates the degradation of NPR1 via the 26S proteasome dependent on AvrPtoB's E3 ligase activity to subvert plant immunity.

suppresses SA-mediated defense by triggering the binding of MYC2 to the promoters of a number of genes, including *ANAC19*, *ANAC55*, and *ANAC72* (Zheng et al., 2012). This leads to expression of three homologous NAC TFs that directly repress *ICS1* (the key gene functioning in SA biosynthesis through the ICS pathway) and activate *BSMT1* (an SA methyl transferase 1 involved in SA metabolism), leading to a reduction in SA biosynthesis and accumulation. An earlier study showed that pathogen-triggered stomata closure requires SA (Melotto et al., 2006). Therefore, inhibition of SA accumulation may prevent stomata closure, thus facilitating pathogen entry into more host cells (Melotto et al., 2006; Zheng et al., 2012).

Targeting the Master Regulator of SA Signaling by the Bacterial Type III Effector AvrPtoB

As the master regulator of SA-mediated plant defense, it is highly likely that NPR1 is a target of plant pathogen effectors. Through a genome-wide screen for *P. syringae* type III effectors that may target NPR1, AvrProB, a well-known type III effector, was found to strongly interact with NPR1 only in the presence of SA (Chen et al., 2017) (Figure 2). This interaction results in the

ubiquitination-mediated degradation of NPR1 via the host proteasome, and NPR1 degradation is dependent on the E3 ligase activity of AvrPtoB in the presence of SA. As a consequence of NPR1 degradation, many NPR1-regulated genes, including those encoding PR1 and callose synthase, are impaired by AvrPtoB during *P. syringae* infection. Thus, AvrPtoB disrupts NPR1-dependent SA signaling to favor bacterial pathogenicity. Since it has been shown that SA facilitates the reduction in the conversion of NPR1 oligomers to monomers (Mou et al., 2003), it would be interesting to investigate if AvrPtoB only targets the monomeric NPR1 protein. Besides NPR1/3/4, recent studies from Dan Klessig's group identified more than two dozen additional SA-binding proteins in plants and several SA-binding proteins in humans (Klessig et al., 2016). The second possibility is that SA binds to either or both NPR1 and AvrPtoB and causes a protein conformational change that facilitates the interaction between AvrPtoB and NPR1.

Interference of SA Signaling by the Oomycete Effector HaRxL44

HaRxL44 is a nuclear-localized effector secreted by the *Arabidopsis* downy mildew pathogen *Hyaloperonospora arabidopsidis* (*Hpa*). HaRxL44 interacts with the Mediator subunit MED19a and degrades MED19a in a proteasome-dependent manner, resulting in enhanced susceptibility to this oomycete pathogen (Caillaud et al., 2013) (Figure 2). As a positive regulator of immunity against *Hpa*, MED19a contributes to the transcriptional balance between the defense responses controlled by JA/ET and SA signaling pathways. Targeting of MED19a by HaRxL44 decreases SA-regulated gene expression but enhances JA/ET signaling, which compromises host plant defense against *Hpa* (Caillaud et al., 2013). HaRxL44 shows no sequence similarity to known plant E3 ligases, and it is likely that HaRxL44 functions as an adaptor for E3 ligases because in yeast two-hybrid screens, HaRxL44 was found to interact with two E3 ligases: BOI and MBR1-like (Caillaud et al., 2013). The next logical experiment would be to show that BOI and MBR1-like are indeed responsible for HaRxL44-mediated degradation of MED19a.

Suppression of SA-Induced Gene Silencing by Plant Viral Pathogens

Plant viral pathogens cause around a $60 billion loss in crop yields worldwide each year. Although many of the SA-induced proteins (e.g., PR proteins) have direct effects on fungal and bacterial pathogens, they are not so essential for plant resistance to viruses, and the mechanism of SA-mediated resistance to viruses is still not well understood (White, 1983; Vanhuijsduijnen et al., 1986). During viral infection, the SA pathway and the small interfering RNA (siRNA) antiviral pathway are activated to antagonize the virus. SA accumulation and signaling are elevated in many incompatible plant–virus interactions, leading to multiple resistance responses at both the inoculated and systemic sites in resistant plants (Jovel et al., 2011; Baebler et al., 2014). SA can reduce virus replication and coat protein accumulation, as well as systemic movement (Chivasa et al., 1997). Plants deficient in SA accumulation, such as the *eds5* mutant and the *NahG* transgenic lines, are highly susceptible to viral infection, showing severe virus accumulation and systemic movement (Ji and Ding, 2001; Takahashi et al., 2004; Huang et al., 2005; Ishihara et al., 2008; Jovel et al., 2011; Baebler et al., 2014). In compatible plant–virus interactions, exogenous application of SA or overexpression of SA biosynthetic genes can enhance plant resistance to viruses, as demonstrated by the reduction of virus replication and coat protein accumulation and the inhibition of systemic virus movement in plants (Chivasa et al., 1997; Mayers et al., 2005; Ishihara et al., 2008; Peng et al., 2013). Furthermore, SA has been found to enhance RNA silencing-mediated antiviral resistance in *Arabidopsis* and tobacco plants (Alamillo et al., 2006). SA induces the expression of RNA-dependent RNA polymerase (*RdRP*) genes (Figure 2). RdRPs synthesize double-stranded RNAs (dsRNAs) that are cleaved by the enzyme Dicer to produce small interfering RNAs (siRNAs. These siRNAs then bind to the AGO (Argonaute)-containing RISC protein complex to guide the complex to complementary viral RNA genome targets for sequence-specific degradation (Figure 2) (Duan et al., 2012; Fang et al., 2016). *AtRdRP1* and its homolog in tobacco, *NtRdRP1*/*NdRdRP1*, have been shown to be essential for virus-induced gene silencing in *Arabidopsis* and tobacco (Yu et al., 2003; Yang et al., 2004).

As a counter strategy, viruses have evolved mechanisms to inhibit RNA silencing induced by SA. For example, plant potyviruses encode an RNA silencing suppressor, the helper-component proteinase (HcPro). In *HcPro* overexpressing transgenic lines, SA-mediated defense was turned down, and the level of *Plum Pox Virus* (PPV)-derived siRNAs was lowered upon PPV infection (Alamillo et al., 2006). Interestingly, a recent study showed that HC Pro interacts with the SA-binding protein SABP3, which compromises the function of SABP3 in the induction of SA accumulation and SAR and the restriction of viral spread and accumulation in the host (Slaymaker et al., 2002). The *Cucumber mosaic virus* (CMV) 2b protein was found to suppress post-transcriptional gene silencing (PTGS) and the miRNA pathway in *Arabidopsis* (Zhang et al., 2006a). The CMV2b protein physically interacts with AGO1 and AGO4 and inhibits their slicer activities, which in turn results in compromised RNA silencing and host defense response (Zhang et al., 2006a; Hamera et al., 2012). Furthermore, expression of CMV2b significantly reduces the inhibitory effect of SA on virus proliferation in local and systemic tissues, indicating that SA probably induces virus resistance by promoting VIGS (virus-induced gene silencing) (Chivasa et al., 1997; Chivasa and Carr, 1998; Ji and Ding, 2001).

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Plant pathogens deploy three major strategies to disrupt SA-mediated plant defense, highlighting the importance of the suppression of SA-mediated immunity in plant pathogenesis. Knowledge gained from these studies can be potentially used to design effective strategies to control plant diseases by preventing the suppression of SA-mediated plant defense. Regarding the degradation of SA by pathogens, a potentially useful approach is to identify active SA analogs that are not degraded by plant pathogen-encoded SA hydrolases. Several SA analogs including 3-chlorosalicylic acid, 4-chlorosalicylic acid, and 5-chlorosalicylic acid have been demonstrated to be potent in activating plant defense against plant viral pathogens (Conrath et al., 1995; Knoth et al., 2009; Cui et al., 2014). The active SA analogs INA and BTH, which are competent to turn on SA-mediated plant defense, cannot be degraded by the SA hydroxylases from the soil bacterium *P. putida* and the citrus greening

pathogen (Fu et al., 2012; Li et al., 2017). However, further efforts are needed to select additional SA analogs that can resist degradation by diverse pathogens because the complex structure of BTH makes it very expensive to synthesize, and INA has been shown to have toxic side effects on plants (Bektas and Eulgem, 2014). To alleviate the binding and inhibition of SA biosynthesis enzymes and signaling components by pathogen effectors, highly specific and effective genome editing methods, such as the CRISPR-Cas9 system, can be employed to change or remove the effector interaction or effector post-translational modification sites on NPR1 or MED19a to prevent these important immune regulators from being targeted by plant pathogens.

Central to SA signaling and SAR is the NPR1 protein. In *Arabidopsis*, NPR1 regulates the expression of over 2000 genes (Wang et al., 2006). In addition to the well-known *PR* genes, NPR1 also positively regulates the expression of important MTI genes, including two callose synthesis genes, MTI marker genes, and genes functioning in the RNA silencing pathway (Pieterse and Van Loon, 2004; Dong et al., 2008; Chen et al., 2017). As a transcriptional co-activator, NPR1 likely interacts with a diverse set of TFs, thereby regulating the expression of cognate defense-related genes. NPR1 is functionally equivalent to NF-kappaB in the mammalian system. In mammalian cells, it was reported that several type III effectors, including PipA, GtgA, GogA, NelB, IpaH4.5, and YopJ, interfere with the functions of NF-kappaB in order to cause disease (Zhou et al., 2005; Gao et al., 2013; Wang et al., 2013; Sun et al., 2016). In addition, many proteins from animal viral pathogens, including oncogenic viruses, have been shown to target the mammalian NF-kappaB pathway (Sun and Cesarman, 2011). Importantly, it remains to be determined if any plant viral pathogens target NPR1-dependent plant immunity. Given the crucial role of NPR1 in plant immunity, we speculate that NPR1 and its interacting proteins may be important targets of plant pathogen effectors in the suppression of SA-mediated immunity. The diverse mechanisms used by mammalian pathogens could shed light on how plant pathogens suppress the function of NPR1. The finding that the type III effector AvrPtoB targets NPR1 for degradation provides direct evidence for this proposition (Chen et al., 2017). Recently, it has been shown that the *P. syringae* type III effector HopD1 targets the TF NTL9, and another *P. syringae* effector HopBB1 interacts with and mediates the degradation of TCP TF TCP14 (Block et al., 2014; Yang et al., 2017). TCP8, TCP14, and TCP15 interact with NPR1 to regulate plant defense gene expression (Li et al., 2018). Therefore, targeting of NPR1-interacting TFs or TFs downstream of NPR1 may be used by many other pathogen effectors, which require further investigations.

In addition to NPR1, other important players in SA-mediated plant defense, including EDS1, PBS3, PAD4, NDR1, ACD6, EPS1, and ICS1, can also be potentially targeted by plant pathogens to suppress SA-mediated plant immunity. These proteins are believed to function upstream of NPR1. PBS3 is also called WIN3 (HOPW1-1-INTERACTING3) because it interacts with the *P. syringae* type III effector HopW1 (Wang et al., 2011). However, it is still not known how HopW1 may modify and affect the biological function of WIN3/PBS3. The *P. syringae* type III effectors AvrRps4 and HopA1 have been shown to interact with EDS1, and one study proposed that they function to disrupt the formation of the EDS1 and RPS4 as well as EDS1 and SRFR1 protein complexes, respectively (Bhattacharjee et al., 2011). However, in another study it was proposed that the function of AvrRps4 is to trigger cell death-independent plant defense through the coordinate actions of EDS-RPS4 protein complexes in the cytoplasm and in the nucleus (Heidrich et al., 2011).

PR1 members are well-known marker genes for SA-mediated plant defense (van Loon, 1975; van Loon et al., 2006). Recently, progress has been made toward understanding the role of PR1 in disease resistance. It was demonstrated that PR1posesses the sterol binding activity, suggesting a direct anti-microbial function (Gamir et al., 2017). In addition, the identification of PR-1-RLKs genes, which encode extracellular PR-1 domains fused with transmembrane and kinase domains, in cocoa suggests a potential role of PR1 proteins in sterol sensing and effector recognition (Teixeira et al., 2013; Lu et al., 2017). Strikingly, the CAPE1 peptide derived from the C-terminal PR1b protein in tomato was proposed to be a DAMP (damage-associated molecular pattern) signal for the induction of plant immunity (Chen et al., 2014). This finding raises several questions. Is there a CAPE receptor that perceives the CAPE1 peptide? How is the CAPE1 peptide cleaved from the PR-1 protein? Is there a protease that participates in the cleavage of PR1 protein to produce the CAPE1 peptide? Plant proteases play a role in basal and induced defense responses in the apoplastic space in many plant species (Tian et al., 2007; Shabab et al., 2008; Song et al., 2009; Kaschani et al., 2010; Bozkurt et al., 2011). Recently, an immune signaling peptide, Zip1 (*Zea mays* immune signaling peptide 1), which is produced after SA treatment, was identified in maize. Zip1 is cleaved from its precursor protein by papain-like cysteine proteases in the apoplast, and Zip1 treatment promotes SA accumulation in maize leaves and resistance to the fungus *U. maydis* (Ziemann et al., 2018). As a countermeasure against proteases, plant pathogens have evolved protease inhibitor effectors targeting host proteases and promoting pathogenesis (Tian et al., 2009). Avr2, secreted by *Cladosporium fulvum*, inhibits the tomato apoplastic cysteine proteases Rcr3 and Pip1 to support pathogen growth in the apoplast (Tian et al., 2007; Shabab et al., 2008; Song et al., 2009).

Recently, it was reported that an effector, ToxA, first discovered in the necrotrophic pathogen wheat tan spot fungus *Pyrenophora tritici-repentis*, interacts with the wheat pathogenesis-related PR-1-5 protein (TaPR-1-5) (Lu et al., 2014). Subsequent mutational analysis identified several residues in both ToxA and TaPR-1-5 that are required for this interaction, as well as for the induction of necrosis (Lu et al., 2014). Another study reported that the SnTox3 effector interacts with the wheat TaPR-1-1 protein. A signaling peptide derived from the C terminus of TaPR-1-1, known as CAPE1, enhanced the infection of wheat by *P. nodorum* in a SnTox3-dependent manner, but played no role in ToxA-mediated virulence (Breen et al., 2016). It is commonly believed that SA plays an important role in plant defense against biotrophic and semi-biotrophic pathogens. The ToxA and SnTox3 effectors may provide novel opportunities for examining the role of SA signaling in plant response to necrotrophic pathogens.

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