**REVIEW**

**Intervention of Phytohormone Pathways by Pathogen Effectors**

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The constant struggle between plants and microbes has driven the evolution of multiple defense strategies in the host as well as offense strategies in the pathogen. To defend themselves from pathogen attack, plants often rely on elaborate signaling networks regulated by phytohormones. In turn, pathogens have adopted innovative strategies to manipulate phytohormone-regulated defenses. Tactics frequently employed by plant pathogens involve hijacking, evading, or disrupting hormone signaling pathways and/or crosstalk. As reviewed here, this is achieved mechanistically via pathogen-derived molecules known as effectors, which target phytohormone receptors, transcriptional activators and repressors, and other components of phytohormone signaling in the host plant. Herbivores and sap-sucking insects employ obligate pathogens such as viruses, phytoplasma, or symbiotic bacteria to intervene with phytohormone-regulated defenses. Overall, an improved understanding of phytohormone intervention strategies employed by pests and pathogens during their interactions with plants will ultimately lead to the development of new crop protection strategies.

**INTRODUCTION**

Plants possess an innate immune system typified by complex defense responses activated upon pathogen detection, which has evolved over millions of years in parallel with the evolution of virulence mechanisms in pathogenic microbes. Membrane proteins such as receptor-like kinases, collectively known as pattern recognition receptors (PRRs), play essential roles in detecting microbe-derived conserved molecules known as microbe-associated molecular patterns (MAMPs). The current paradigm of plant immunity proposes that host defenses of increasing amplitude and specificity are pitted against counterattacks by pathogens (Jones and Dangl, 2006) (Figure 1). MAMP detection initiates basal and broad-spectrum defenses effective in stopping the invasion by most potential pathogens in a process termed pattern-triggered immunity (PTI). In return, pathogens have evolved molecules collectively known as “effectors” that can be used to overcome PTI by interfering with MAMP detection and/or subsequent defense signaling. To directly or indirectly detect pathogen effectors, plants have coevolved a large number of resistance (R) genes, often encoding intercellular proteins (e.g., nucleotide binding domain leucine-rich repeat containing receptors) (Jones and Dangl, 2006). In resistant or immune hosts, effectors alert the plant to the presence of pathogens, resulting in R protein–mediated defense that inhibits pathogen invasion. This phenomenon is known as effector-triggered immunity or ETI. In susceptible interactions, pathogens may either fail to trigger ETI in the host or inhibit ETI via their effector arsenal and reprogram the host transcriptome, proteome, hormonome, as well as vesicle trafficking to promote pathogen virulence. This latter scenario is known as effector-triggered susceptibility (reviewed in Dodds and Rathjen, 2010; Mengiste, 2012; Xin and He, 2013).

This model, which predicts a multilayered-host defense system, applies particularly well to the interaction of plants with many oomycete and biotrophic and hemibiotrophic fungal and bacterial pathogens. However, for necrotrophic fungal and bacterial pathogens that produce nonspecific toxins and a large number of cell wall degrading and defense suppressing enzymes, there is often little effective resistance, suggesting that these powerful virulence functions may override PTI and ETI processes. In some cases, toxin effectors are specifically detected by host proteins, and this may lead to susceptibility rather than resistance (reviewed in Friesen et al., 2008). Thus, in addition to MAMPs, detection of damage-associated molecular patterns (e.g., elicitors released from host cells in response to cellular damage) probably plays a major role for cellular defense against necrotrophs (Mengiste, 2012). Interestingly, the type III secretion system, which is essential for effector delivery and the pathogenicity of hemibiotrophic bacteria such as *Pseudomonas syringae* (Büttner and He, 2009; Xin and He, 2013), does not seem to be required for the virulence of necrotrophic bacteria such as *Pectobacteria* that cause soft rot disease in many plant species (Davidsson et al., 2013).

The ability to distinguish friends from foes is another intriguing feature of the plant’s innate immune system, given that both pathogenic and symbiotic microbes contain conserved MAMPs (reviewed in Zamioudis and Pieterse, 2012). Emerging evidence suggests that both the host and the microbe play critical roles in plant–beneficial microbe interactions. An initial host defense
response instigated against a “foreign” or potentially pathogenic microbe can be swiftly suppressed by the beneficial microorganism (Maunoury et al., 2010). Certain beneficial bacteria (e.g., rhizobacteria) have evolved mutations in MAMPs (e.g., bacterial flagellin), which allow them to evade detection by the plant surveillance system (Lopez-Gomez et al., 2012; Trdá et al., 2014). The ability of plants to sense pathogen-mediated cellular damage via host-derived damage-associated molecular patterns (Mengiste, 2012) can also be important to distinguish pathogenic microbes from the symbiotic ones.

In contrast to vertebrates, plants do not possess adaptive immunity, which is acquired through exposure to microbes or microbial derivatives during the lifetime of an individual. However, exposure to microbes acts on the plant innate immune system to generate a “working memory” known as systemic acquired resistance (SAR) (reviewed in Netea et al., 2011). SAR provides a broad-spectrum and long-lasting resistance to multiple pathogens in tissues not directly exposed to pathogens (Durrant and Dong, 2004). Remarkably, memories of microbial exposure can also be transmitted to the next generation (Luna et al., 2012; Slaughter et al., 2012). Epigenetic processes such as DNA methylation and chromatin modifications seem to play prominent roles in this phenomenon known as “transgenerational immunity” (Holeski et al., 2012).

**INTERVENTION OF PHYTOHORMONE PATHWAYS: A UNIVERSAL STRATEGY ADOPTED BY PATHOGENS**

The activation of complex phytohormone signaling networks is a universal defense response employed by plants (Schenk et al., 2000). In particular, essential defensive roles of primary defense hormones, jasmonates (JAs), salicylates (SAs), and ethylene (ET), have been well established. Other phytohormones, such as abscisic acid (ABA), auxins (indole-3-acetic acid [IAA]), cytokinins (CKs), brassinosteroids (BRs), gibberellins (GA), and strigolactones, which are better known for their roles in stress tolerance or plant growth and development, also regulate plant defense, either alone or in conjunction with the primary defense hormones (Figure 2) (Robert-Seilaniantz et al., 2011; Torres-Vera et al., 2014). Therefore, it is not surprising that pathogens have developed capabilities to manipulate or subvert plant phytohormone signaling pathways for their benefit.

From a mechanistic point of view, pathogen-mediated phytohormone intervention strategies can be grouped into a few broad categories. First, suppression or evasion of host phytohormone biosynthesis and/or signaling pathways involved in pathogen resistance appears to be a common tactic employed by multiple pathogens. Various pathogens also manipulate phytohormone signaling pathways to alter the plant host's essential developmental and/or physiological features, such as stomatal opening and senescence that facilitate pathogen entry and disease symptom development, respectively (Melotto et al.,...
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2008; Kazan and Manners, 2009). In other instances, pathogens take advantage of phytohormone crosstalk to promote disease development (Figure 2). As discussed below, pathogen-mediated activation of a phytohormone signaling pathway that promotes disease by suppressing another phytohormone pathway that confers resistance is a typical example of this latter phenomenon (Kazan and Manners, 2009, 2012; Xin and He, 2013).

The lifestyle of a pathogen often dictates the type of phytohormone intervention strategy adopted. Activation of a phytohormone signaling pathway that negatively regulates cell death and senescence can be beneficial for biotrophic fungal pathogens that require living host cells to complete their life cycles. In addition or alternatively, necrotrophic fungal pathogens manipulate phytohormone pathways that enable these pathogens to kill and feed on dead cells. Pathogens also exploit phytohormone crosstalk during their interaction with plants. A well-known example of phytohormone crosstalk hijacked by bacterial, viral, fungal, as well as oomycete pathogens is the mutual antagonism between the SA and the JA pathway. While the SA pathway often confers resistance to biotrophic pathogens, activation of this pathway attenuates JA signaling, thereby compromising resistance to necrotrophic pathogens; vice versa, the activation of JA pathway enhances resistance to some necrotrophs but inhibits the SA pathway and resistance to biotrophic pathogens (reviewed in Thaler et al., 2012). Pathogens also use “phytohormone mimics,” molecules that structurally and/or functionally resemble phytohormones or phytohormone signaling components, to trick the host into behaving inappropriately. Forceful opening of stomata by coronatine (COR), a bacterial toxin and JA mimic, is a typical example of this phenomenon (Melotto et al., 2006; Lee et al., 2013) (Table 1). Most developmental alterations (e.g., stunting, elongation, and flowering time) observed in infected plants can often be explained by pathogen-mediated alterations in host’s hormone homeostasis and/or signaling.

Over recent years, significant progress has been made to understand the mechanistic basis of pathogen-mediated phytohormone intervention strategies. In this review, we present an overview of diverse tactics used by pathogens via their effector arsenal. We use the term effector, which is often defined as a low molecular weight and cysteine-rich protein secreted by pathogens during their interaction with plants, broadly to refer to both proteinaceous and nonproteinaceous (e.g., toxins and nucleic acids) pathogen-derived molecules that render the host environment conducive to infection. Many pathogens are capable of producing a wide range of compounds that can act as phytohormone mimics during pathogenesis (Inomata et al., 2004). Pathogen-derived phytohormones are often synthesized through biochemical pathways different from those in plants, suggesting that microbes and plants have evolved phytohormone biosynthesis pathways independently. In this review, we consider pathogen-derived hormone mimics as well as proteins

<table>
<thead>
<tr>
<th>Type III Effector</th>
<th>Function</th>
<th>Reference</th>
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<tbody>
<tr>
<td>AvrRpt2 (cysteine protease)</td>
<td>Alters auxin physiology through AUX/IAA degradation</td>
<td>Chen et al. (2007); Cui et al. (2013)</td>
</tr>
<tr>
<td>AvrB (kinase)</td>
<td>Activates JA signaling through MPK4, HSP90, and RIN4</td>
<td>Shang et al. (2006); Cui et al. (2010)</td>
</tr>
<tr>
<td>HopZ1a (cysteine protease/acyltransferase)</td>
<td>Activates JA signaling by degrading JAZ repressors</td>
<td>Jiang et al. (2013)</td>
</tr>
<tr>
<td>HopX1 (cysteine protease)</td>
<td>Activates JA signaling by interacting with JAZ repressors and promoting their degradation</td>
<td>Gimenez-Ibanez et al. (2014)</td>
</tr>
<tr>
<td>Coronatine (toxin)</td>
<td>Activates JA signaling through interaction with the JA receptor COI1</td>
<td>Katsir et al. (2008); Geng et al. (2012)</td>
</tr>
<tr>
<td>Syringolin A (toxin)</td>
<td>Suppresses SA defense</td>
<td>Groll et al. (2008); Misas-Villamil et al. (2013)</td>
</tr>
<tr>
<td>AvrPto and AvrPtoB</td>
<td>Elevate ABA levels to antagonize SA signaling</td>
<td>de Torres et al. (2006); de Torres-Zabala et al. (2007)</td>
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<td></td>
<td>Promote ethylene signaling and biosynthesis</td>
<td>Cohn and Martin (2005)</td>
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<td></td>
<td>Target brassinosteroid receptor BAK1</td>
<td>Cheng et al. (2011); Shan et al. (2008)</td>
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<tr>
<td>HopF2</td>
<td>Targets BAK1 (currently no direct evidence that it disrupts BR signaling)</td>
<td>Zhou et al. (2014)</td>
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<tr>
<td>HopAM1</td>
<td>Promotes ABA signaling</td>
<td>Goel et al. (2008)</td>
</tr>
<tr>
<td>HopM1</td>
<td>Suppresses SA defense</td>
<td>DebRoy et al. (2004); Geng et al. (2012); Nomura et al. (2011)</td>
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<tr>
<td>HopQ1</td>
<td>Alters auxin efflux</td>
<td>Nomura et al. (2006) (2011)</td>
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<td>AvrE</td>
<td>Activates cytokinin pathway to suppress FLS2-mediated defense signaling</td>
<td>Hann et al. (2014)</td>
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<tr>
<td>AvrE</td>
<td>Suppresses SA-dependent callose response</td>
<td>DebRoy et al. (2004)</td>
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Please note that these effectors may overcome host defense in several different ways, but only roles relevant to hormone manipulation are shown for the effectors discussed in the text.
produced by intracellular pathogens such as viruses using the host-translation machinery as effectors. We will focus mostly on relatively recent and mechanistically better described examples where specific roles of pathogen effectors in phytohormone intervention have been demonstrated.

**EFFECTOR-MEDIATED MANIPULATION OF THE SA PATHWAY**

The importance of the SA pathway as a regulator of plant defense in plants is well established (reviewed in An and Mou, 2011; Pajerowska-Mukhtar et al., 2013). SA is required for both local and systemic immunity against a wide range of pathogens. Indeed, the removal of endogenous SA through transgenic expression of the bacterial salicylate hydroxylase (NahG) enzyme renders the plants susceptible to bacterial, fungal, and viral pathogens (Gaffney et al., 1993; Reuber et al., 1998). Furthermore, SA induction-deficient (sid) mutants, which lack the iso-chorismate synthase gene involved in SA synthesis, fail to induce SA upon pathogen challenge and are more susceptible to bacterial and fungal pathogens (Nawrath and Métraux, 1999; Wildermuth et al., 2001). SA is required for the activation of genes encoding pathogenesis-related (PR) proteins such as PR1. SA also potentiates the hypersensitive response triggered when pathogen effectors are directly or indirectly detected by R proteins (Brodersen et al., 2005; Raffaele et al., 2006). Given the central importance of SA for host defense, it is not surprising that pathogens have developed innovative strategies to attenuate biosynthesis and/or signaling of this important phytohormone.

**Effectors Targeting SA Biosynthesis**

In Arabidopsis thaliana, SA is synthesized in the plastid from chorismate via the isochorismate pathway and in the cytosol through the phenylalanine ammonia-lyase pathway. Of these two pathways, the isochorismate pathway is the predominant source of both basal and pathogen-induced SA production (reviewed in Dempsey et al., 2011). The SA pathway is known to confer resistance to the bacterial pathogen P. syringae. To facilitate colonization of its host, P. syringae injects multiple effector proteins into host cells via its type III secretion system (Xin and He, 2013). Hop1, one of the type III P. syringae effectors, interferes with SA accumulation in Arabidopsis during disease development (Table 1). Hop1 is targeted to chloroplasts where it presumably interferes with the plastid-specific SA biosynthesis pathway. Arabidopsis plants expressing Hop1 show significantly reduced levels of both SA levels and PR gene expression, as well as altered chloroplast thylakoid membranes. Hop1 directly binds to and disrupts the activity of HSP70 (HEAT SHOCK PROTEIN70) in chloroplasts, which may be required for the assembly of components required for SA biosynthesis (Jelenska et al., 2007, 2010). However, the precise mechanism by which Hop1 attenuates SA biosynthesis is currently unclear.

The biotrophic fungus Ustilago maydis causes smut disease in maize (Zea mays) plants by U. maydis, interferes with the SA pathway during disease development. Cmu1 encodes a chorismate mutase, an isomerase enzyme that converts SA precursor chorismate to prephenate (Djamei et al., 2011). Transgenic strains of U. maydis lacking Cmu1 trigger increased SA accumulation and show reduced virulence on maize plants (Djamei et al., 2011). Cmu1 dimerizes with and deregulates a maize chorismate mutase. This presumably alters the translocation of chorismate from plastids to cytoplasm, consequently reducing the levels of chorismate available for SA biosynthesis (Djamei et al., 2011; Djamei and Kahmann, 2012). U. maydis also contains a gene (Shy1) that encodes a cytosolic NahG-like enzyme, suggesting that this pathogen has evolved multiple effectors potentially targeting SA-regulated host defenses (Rabe et al., 2013). SA-degrading ability is also known in the necrotrophic fungal pathogen Sclerotinia sclerotiorum (Penn and Daniel, 2013). However, further research is needed to establish if such ability contributes to pathogen virulence.

**Effectors Targeting SA Signaling**

Protein ubiquitination via the 26S proteasome is intimately linked to the regulation of hormone signaling in plants (Kelley and Estelle, 2012), and plant pathogens often target this essential cellular process to subvert phytohormone signaling pathways (reviewed in Magori and Citovsky, 2011; Dudler, 2013). Syringolin A (SylA), a virulence factor and a proteasome inhibitor produced by P. syringae pv syringae, plays a role in defense suppression as evidenced by the inability of sylA mutants to inhibit SA accumulation and associated resistance responses in bean (Table 1) (Groll et al., 2008; Misas-Villamil et al., 2013). SylA reverts PPI-associated stomatal closure that is also dependent on both SA and NPR1 (NONEXPRESSOR OF PATHOGENESIS-RELATED GENES1), a master regulator of SA signaling (Figure 3) (Schellenberg et al., 2010). This facilitates enhanced entry of the pathogen into the plant cell via a mechanism that is dependent on its proteasome inhibitory activity. While sylA mutants fail to reopen stomata in inoculated Arabidopsis plants, addition of SylA or the proteasome inhibitor MG132 rescues the stomatal opening (Schellenberg et al., 2010).

The type III effector XopJ of the bacterial pathogen Xanthomonas campestris pv vesicatoria also suppresses SA-mediated defenses and the development of leaf necrosis by inhibiting proteasome activity. Pepper (Capsicum annuum) plants inoculated with XopJ-deficient X. c. pv vesicatoria strains show increased SA levels, reduced symptom development, and delayed necrosis, which can be rescued by treatment with MG132 (Üstün et al., 2013). XopJ interacts with the RPT6 (regulatory particle ATPase 6) subunit of the proteasome complex at the plasma membrane (Üstün et al., 2013), but exactly how this interaction contributes to X. c. pv vesicatoria virulence is yet to be determined. NPR1, however, appears to be required for XopJ-mediated disease symptom development (Figure 3). Thus, it has been proposed that both SylA and XopJ may interfere with the proteasome-mediated turnover of NPR1 required for activation of SA responses (discussed below) (Schellenberg et al., 2010; Üstün et al., 2013).

In addition to XopJ, X. c. pv vesicatoria suppresses the SA biosynthesis gene ICS1 (ISOCHORISME1) and host defenses through XopD, another type III effector produced by this pathogen (Canonne et al., 2011) (discussed further below in the ET section). Similar to xopJ mutants, a xopD null mutant shows
reduced growth and symptom development and increased SA levels and defense gene expression when inoculated onto tomato (*Solanum lycopersicum*). A XopD homolog from the *Arabidopsis*-infecting *X. campestris pv. vesicatoria* strain directly binds to and represses transcription of MYB30, a positive regulator of hypersensitive response and other defense responses in *Arabidopsis* (Tada et al., 2008). The 2b protein of CMV targets NPR1 to exploit SA-JA antagonism, while the CMV P6 protein interferes with the nuclear localization of NPR1 to suppress SA and activate JA signaling (Lewsey et al., 2010; Love et al., 2012). Syringolin A, a toxin and proteasome inhibitor produced by the bacterial pathogen *P. syringae pv syringae*, has been proposed to inhibit the degradation of NPR1 (Schellenberg et al., 2010), which is required for the activation of SA-mediated defenses (Soppe et al., 2009). Unrelated effectors from bacterial (e.g., *P. syringae*), viral (e.g., Geminivirus), and oomycete (e.g., *H. arabidopsidis*) pathogens interact with CSN5 (Mukhtar et al., 2011), which in turn interacts with NIMIN1 (Weigel et al., 2005), a regulatory protein and interacting partner of NPR1. See text for details.

Pathogen effectors that suppress SA signaling without affecting SA biosynthesis are also known. For example, Ha-Rxl96 and Ps-Avh163, the two RXLR secretion motif–containing effectors from the oomycete downy mildew–causing pathogen *Hyaloperonospora arabidopsidis* and root rot–causing pathogen *Phytophthora sojae*, respectively, suppress the pathogen-mediated induction of SA marker genes, including PR1, when expressed in *Arabidopsis*. Transgenic expression of these effectors also causes increased susceptibility to *H. arabidopsidis* and decreased MAMP-triggered callose deposition but does not lead to increased SA production, suggesting that these effectors act independently or downstream of the SA biosynthesis pathway (Anderson et al., 2012). Effectors in the conserved effector loci of *P. syringae*, including AvrE and hopP-toM (or HopM1), are thought to act redundantly to promote

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**Figure 3.** Effectors from Diverse Pathogens Indirectly Target NPR1, a Master Regulator of SA Signaling, to Promote Disease Development.

An exopolysaccharide produced by the necrotrophic fungus *B. cinerea* (the causative agent of the gray mold disease) activates SA signaling via a tomato NPR1 homolog to exploit the antagonistic crosstalk between SA and JA signaling (El Oirdi et al., 2011). Victorin, a toxin produced by the necrotrophic fungus *C. victoriae* (the causative agent of Victoria blight disease) indirectly targets NPR1 by binding to TRX-h5, which is required for the nuclear localization of NPR1 (Tada et al., 2008). The 2b protein of CMV targets NPR1 to exploit SA-JA antagonism, while the CMV P6 protein interferes with the nuclear localization of NPR1 to suppress SA and activate JA signaling (Lewsey et al., 2010; Love et al., 2012). Syringolin A, a toxin and proteasome inhibitor produced by the bacterial pathogen *P. syringae pv syringae*, has been proposed to inhibit the degradation of NPR1 (Schellenberg et al., 2010), which is required for the activation of SA-mediated defenses (Soppe et al., 2009). Unrelated effectors from bacterial (e.g., *P. syringae*), viral (e.g., Geminivirus), and oomycete (e.g., *H. arabidopsidis*) pathogens interact with CSN5 (Mukhtar et al., 2011), which in turn interacts with NIMIN1 (Weigel et al., 2005), a regulatory protein and interacting partner of NPR1. See text for details.
NPR1, a phytohormone signaling hub indirectly targeted by pathogen effectors

NPR1 is a key regulator of the SA pathway in Arabidopsis and is functionally conserved in diverse plant species (reviewed in Pajerowska-Mukhtar et al., 2013). NPR1 and its paralogs NPR3 and NPR4 in Arabidopsis recently have been proposed to be SA receptors (Fu et al., 2012; Wu et al., 2012). In the absence of elicitation, NPR1 is mainly sequestered in the cytoplasm as an oligomeric complex. In response to elevated SA levels triggered by pathogen challenge, NPR1 is reduced to its monomeric form and is translocated to the nucleus where it interacts with TGA-bZIP transcription factors, leading to activation of SA-dependent defense gene expression and SAR (Mou et al., 2003; Tada et al., 2008; Pajerowska-Mukhtar et al., 2013). NPR3 and NPR4, which encode proteasomal adaptor proteins, regulate proteasome-mediated turnover of NPR1 in an SA-dependent manner. In unelicited cells, NPR1-mediated defenses are kept under wraps by continuous degradation of NPR1 by NPR4. In response to increased levels of SA, NPR4-mediated turnover of NPR1 is inhibited, and this allows the activation of SAR (Fu et al., 2012). A second model of SA perception suggests that NPR1 itself binds SA, leading to the disassembly of the cytoplasmic oligomeric complex and conformational changes that allow NPR1 activation (Wu et al., 2012). NPR1 also interacts with regulatory proteins such as NIMIN1 (NIM1 INTERACTING1), which regulates SA-dependent defenses (Weigel et al., 2005). While the nuclear localization of NPR1 is required for the regulation of SA-dependent defenses, the cytoplasmic form of NPR1 plays a key role in the regulation of SA-JA antagonism (Spoel et al., 2003).

The elaborate defense-related functions performed by NPR1 make this protein an attractive effector target. Surprisingly, so far no pathogen effector directly targeting NPR1 has been reported. However, emerging evidence suggests that NPR1 function may be indirectly targeted by diverse pathogens (Figure 3). For instance, the bacterially secreted proteasome inhibitors SyA and XopM mentioned above have been proposed to inhibit the proteasome-mediated degradation of phosphorylated NPR1, thereby diminishing its cotranscriptional activity within the SA signaling pathway (Schellenberg et al., 2010; Üstün et al., 2013).

An intriguing tale of evolutionary one-upmanship involving NPR1 is the interaction of Arabidopsis with the necrotrophic fungal pathogen Cochliobolus victoriae (Figure 3). LOV1 (LOCUS ORCHESTRATING VICTORIN1) is a CC-NB-LRR (COILED-COIL-NUCLEOTIDE BINDING-LEUCINE RICH REPEAT) protein that presumably evolved as a guard protein or R protein against an unknown pathogen but has been exploited by C. victoriae to promote disease. Victorin, a mycotoxin effector produced by the fungal pathogen C. victoriae, binds to the active site of TRX-h5 (THIOREDOXIN-h5; Lorang et al., 2012), a thioredoxin implicated in pathogen and SA-mediated reduction of NPR1 oligomers to NPR1 monomers in the cytosol (Tada et al., 2008). In lov1 mutants, the TRX-h5–victorin interaction results in reduced SA-mediated defenses and increased susceptibility to the biotrophic pathogen P. syringae pv maculicola, similar to what is observed in npr1 plants. In wild-type plants, victorin-bound TRX-h5 colocalizes with LOV1 and is required for LOV1 activation. Given the importance of TRX-h5 in the reduction of NPR1 and activation of SA responses, it was proposed that TRX-h5 is guarded by LOV1 (Figure 3). However, inappropriate LOV1 activation leads to cell death, which promotes C. victoriae disease (Lorang et al., 2012, 2007).

The nuclear effector Ha-RxL44 from the oomycete downy mildew pathogen H. arabidopsidis has recently been shown to interact with the mediator subunit MED19a (MEDIATOR19a) and modulate SA-mediated immunity in Arabidopsis. The RxL44-MED19a interaction leads to the proteasome-dependent degradation of MED19a and reduced expression of SA-dependent defenses (Caillaud et al., 2013). Indeed, the Mediator complex, which fine-tunes transcription by facilitating the interaction between DNA-bound transcription factors and RNA polymerase II (reviewed in Kidd et al., 2011a), has recently emerged as a regulator of plant defense. The MED25 subunit of the Arabidopsis Mediator complex has been shown to be an interaction partner of several defense-related transcription factors such as ERF1 (ETHYLENE RESPONSE FACTOR1), ORA59 (OCTADECANOID RESPONSIVE ARABIDOPSIS AP2/ERF59), and MYC2 (Çevik et al., 2012). A few other subunits of the Mediator complex also play important roles in phytohormone-regulated expression of plant defense genes and disease resistance (Dhawan et al., 2009; Kidd et al., 2009; Canet et al., 2012; X. Zhang et al., 2012; Zhang et al., 2013; Lai et al., 2014). Effectors from animal pathogens, and in particular viruses, often target Mediator subunits to disrupt cellular homeostasis (Yamamoto et al., 2009). Given defense-related functions performed by the plant...
Mediator complex, it is expected that plant pathogens have similarly evolved strategies to target Mediator subunits to alter phytohormone pathways.

(COP9 SIGNALOSOME5), a protein targeted by diverse effectors (Mukhtar et al., 2011; discussed below), interacts with NIMIN1 and NIMIN2, which in turn interact with NPR1 (Weigel et al., 2005), suggesting that CSN5-NIMIN1 interaction may affect NPR1-regulated defense responses (Figure 3). Finally, the P6 protein of cauliflower mosaic virus inhibits SA-dependent defenses while enhancing JA-dependent defenses by affecting NPR1 function. Arabidopsis plants transgenically expressing P6 show increased susceptibility to P. syringae but increased resistance to Botrytis cinerea, which is sensitive to JA-dependent defenses. P6 is thought to act by altering the expression and localization of NPR1 (Figure 3) as P6 expressing plants accumulate high levels of NPR1 in the nucleus even in unelicited plants. Thus, it was proposed that an inactive form of NPR1 disrupts NPR1-mediated SA defense gene transcription in the presence of a pathogen that activates SA signaling (Love et al., 2012).

**EFFECTOR-MEDIATED MANIPULATION OF THE JA PATHWAY**

Plant defense responses regulated by JA promote resistance against necrotrophic pathogens and herbivorous insects (reviewed in Glazebrook, 2005; Kazan and Manners, 2008; Mengiste, 2012). JA signaling can also promote susceptibility to viruses (Oka et al., 2013) as well as biotrophic and hemibiotrophic pathogens, which have evolved effectors to hijack this pathway and to promote disease. Disruption or activation of JA signaling by such pathogens often promotes disease by exploiting JA-SA antagonism. Examples of key effectors known to target components of JA signaling are outlined in the section on SA-JA antagonism below.

**Effectors Targeting JA Signaling**

Activation of JA pathway promotes susceptibility to P. syringae in Arabidopsis. One of the P. syringae effectors involved in altering JA signaling in the host is the type III effector AvrB, a kinase-like protein that activates JA signaling (Table 1). AvrB associates with RAR1, which encodes a critical defense signaling component (Shang et al., 2006). AvrB also phosphorylates MPK4, a mitogen-activated protein kinase that acts as a positive regulator of JA signaling. An avrB mutant unable to phosphorylate MPK4 fails to induce the expression of the JA marker gene PDF1.2. Similarly, AvrB was unable to elicit PDF1.2 expression in mpk4 mutant plants, suggesting that MPK4 is required for AvrB-mediated promotion of JA signaling. AvrB also interacts with the guard protein RIN4 (RPM-INTERACTING4), which acts downstream of MPK4 to promote JA signaling (Cui et al., 2010). Finally, AvrB-mediated defense suppression seems to require the JA receptor COI1 (CORONATINE INSENSITIVE1) as overexpression of AvrB in the coi1 mutant background fails to enhance susceptibility to P. syringae (Shang et al., 2006). Thus, AvrB seems to target the JA pathway redundantly.

The JA pathway also promotes susceptibility to the root infecting hemibiotrophic fungus Fusarium oxysporum based on the analysis of Arabidopsis loss-of-function mutants coi1, myc2, and ptfl/med25, all of which show increased resistance to this pathogen (Anderson et al., 2004; Kidd et al., 2009; Thatcher et al., 2009). The F. oxysporum effector Fo-SIX4 (SECRETED IN XYLEM4) contributes to F. oxysporum disease development when transgenically expressed in Arabidopsis, whereas six4 mutants show reduced virulence on Arabidopsis (Thatcher et al., 2012a). Arabidopsis plants inoculated with six4 mutants exhibit a reduced induction of JA-responsive genes, suggesting that SIX4 promotes pathogen virulence via the host JA pathway (Thatcher et al., 2012a).

Two recent studies revealed that bioactive JAs are produced by tomato- and Arabidopsis-infecting F. oxysporum isolates (Brodhun et al., 2013; Cole et al., 2014). The tomato-infecting F. oxysporum f. sp lycopersici produces JAs using a lipooxygenase enzyme related to that found in plants, suggesting that JA biosynthesis in pathogenic fungi occurs via a pathway similar to that in plants (Brodhun et al., 2013). The Arabidopsis-infecting F. oxysporum strains F. oxysporum f. sp conglutinans and F. oxysporum f. sp matthioli produce bioactive JA-like (e.g., JA-isoleucine) (Cole et al., 2014), and Arabidopsis JA-insensitive mutants show increased resistance against these fungi. In contrast, JA-insensitive Arabidopsis and tomato mutants do not show any altered resistance against the JA nonproducing strains F. oxysporum f. sp raphani and F. oxysporum f. sp lycopersici, respectively (Cole et al., 2014). It was suggested that fungally produced JAs in the roots activate the JA pathway to promote symptom development in aboveground part of the plant (Thatcher et al., 2009). Several other fungi (Miersch et al., 1999; Tsukada et al., 2010) are capable of producing JA-like oxylipins, but the biosynthesis pathway and known action of these oxylipins on host plants is elusive.

In contrast to JA-mediated susceptibility to certain hemibiotrophic pathogens, the JA pathway provides resistance to various necrotrophic fungal pathogens, some of which have evolved abilities to suppress this pathway. For instance, SSITL (SCLEROTINIA SCLEROTIORUM INTEGRIN-LIKE) protein, a secretory effector produced by the necrotrophic fungal pathogen S. sclerotiorum, suppresses JA-dependent defenses (Zhu et al., 2013). The mechanism by which SSITL suppresses JA-dependent defense is currently unknown. However, it was proposed that SSITL might mimic plant integrin-like proteins (e.g., NONRACE-SPECIFIC DISEASE RESISTANCE1 [NDR1]) involved in plant defense (Zhu et al., 2013) to interfere with host resistance. Further supporting the roles of NDR1-like proteins in plant defense, P. syringae effectors AvrB2 and AvrD1 directly interact with a soybean (Glycine max) NDR1-like protein called GmNDR1a (Selote et al., 2014).

Plant viruses have also evolved effectors targeting the JA pathway. For instance, the C2 protein from the geminivirus Tomato yellow leaf curl virus and Tomato yellow leaf curl Sardinia virus or the homologous protein L2 from Beet curly top virus are viral pathogenicity factors that interact with the Arabidopsis CSSN5 (Lozano-Durán et al., 2011). This interaction interferes with the CSSN5-mediated ubiquitination process, which is known to be an integral part of the JA signaling pathway (Hind et al., 2011). Arabidopsis plants expressing C2/L2 show reduced JA-mediated defenses that seem to confer resistance against these
viruses (Lozano-Durán et al., 2011). Other viral effectors that either manipulate SA-JA crosstalk or are exploited by insect pests are discussed below.

EFFECITOR-MEDIATED MANIPULATION OF SA-JA CROSSTALK

As shown in Figure 2, extensive crosstalk is known to occur between phytohormone signaling pathways (Kazan and Manners, 2008, 2012; Robert-Seilaniantz et al., 2011; De Vleesschauwer et al., 2012; Naseem and Dandekar, 2012; B. Kim et al., 2013; Nahar et al., 2013). Of these, the antagonistic crosstalk between the SA and JA pathways is particularly well characterized (Thaler et al., 2012; Gimenez-Ibanez and Solano, 2013; Lyons et al., 2013a). Given that SA and JA pathways are effective against different groups of pathogens and insects, the antagonistic crosstalk between these two pathways may have evolved to enable the plant to invest greater resources in one of the pathways at a time, depending on the type of the attacker. However, pathogens exploit this crosstalk to rewire host defenses for their own benefit (Spoel and Dong, 2008; Robert-Seilaniantz et al., 2011; Pieterse et al., 2012; Denancé et al., 2013; Grant et al., 2013). Below, we briefly review effector-mediated mechanisms used by diverse microbes that interfere with SA-JA crosstalk.

Bacterial Effectors

Arabidopsis and tomato mutants impaired in JA signaling such as coi1 (Feys et al., 1994; Kloek et al., 2001) and jasmonate insensitive-1 (Laurie-Berry et al., 2006) exhibit enhanced resistance to P. syringae, suggesting that JA promotes susceptibility to P. syringae. Promotion of host SA signaling by P. syringae effectors enhances disease by antagonizing SA-based defenses (discussed further below) and by SA-independent pathways (Laurie-Berry et al., 2006).

The phytotoxin COR produced by P. syringae promotes virulence by manipulating SA-JA crosstalk (reviewed in Xin and He, 2013) (Table 1). COR, a structural mimic of JA-Ile, binds to the JA coreceptor COI1 and activates the JA pathway (Weiler et al., 1994). The COR-bound COI1 receptor complex (SCF^{COI1}-COR E3 ubiquitin ligase) degrades JASMONATE ZIM DOMAIN (JAZ) proteins acting as negative regulators of the JA pathway and allows the master regulator MYC2 to activate JA-responsive gene expression while attenuating SA responses and SA accumulation (Katsir et al., 2008; Melotto et al., 2008; Lee et al., 2013; Zheng et al., 2012; reviewed by Kazan and Manners, 2013). COR promotes susceptibility to P. syringae, and P. syringae mutants defective in COR production cause reduced disease on Arabidopsis plants. However, when inoculated onto Arabidopsis mutants compromised in SA biosynthesis or signaling, cor- P. syringae accumulates to a similar level as the wild type strain, supporting the hypothesis that COR promotes disease by suppressing SA signaling (Brooks et al., 2005). Additionally, cor- P. syringae strains are unable to inhibit MAMP-induced stomatal closure mediated by SA and ABA (Melotto et al., 2006).

Interestingly, in addition to previously described suppressive effects of this toxin on SA signaling through JA-SA antagonism, COR also seems to interfere directly with SA-independent defenses. Thus, P. syringae COR-deficient mutants elicit increased callose deposition relative to the wild-type strain, even in SA-deficient plants, suggesting that COR inhibits callose deposition via an SA-independent pathway. Furthermore, COR could inhibit callose deposition and promote bacterial growth independently of COI1. COR-mediated inhibition of callose biosynthesis seems to occur through suppression of indole glucosinolate biosynthesis via a PENETRATION2-dependent pathway, but precise targets for COR other than COI1 are yet to be determined (Millet et al., 2010; Geng et al., 2012).

The P. syringae type III effector HopZ1a, a cysteine protease/acyltransferase, activates the JA pathway by targeting JAZ proteins (Table 1), which act as repressors of JA signaling. During bacterial infection, HopZ1a directly binds to and acetylates JAZ proteins, and this leads to their degradation in a COI1-dependent manner (Figure 4). This results in the activation of JA and repression of SA-dependent transcription (Jiang et al., 2013). Interestingly, HopX1, another P. syringae effector with cysteine protease activity (Table 1), also physically interacts with most JAZ proteins via their ZIM domains, and this promotes JAZ degradation and the activation of JA signaling, which in turn promotes susceptibility to P. syringae by downregulating SA responses (Gimenez-Ibanez et al., 2014). The P. syringae strain secreting HopX1 does not produce COR, suggesting that this pathogen has evolved multiple strategies to interfere with SA-JA antagonism of the host plant (Gimenez-Ibanez et al., 2014).

Fungal and Oomycete Effectors

β-(1,3)(1,6)-β-glucan, an exopolysaccharide (EPS) effector secreted by B. cinerea, was the first fungal effector shown to contribute to disease development by exploiting the SA-JA antagonism. Tomato plants pretreated with this EPS showed increased susceptibility to B. cinerea, repression of JA-regulated defense genes encoding protease inhibitors, and increased accumulation of SA. Since NPR1 is required to promote disease, it was proposed that EPS acts by activating the SA pathway, which then represses JA signaling through NPR1 (El Oirdi et al., 2011).

The COP9 signalosome, a hub protein targeted by multiple effectors, as described earlier, interacts with COI1 to regulate its activity and the JA response (Feng et al., 2003). Silencing of the COP9 subunit CSN5 in tomato causes a reduction in JA levels and JA-responsive gene expression, resulting in increased susceptibility to the insect pest Manduca sexta and the necrotrophic fungus B. cinerea (Hind et al., 2011). Although the expression of genes encoding pathogenesis-related SA-responsive genes such as PR-1a, PR2-a, and PR-5 are increased in CSN5 silenced plants, SA levels and response to tobacco mosaic virus (TMV) remains unchanged, suggesting that in this case, JA inhibition can reduce SA defenses independently of SA biosynthesis (Hind et al., 2011).

Insect, Viral, and Nematode Effectors

Similar to pathogenic microbes, herbivores manipulate SA-JA crosstalk, although currently very little is known how this is achieved mechanistically. For example, Colorado potato beetle
larvae (*Leptinotarsa decemlineata*) secrete bacteria onto the leaf while feeding. This induces SA-mediated defense and antagonizes the JA pathway, allowing enhanced Colorado potato beetle larval growth, although actual effectors involved in this phenomenon are unknown. Attenuation of the JA defense responses are dependent on SA-JA antagonism since the bacteria fail to disrupt JA defenses in NahG plants (Figure 5) (Chung et al., 2013). More recently, SA has been detected in the mucus secreted by the slug *Deroceras reticulatum*, suggesting that the slug exploits SA-JA antagonisms to attenuate JA-dependent defenses that are effective against this herbivore (Kästner et al., 2014).

It is remarkable that a number of viruses exploit the antagonistic interactions between SA and JA pathways either for their own benefit or the benefit of insect vectors that transmit them. For instance, tobacco spotted wilt virus (TSWV), which is vectored by western flower thrips (*Frankliniella occidentalis*), promotes WFT infection and, thus, virus transmission by exploiting JA-SA antagonism. TSWV induces increased SA levels and SA-mediated defenses, leading to a suppression of JA-mediated defenses. Consequently, WFT prefer feeding on TSWV-infected plants because the JA pathway provides resistance to WFT (Figure 5) (Abe et al., 2012). However, in contrast to the previously discussed P6 effector of cauliflower mosaic virus, which may modulate SA-JA antagonism via NPR1, the mechanism involved in TSWV-mediated modulation of this phenomenon is currently unknown.

These examples suggest exploiting SA-JA antagonism may be widespread among pests and pathogens. Adding to the complexity, however, pathogen effectors that suppress both JA and SA pathways are also known. For instance, the calreticulin Mi-CRT secreted by the root-knot nematode *Meloidogyne incognita* plays a role as a suppressor of both JA- and SA-dependent defenses. *Arabidopsis* plants expressing the secreted apoplastically located form of Mi-CRT show increased susceptibility to both *M. incognita* and the root-infecting oomycete pathogen *Phytophthora parasitica* and a suppression of PTI. In response to MAMP treatment, Mi-CRT–expressing *Arabidopsis* plants show attenuated induction of both SA and JA pathways (Jaouannet et al., 2013). Although possible plant
targets of Mi-CRT are currently unknown, it was suggested that the Ca binding properties may be important for defense-suppressing effects of this protein (Jaouannet et al., 2013).

HIRING A HITMAN: INSECT PESTS EMPLOY OBLIGATE PATHOGENS AND SYMBIOTIC BACTERIA TO ATTENUATE JA-DEPENDENT DEFENSES

As stated above, the JA pathway confers resistance against herbivorous insects. One of the remarkable strategies adopted by such insects to disable JA-dependent defenses is to employ obligate pathogens that are able to suppress JA-dependent defenses. Plant viruses are obligate pathogens often transmitted by insects and exploit host cells to reproduce. During their interaction with plants, viruses employ effector molecules to manipulate host phytohormone signaling (Figure 5). For instance, the *tomato yellow leaf curl China virus* (TYLCCNV) and *tobacco curly shoot virus* (TbCSV) are whitefly (*Bemisia tabaci B biotype*)–transmitted viruses that cause disease on tomato and other crops. When placed on TYLCCNV- or TbCSV-infected tobacco plants, the invasive *B. tabaci B* biotype shows increased growth rates, compared with when placed on un-inoculated plants (Jiu et al., 2007). The viral satellite bC1 protein is required for TYLCCNV pathogenicity. bC1-expressing *Arabidopsis* plants show attenuated expression of JA-responsive defense genes such as PDF1.2 and PR4 and reduced production of JA in response to wounding (Yang et al., 2008; Salvaudon et al., 2013). No experimental evidence that JA is required for defense against TYLCCNV currently exists. However, JA inhibits *B. tabaci B* survival (T. Zhang et al., 2012), supporting the view that the whitefly employs TYLCCNV to protect itself from JA-dependent defenses.

The 2b RNA silencing suppressor from cauliflower mosaic virus (CMV) is another viral effector that interferes with the JA signaling pathway, seemingly to act as a decoy to promote its own transmission by the aphid *Myzus persicae* (Figure 5). *Arabidopsis* plants expressing 2b show reduced expression of JA-responsive genes upon CMV infection (Lewsey et al., 2010),

Figure 5. Insect Pests Employ Effectors from Obligate Pathogens to Interfere with Host Phytohormone Pathways.
Diverse insects have adopted common strategies in complex tritrophic (insect-microbe-plant) interactions to disable host jasmonate-dependent defenses that confer resistance to insect pests. See text for additional information.
leading to the hypothesis that 2b-mediated suppression of JA-dependent defenses is beneficial for the aphid. Indeed, aphid survival is increased on tobacco (Nicotiana tabacum) plants infected with CMV, whereas it is reduced on tobacco plants infected with a CMV strain lacking the 2b protein (Ziebell et al., 2011).

Insects also exploit phytoplasma, which are obligate bacterial pathogens, to interfere with JA-dependent defenses. Secreted AY-WB protein 11 (SAP11), an effector produced by the Aster Yellows Witches’ Broom (AY-WB) phytoplasma, interferes with JA biosynthesis in Arabidopsis by binding and destabilizing class II CIN-TCP (CINCINATA-RELATED-TEOSINTE BRANCED1, CYCLOIDEA, PCF) transcription factors acting as positive regulators of the LOX2 (LIPOXYGENASE2) gene involved in JA biosynthesis (Schommer et al., 2008) (Figure 5). Arabidopsis plants transgenically expressing SAP11 as well as wild-type plants infected with AY-WB show downregulated LOX1 expression and reduced JA levels when wounded. Consequently, the leafhopper pest Macrostelus quadriilineatus, which transmits the phytoplasma, produces more progeny on AY-WB-infected, SAP11-expressing or lox2-s silenced plants (Sugio et al., 2011) (Figure 5). These examples suggest that independently evolved complex tritrophic interactions, where insects exploit microbes to disarm plant defenses while microbes (e.g., viruses) gain increased dispersal to host plants which may not be possible in the absence of an insect.

**EFFECTOR-MEDIATED MANIPULATION OF THE AUXIN PATHWAY**

The plant hormone auxin, which regulates many aspects of plant growth and development, is also increasingly associated with plant biotic and abiotic stress tolerance (Kazan and Manners, 2009; Kazan, 2013) (Figure 6). Auxin promotes susceptibility to diverse pathogens including *P. syringae*, *Xanthomonas oryzae*, and *Magnaporthe oryzae*. Several gall-producing bacteria secrete pathogen-synthesized auxins and cytokinins into the host to enable tumor or gall production and infection (reviewed in Fu and Wang, 2011; Patten et al., 2013; see below). Conversely, auxin signaling promotes resistance to the necrotrophic fungal pathogens *B. cinerea*, *Plectosphaerella cucumerina*, and *Alternaria brassicicola* (Llorente et al., 2008). However, the effect of different auxins on different *B. cinerea* strains seems to be different (González-Lamothe et al., 2012). Suppression of the SA pathway by auxin during the *Arabidopsis–P. syringae* interaction has been reported (Wang et al., 2007; Iglesias et al., 2011). However, more recent work indicates that auxin-mediated susceptibility to *P. syringae* may be independent from auxin-mediated suppression of the SA pathway (Mutka et al., 2013). Auxin signaling may also affect disease development through synergistic crosstalk with JA signaling (Kazan and Manners, 2009; Kidd et al., 2011b; Qi et al., 2012), although additional work is required to dissect these complex phytohormone interactions.

**Effectors Targeting Auxin Biosynthesis or Signaling**

The activation of auxin signaling by pathogens often seems to be achieved by effector-mediated disruption of AUXIN/INDOLE ACETIC ACID (AUX/IAA) proteins that act as repressors of the auxin signaling pathway (Dharmasiri et al., 2005). Auxin signaling...
is downregulated during the defense response to *P. syringae*. The MAMP fgl22 induces a host microRNA (miR393), which downregulates the auxin receptor TIR1 (TRANSPORT INHIBITOR RESPONSE1) and related auxin receptors AFB2 (AUXIN SIGNALING F-BOX PROTEIN1) and AFB3 (Figure 6, top panel) (Navarro et al., 2006). Upon auxin binding, auxin receptors mediate the removal of AUX/IAA proteins (Dharmasiri et al., 2005). Therefore, downregulation of auxin receptors during defense results in the stabilization of AUX/IAA proteins and the suppression of the auxin pathway conferring susceptibility to *P. syringae*.

The *P. syringae* type III effector AvrRpt2 encodes a cysteine protease that interferes with the auxin pathway in *Arabidopsis* (Table 1). AvrRpt2-expressing *Arabidopsis* plants exhibit increased sensitivity to exogenously applied auxin and increased endogenous free auxin levels during pathogenesis (Chen et al., 2007). AvrRpt2 also activates the auxin pathway by promoting the proteasome-dependent destabilization of AUX/IAA proteins and promotes susceptibility to this pathogen (Figure 6) (Cui et al., 2013). Similarly, TMV infection activates host auxin signaling by targeting AUX/IAA proteins. The TMV replicase protein interacts directly with AUX/IAA family members in *Arabidopsis* and tomato, disrupting their subcellular location and stability. Plants infected with TMV mutants compromised in their ability to interact with AUX/IAA targets accumulate less virus and show reduced disease symptoms. Furthermore, *Arabidopsis* IAA26 (INDOLE-3-ACETIC ACID INDUCIBLE26) knockdown mutants display developmental alterations that are similar to those induced by TMV (Padmanabhan et al., 2005, 2008), further supporting the idea that viral effectors activate auxin signaling to promote disease symptoms.

Bacterial effectors also target auxin signaling components. For instance, to successfully infect pepper plants, *X. c. pv vesicatoria* secretes the type III effector AvrBs3, which encodes a TAL (TRANSCRIPTION ACTIVATOR-LIKE) protein. AvrBs3 contains a DNA binding domain and regulates auxin responsive genes by binding their promoters (Figure 6, top panel) (Marois et al., 2002; Kay et al., 2007). Presumably, this increases the vulnerability of pepper to infection by this pathogen.

Auxin levels also increase during colonization of wheat (*Triticum aestivum*) plants by the stem rust fungus *Puccinia graminis f. sp tritici* (Pgt) (Yin et al., 2014). Increases in auxin levels correlate with the induction of the Pgt gene *Pgt-IaaM* in fungal haustorial cells. *Pgt-IaaM* encodes a putative tryptophan 2-monoxygenase involved in the production of the IAA precursor indole-3-acetamide (IAM). Interestingly, transient inactivation of *Pgt-IaaM* by host-induced gene silencing compromises fungal virulence, while overexpression of *Pgt-IaaM* in *Arabidopsis* leads to developmental alterations and reduced resistance to *P. syringae*, suggesting that *Pgt-IaaM*-mediated auxin production acts as a virulence factor for the rust fungus (Yin et al., 2014).

Phytoplasma, which causes witches’ broom disease characterized by severe developmental alterations in infected plants, also appears to alter the plant’s hormone balance. TENGU, a phytoplasma effector, contributes to symptom development by suppressing the auxin pathway (Figure 6, top panel) (Hoshi et al., 2009). Several parasitic nematodes including the root knot nematode *Meloidogyne javanica* (Lambert et al., 1999), *H. schachtii* (Vanholme et al., 2009), and the soybean cyst nematode *Heterodera glycines* (Bekal et al., 2003) secrete chorismate mutase, an enzyme implicated in SA degradation, as discussed above (Djamei et al., 2011), into the host cells. Soybean hairy roots expressing the *M. javanica* chorismate mutase (*MjCM-1*) show altered root morphology that can be rescued by exogenous auxin treatment, suggesting that *MjCM-1* reduces auxin levels in the roots. How this might promote nematode infection requires further investigation (Doyle and Lambert, 2003).

Diverse bacterial and fungal pathogens are capable of producing auxins via multiple pathways (reviewed in Reineke et al., 2008; Fu and Wang, 2011; Spaepen and Vanderleyden, 2011; Tsavkelova et al., 2012; Patten et al., 2013). A nitrilase enzyme found in *P. syringae pv syringae* catalyzes the production of auxin from indoleacetonitrile, but whether this affects pathogen virulence is yet to be determined (Howden et al., 2009). Gall or tumor-inducing phytopathogens synthesize and secrete auxins and cytokinins into the host to facilitate gall initiation and/or development. Gall-forming bacterial species harbor a horizontally transferred gene cluster that controls auxin biosynthesis via the IAM pathway. Mutants of *Pseudomonas savastanoi*, the causal agent of olive and oleander knot, which lack this operon, show reduced auxin biosynthesis and attenuated knot symptoms on olive plants (Aragón et al., 2014). *Pantoaea agglomerans* (previously known as *Erwinia herbicola*) pv *gypsophilae* harbors machinery to produce auxins via both the IAM and indole-3-pyruvate (IpyA) pathways. These pathways differentially contribute to pathogen virulence and infection strategies.

*P. agglomerans* mutants deficient in the IAM pathway exhibited reduced gall formation, *P. agglomerans* mutants deficient in the IpyA pathway showed reduced epiphytic colonization (Manulis et al., 1998).

Secretion of auxins into the host by *Xanthomonas* spp and *M. grisea* induces host auxin production, increasing susceptibility to these pathogens (Fu et al., 2011). The root wilt bacterial pathogen *R. solanacearum* produces auxins and ET (Valls et al., 2006). *R. solanacearum* mutants lacking components of the Hrp type II secretion system fail to induce root lateral structures on their petunia host. Since auxin promotes lateral root production, *R. solanacearum*–derived auxin may promote this morphological change to facilitate efficient colonization and multiplication of the host roots (Zolobowska and Van Gijsegem, 2006).

**Effectors Targeting Auxin Transport**

Auxin transport plays an integral role in maintaining cell and tissue homeostasis of this phytohormone and diverse pathogens seem to manipulate host auxin influx and efflux pathways to promote disease on plants. For example, the HopM1 effector from *P. syringae* perturbs auxin transport (Table 1). HopM1 binds to and promotes the proteasome-mediated degradation of *Arabidopsis* MIN7 (HopM INTERACTOR 7), a protein from the ADP ribosylation factor guanine nucleotide exchange factor family that acts as a regulator of the host vesicle trafficking pathway (Nomura et al., 2006). HopM1 does not show any homology to proteases. Thus, it is thought that HopM1 recruits components of the host proteasome to degrade MIN7 and promotes defense against *P. syringae*, possibly by regulating the secretion of defense-associated proteins (Nomura et al., 2006, 2008; Fu and Wang, 2011; Spaepen and Vanderleyden, 2011; Tsavkelova et al., 2012; Patten et al., 2013). A nitrilase enzyme found in *P. syringae pv syringae* catalyzes the production of auxin from indoleacetonitrile, but whether this affects pathogen virulence is yet to be determined (Howden et al., 2009). Gall or tumor-inducing phytopathogens synthesize and secrete auxins and cytokinins into the host to facilitate gall initiation and/or development. Gall-forming bacterial species harbor a horizontally transferred gene cluster that controls auxin biosynthesis via the IAM pathway. Mutants of *Pseudomonas savastanoi*, the causal agent of olive and oleander knot, which lack this operon, show reduced auxin biosynthesis and attenuated knot symptoms on olive plants (Aragón et al., 2014). *Pantoaea agglomerans* (previously known as *Erwinia herbicola*) pv *gypsophilae* harbors machinery to produce auxins via both the IAM and indole-3-pyruvate (IpyA) pathways. These pathways differentially contribute to pathogen virulence and infection strategies. While *P. agglomerans* mutants deficient in the IAM pathway exhibited reduced gall formation, *P. agglomerans* mutants deficient in the IpyA pathway showed reduced epiphytic colonization (Manulis et al., 1998).

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Another effector that perturbs auxin efflux is PSE1 (PENETRATION SPECIFIC EFFECTOR1), an RXLR secretion motif-containing effector from the oomycete pathogen *P. parasitica* (Figure 6, bottom panel). *Arabidopsis* plants constitutively expressing PSE1 show increased susceptibility to *P. parasitica* as well as developmental alterations similar to those observed in mutants affected in auxin physiology. 2,4-D treatment partially rescues the enhanced susceptibility of PSE1-expressing plants to *P. parasitica*, suggesting that reduced auxin levels promote *P. parasitica* infection. The developmental alterations displayed by PSE1-expressing plants such as coiled roots and impaired root hair development were not restored by exogenous auxin application but were restored by treatment with 2,3,5-triiodobenzoic acid and N-1-naphthylphthalamic acid, chemical inhibitors of auxin efflux. Furthermore, PSE1-expressing plants altered accumulation of the two members of the PIN family of auxin efflux proteins, PIN4 and PIN7 at the root apex, suggesting that PSE1-mediated alterations in root auxin transport is responsible for these developmental changes (Evangelisti et al., 2013).

Cyst nematodes, obligate biotrophic parasites that penetrate plant roots and establish specialized feeding structures called syncytia, also require the host plant’s auxin signaling and transport pathways to efficiently colonize plant roots. *Arabidopsis* pin1 plants support reduced cyst formation by the beet cyst nematode *H. schachtii* (Grunewald et al., 2009). The *H. schachtii* effector Hs19C07 interacts with the *Arabidopsis* LAX3 (LIKE AUXIN13) auxin influx transporter and may stimulate its activity. LAX3 presumably promotes auxin influx into the developing syncytia (Figure 6, bottom panel). However, a direct role for LAX3 in *H. schachtii* infestation is unclear since lax3 plants show similar levels of resistance to wild-type plants (Lee et al., 2011). Recent revelation that many *Arabidopsis* ARF (auxin response factors) transcription factors show distinct expression patterns in the syncytium is also consistent with the view that components of host auxin pathway are essential for syncytium development (Hewezi et al., 2014).

**EFFEC TOR-MEDIATED MANIPULATION OF THE ABA PATHWAY**

ABA is the major phytohormone involved in responses to abiotic stresses, including drought, salt, and cold (Raghavendra et al., 2010), but also regulates aspects of plant immunity. ABA provides susceptibility to a wide range of pathogens including *B. cinerea* (Aуденаерт et al., 2002), *F. oxysporum* (Anderson et al., 2004), *M. grisea* (Koga et al., 2004; Yazawa et al., 2012), *P. sojae* (McDonald and Cahill, 1999), and the bacterial pathogen *X. oryzae pv oryzae* (*J. Xu et al., 2013*), while it promotes resistance to pathogens such as the rice-infecting fungal pathogen *Cochliobolus miyabeanus* (*De Vleeschauwer et al., 2010*) and the oomycete pathogen *Pythium irregular* (Adie et al., 2007). ABA-mediated resistance or susceptibility is often thought to be a consequence of crosstalk with defense hormones such as JA, SA, or ET (Anderson et al., 2004; De Vleeschauwer et al., 2010; Z.Y. Xu et al., 2013). During drought stress, ABA promotes stomatal closure. This response restricts water loss as well as entry of pathogens such as *P. syringae* into leaves (reviewed in Sawinski et al., 2013). The JA analog COR produced by *P. syringae* is capable of reverting both pathogen- and ABA-induced stomatal closure (Melotto et al., 2006). Similarly, *X. c. pv campestris* can revert stomatal closure, but the identity of the effector(s) responsible for this process remains elusive (Gudesblat et al., 2009). More recent evidence also implies that an oxylipin-dependent but ABA-independent pathway controls stomatal closure during plant defense against bacterial pathogens (Montillet et al., 2013).

ABA both negatively and positively regulates resistance to *P. syringae*, depending on the stage of infection. ABA-deficient mutants show increased susceptibility to *P. syringae* upon spray inoculation onto *Arabidopsis* plants, presumably due to the inhibition of MAMP-triggered stomatal closure (Melotto et al., 2006). On the other hand, ABA-deficient plants show enhanced resistance to syringe-inoculated *P. syringae* (Thaler and Bostock, 2004; de Torres-Zabala et al., 2007), and ABA-treated tomato and *Arabidopsis* plants show increased susceptibility to this pathogen (Mohr and Cahill, 2003; de Torres-Zabala et al., 2007). The different effects of ABA on *P. syringae* were explained based on the proposal that ABA is required to prevent initial infection by *P. syringae*, but once inside the plant, ABA signaling is hijacked by the pathogen to maintain a high water potential in the apoplastic, which is necessary for *P. syringae* colony growth (Beattie, 2011).

Indeed, ABA concentration increases upon *P. syringae* infection, and this is dependent on a functioning type III secretion system. The type III effector AvrPtoB (Table 1) seems to be specifically involved in this response as transgenic expression of this effector protein in *Arabidopsis* elevates ABA levels and enhances susceptibility to *P. syringae* (de Torres et al., 2006; de Torres-Zabala et al., 2007). Possible mechanisms of how AvrPtoB affects ABA levels are not clear. However, by increasing ABA levels, *P. syringae* seems to antagonize the SA pathway required for resistance to this pathogen (de Torres-Zabala et al., 2003).

HopAM1, another type III effector of unknown function produced by *P. syringae*, promotes pathogen virulence on plants exposed to water stress (Table 1). HopAM1-expressing *Arabidopsis* plants show enhanced disease symptoms and hypersensitivity to ABA-mediated stomatal closure when infected with *P. s. pv maculicola*, suggesting that HopAM1 modulates ABA signaling downstream of ABA perception (Goel et al., 2008). The AvrB AvrC domain of the AvrXccC80044 from the bacterial pathogen *X. c. pv campes tras* elicits ABA accumulation by inducing the ABA biosynthesis gene *NCED5* (NINE-CIS-EPOXYCATENOID DIOXYGENASE5) when expressed transgenically in *Arabidopsis*. Compared with the wild-type strain, an *X. c. pv campes tras* mutant strain deficient in *AvrXccC8004* triggers reduced ABA levels when inoculated onto *Arabidopsis*. Furthermore, exogenous ABA application allows increased growth of the *AvrXccC8004*-deficient strain, suggesting that *X. c. pv campes tras* mediated ABA induction promotes virulence (Ho et al., 2013).

**EFFEC TOR-MEDIATED MANIPULATION OF THE ETHYLENE PATHWAY**

ET is a gaseous hormone that regulates a large number of plant processes, including defense against pathogens (Broekaert et al., 2011). MIN7 enables PIN1 to efflux auxin (Tanaka et al., 2009), suggesting that degradation of MIN7 by HopM1 may promote disease via modulation of auxin accumulation.
et al., 2006). ET signaling often works synergistically with JA to promote resistance to necrotrophic pathogens such as *B. cinerea* and *Rhizoctonia solani* in *Arabidopsis* (Thomma et al., 1999) and *Medicago*, respectively (Anderson et al., 2010). In tomato, the ET pathway inhibits symptom development of the bacterial pathogens *P. syringae* and *X. c. pv vesicatoria* (Lund et al., 1998). However, similar to other phytohormones, the involvement of ET in disease susceptibility, either alone or in combination with other phytohormones, has also been documented (Chen et al., 2009; Jia et al., 2013; Pantelides et al., 2013; Wang et al., 2013). Inability of *Arabidopsis* and tomato to perceive ET due to a mutation in the receptor encoding gene *ETR1* (ETHYLENE RECEPTOR1) makes the plants resistant to *F. oxysporum* (Pantelides et al., 2013). Furthermore, pathogen-mediated activation of ET signaling promotes systemic susceptibility to herbivores (Groen et al., 2013), indicating the complexity of signaling crosstalk triggered by different attackers.

*Arabidopsis* flg22 perception activates ET biosynthesis via MPK6-mediated phosphorylation of the ET biosynthesis enzyme ACS (1-AMINOCYCLOPROPANE-1-CARBOXYLIC ACID SYNTHASE) (Liu and Zhang, 2004). MPK6 also interacts with ERF104, a transcription factor acting as a positive regulator of ET signaling. It is proposed that flg22 perception results in the loss of MPK6–ERF104 interaction and subsequently allows ERF104 to activate its targets (Bethke et al., 2009). In Arabidopsis, the expression of the FLS2 (FLAGELLIN SENSING2) gene encoding a flg22 receptor is controlled by ET signaling regulators EIN3 (ETHYLENE INSENSITIVE3) and EIL1 (ETHYLENE-INSENSITIVE3-LIKE1) (Boutrot et al., 2010; Mersmann et al., 2010). Further supporting the importance of ET in basal plant defense, EIN2, a master regulator of ET signaling, is required for sensitivity to bacterial MAMPs flg22 and elf18 (elongation factor 18) (Tintor et al., 2013). Given that PTI triggers ethylene biosynthesis and signaling in *Arabidopsis*, it seems somewhat paradoxical that the *P. syringae* type III effectors AvrPto and AvrPtoB, which are known to repress PTI by targeting MAMP PRRs (as discussed in the next section), promote the expression of ET biosynthesis genes and production of ET in tomato (Cohn and Martin, 2005) (Table 1).

XopD from *X. c. pv oryzae* encodes a small ubiquitin-like modifier protease with helix-loop-helix and EAR (ERF-Associated Repression) DNA binding domains (Kim et al., 2008). The latter motif acts as a transcriptional repressor in plants (reviewed in Kazan, 2006). *xopD* mutants lacking either of these domains show reduced virulence, suggesting that XopD represses host defenses by repressing defense genes via transcriptional repressor activity and/or by degradation of key transcriptional regulators (Kim et al., 2008). Indeed, as discussed further below, the type III effector XopD from the related bacterial species *X. c. pv vesicatoria* has recently been shown to target tomato ERF4 (ETHYLENE RESPONSE FACTOR4) to suppress ET responses (J.G. Kim et al., 2013).

In plants, ET is produced using the 1-aminocyclopropane-1-carboxylic acid pathway (Kende, 1993). Several phytopathogenic microbes, including *R. solanacearum*, *P. syringae* pv *glycinea* and *phaseolicola*, and *B. cinerea* have evolved alternative biochemical pathways to produce ET (Weingart and Volksch, 1997; Cristescu et al., 2002; Valls et al., 2006). The *R. solanacearum* type III effector RsSp1529 is a putative ET forming enzyme. A mutant *R. solanacearum* strain lacking RsSp1529 triggers a marked reduction in ET-regulated defense gene expression, but pathogen growth is not affected (Valls et al., 2006). In addition, bacterial wilt symptoms caused by *R. solanacearum* are reduced in ET signaling mutants, suggesting that *R. solanacearum*–derived ET may be used to activate the host ET signaling pathway. Although *B. cinerea* can produce ET (Inomata et al., 2004), a role for *B. cinerea*–derived ET in manipulating host hormone homeostasis would seem counterproductive since ET biosynthesis and signaling promotes resistance to *B. cinerea* in tomato and *Arabidopsis* (Thomma et al., 1999; Diaz et al., 2002).

**EFFICACY-S cụ THỂ MEDICATED MANIPULATION OF THE CYTOKININ PATHWAY**

Although CK have long been implicated in the modulation of plant defense, currently relatively little is known about their possible mechanism of action (Choi et al., 2011; Grosskinsky et al., 2011; Argueso et al., 2012; Reusche et al., 2013). HopQ1, a type III effector from *P. syringae*, induces CK signaling in *Arabidopsis* to promote disease development (Table 1), and this seems to be correlated with reduced FLS2 accumulation and attenuated FLS2-mediated defenses, suggesting that effector-mediated increase in host CK levels negatively regulate PTI (Hann et al., 2014). CK treatment of plants also suppresses FLS2 accumulation and promotes pathogen susceptibility. HopQ1 seems to be conserved in other pathogenic bacteria, such as *Xanthomonas* and *Ralstonia* (Hann et al., 2014). However, it is currently unknown whether HopQ1 homologs in these bacteria would perform functionally similar roles to HopQ1.

CK secreted by biotrophic fungal pathogens alters the sensitivity of tissue to senescence promoting signals (reviewed in Walters and McRoberts, 2006; Walters et al., 2008). Several gall-producing bacteria produce CK and auxins, as previously discussed, to modulate plant development to suit their requirements. For instance, *Rhodococcus fascians*, the causal agent of leafy gall disease, requires CK for disease development (reviewed by Stes et al., 2011). The *Arabidopsis* double mutant ahk3 ahk4 defective in CK receptors does not cause leafy gall disease when inoculated with *R. fascians*, a CK-producing microbe (Pertry et al., 2009). Some forms of CK synthesized by *R. fascians* are somewhat calcitrant to host-mediated degradation, allowing them to accumulate in the plant and reprogram development, resulting in disease symptoms (Pertry et al., 2009).

**EFFICACY-S cứngiated MANIPULATION OF THE BRASSINOSTEROID PATHWAY**

Given that hormone receptors control a large number of downstream responses, interfering with hormone receptor function would be an efficient approach for a pathogen to disrupt the phytohormone pathway. However, so far only two hormone receptors, the JA receptor COI1 and the BR coreceptor BAK1 (BR1-ASSOCIATED KINASE1), have been shown to be direct targets of pathogen effectors (Katsir et al., 2008; Shan et al., 2008; Cheng et al., 2011). BAK1 was originally described as
a coreceptor for the brassinosteroid receptor BR1 but was subsequently found to be associated with the PAMP receptors FLS2 and EFR upon PAMP binding (Chinchilla et al., 2007; Roux et al., 2011), suggesting that BAK1 functions both in plant defense and hormone signaling. BRs and BR signaling can promote resistance or susceptibility against different pathogens (Nakashita et al., 2003; Kemmerling et al., 2007; Komer et al., 2013), but whether the roles of BAK1 in PTI and BR signaling are genetically separate is not completely understood. Although fig22 treatment fails to elicit or suppress BR signaling pathways, overexpression of BR1 or BR application in Arabidopsis suppresses PTI (Belkhadir et al., 2012). Activation of the BR-activated transcription factor BZR1 affects the expression of WRKY and other defense genes, which goes some way to explaining how BR suppresses PTI (Lozano-Durán et al., 2013). However, inhibition of FLS2-mediated immune signaling by BR perception independently from BAK1 or BAK1-associated phosphorylation pathway has also been reported (Albrecht et al., 2012).

The P. syringae type III effectors AvrPto and AvrPtoB target BAK1 (Table 1), interfering with its ability to bind FLS and trigger PTI. AvrPtoB/AvrPto-deficient P. syringae strains show reduced virulence on Arabidopsis, and transgenic Arabidopsis plants expressing AvrPto show morphological phenotypes such as stunting that is reminiscent of BR-insensitive mutants. AvrPtoB is known to interact with the BAK1 kinase domain, inhibiting its ability to bind with FLS2/EFR (ELONGATION FACTOR) and elicit PTI, while the mechanism of how AvrPto interferes with BAK1-FLS2 remains unclear (Shan et al., 2008; Cheng et al., 2011). More recently, BAK1 has also been identified as one of the targets of HopF2 (Table 1), another type III effector from P. syringae (Zhou et al., 2014). Xoo2875, a type III effector from the bacterial pathogen X. o. pv oryzae also interacts with OsBAK1 to inhibit innate immunity as well as BR signaling. Consistent with this, transgenic rice (Oryza sativa) plants expressing Xoo2875 display, in addition to increased X. o. pv oryzae susceptibility, a semi-dwarf plant phenotype that is reminiscent of rice plants with silenced OsBAK1 (Yamaguchi et al., 2013). BIK1 (BOTRYTIS-INDUCED KINASE1), which is required for PTI, interacts with the flagellin receptors FLS2 and BAK1. BIK1 is also phosphorylated by BAK1. The P. syringae type III effector AvrPphB, which encodes a cysteine protease, degrades BIK1, inhibiting PTI. Interestingly, although BIK1 is a positive regulator of defense signaling, it negatively regulates BR signaling (Lin et al., 2013). Furthermore, it appears that BR-mediated plant growth and plant defense are negatively correlated (Albrecht et al., 2012). These examples clearly demonstrate the complex nature of interactions between defense and BR signaling.

**EFFECCTOR-MEDIATED MANIPULATION OF THE GIBBERELLIC ACID PATHWAY**

GAs promote plant growth and also promote susceptibility to several pathogens in rice (reviewed in Yang et al., 2013). Thus, the GA-insensitive dwarf mutant gid1, which hyperaccumulates endogenous GA shows increased susceptibility to the rice blast fungus Pyricularia oryzae (Tanaka et al., 2006), whereas rice plants compromised in GA biosynthesis show increased resistance to M. oryzae and X. o. pv oryzae (Qin et al., 2013). GAs produced as secondary metabolites in the rice-infecting pathogenic fungus Fusarium fujikuroi are well known examples of phytohormone mimics (Bömke and Tudzynski, 2009). Rice plants infected with this fungus display spindly and elongated stems and chlorotic leaves caused by fungally secreted GA. A GA nonproducing F. fujikuroi strain is not compromised in initial infection of rice cells but is restricted in subsequent invasion of the host (Wiemann et al., 2013). Interestingly, other Fusarium species seem to have lost the ability to synthesize GA, suggesting that this provides an advantage for F. fujikuroi over other pathogens (Wiemann et al., 2013).

**PHYTOHORMONE SIGNALING HUBS, TRANSCRIPTIONAL ACTIVATORS, AND REPRESSORS TARGETED BY PATHOGEN EFFECTORS**

Recent genome-wide protein–protein interaction studies have identified proteins that are commonly targeted by effectors from two diverse pathogens: namely, the bacterial pathogen P. syringae and the oomycete pathogen H. arabidopsidis (Mukhtar et al., 2011). Interestingly, among the 17 so-called “hub” proteins identified to interact with effectors from both pathogens, relatively few proteins directly involved in plant hormone signaling were found (Mukhtar et al., 2011). This seems to suggest that hormone signaling pathways may often be indirectly targeted by pathogen effectors. Indeed, LSU1 (RESPONSE TO LOW SULFUR1) is a common effector target that interacts with 80 other plant proteins including the JA signaling components JAZ1 and JAZ9 (Arabidopsis Interactome Mapping Consortium, 2011). Two other common effector targets, CSN5a (COP9 SIGNALOSOME5a) and CSN5b, two separate subunits of the COP9 signalosome multicellular protein complex involved in cullin-RING E3 ubiquitin ligase regulation, interact with 39 and 148 plant proteins, respectively. The auxin signaling proteins IAA7 and IAA8, as well as the SA signaling components SCN4 (SUPPRESSOR OF NPR1-1 CONSTITUTIVE4) and NIMIN2 (NIM1-INTERACTING2), were found to interact with the HUB proteins LSU1 and CSN5A, respectively (Arabidopsis Interactome Mapping Consortium, 2011). As stated earlier, CSN5a and CSN5b are targeted by the geminivirus 2C protein (Lozano-Durán et al., 2011), further suggesting that CSN5 protein is a direct target of diverse pathogen effectors.

Phytohormone responses often are regulated by a large number of transcription factors. Therefore, a potential way for pathogens to disrupt phytohormone pathways is to target transcription factors. As stated above, the Xanthomonas effector XopD interacts with ERF4 in tomato and the MYB transcription factor MYB30 in Arabidopsis. The latter is a key regulator of multiple hormone signaling pathways, including SA, ABA, and BR signaling (reviewed in Raffaele and Rivas, 2013). In addition, ERF19 in Medicago truncatula is targeted by a secreted effector (SP7) from the arbuscular mycorrhizal fungus Glomus intraradices. The physical interaction between SP7 and ERF19 facilitates increased mycorrhizal colonization by G. intraradices and prolongs the biotrophic phase in rice roots when SP7 is expressed in the hemibiotrophic rice blast fungus M. grisea (Kloppholz et al., 2011). Host transcription factors also seem to be indirectly targeted by pathogens. For instance, a recent study
showed that flg22 induces alternatively polyadenylated forms of *Arabidopsis* ERF4 (Lyons et al., 2013b). The full-length At-ERF4 isoform, which contains an EAR domain, is involved in transcriptional repression, while the flg22-induced ERF4 isoform that does not contain the EAR domain performs novel defense-related roles (Lyons et al., 2013b).

In addition to the members of the ERF and MYB transcription factor families, various members of the NAC (NAM/ATAF1/2/CUC2) family transcription factors involved in disease resistance or susceptibility (Delessert et al., 2005) have recently been shown to be targeted by pathogen effectors. For example, HopD1 from *P. syringae* targets the *Arabidopsis* NAC transcription factor NTL9 (NAC TRANSCRIPTION FACTOR-LIKE9) (Block et al., 2014). An RxLR effector from *P. infestans* interferes with nuclear localization of the two tobacco (*Nicotiana benthamiana*) NAC transcription factors called NTP1 (NAC TARGETED BY PHYTOPHTHORA1) and NTP2 (McLellan et al., 2013). Turnip crinkle virus coat protein binds to the *Arabidopsis* NAC transcription factor TIP (TCV-INTERACTING PROTEIN1, also known as ANAC091) to interfere with defense response (Donze et al., 2014). More recently, Cs-LOB encoding a LOB (LATERAL ORGAN BOUNDARIES) domain transcription factor in citrus has been identified as a susceptibility gene whose product is targeted by the TAL effector pthA from *Xanthomonas citri*, the bacterial pathogen that causes bacterial canker disease in citrus (Hu et al., 2014; Z. Li et al., 2014). Other LOB domain genes that potentially are involved in hormone signaling have been identified as TAL effector targets (Pereira et al., 2014). The involvement of *Arabidopsis* LBD20 in JA signaling and *Fusarium* wilt susceptibility is also known (Thatcher et al., 2012b). Given the large number of transcriptional regulators potentially involved in pathogen defense (McGrath et al., 2005), future research will probably identify additional phytohormone-related regulators that are directly or indirectly targeted by pathogen effectors to promote disease susceptibility.

Recent research has also established that transcriptional repressors play a major role in regulating phytohormone responses. Therefore, repressors present a convenient target for pathogens that benefit from the improper activation of hormonal responses. For instance, *P. syringae* targets DELLA repressors of GA signaling to promote disease development (Figure 4) (Navarro et al., 2008), although a specific bacterial effector directly or indirectly involved in targeting DELLA's has not yet been identified. Examples of pathogen effectors that target repressors of phytohormone pathways are discussed earlier and include viral and bacterial effectors (e.g., AvrRpt2) targeting repressors of auxin signaling (Cui et al., 2013). As discussed above, the *P. syringae* effector and HopX1 and HopZ1a target JAZ repressors to activate the JA pathway (Jiang et al., 2013; Gimenez-Itzan et al., 2014) (Figure 4). More recently, an interaction between MiSSP7 (Mychorriza-Induced Small Secreted Protein 7) from the beneficial fungus *Laccaria bicolor* and the *Populus trichocarpa* JAZ6 protein has been identified. This interaction inhibits JAZ6 degradation, leading to the repression of the JA pathway and the promotion of symbiosis in *P. trichocarpa* colonized roots (Plett et al., 2014). Therefore, effector-mediated targeting of phytohormone repressors appears to be a common theme in both pathogenic and beneficial plant-microbe interactions.

**CONCLUSIONS AND FUTURE PROSPECTS**

In recent years, great progress has been made toward discovering specific targets of effectors produced by bacterial, viral, fungal, and oomycete pathogen effectors. In this review, the term “effector” was used to broadly refer to pathogen derived molecules that make the host environment conducive to infection. In fact, in the light of recent evidence indicating that small RNAs produced by the fungal pathogen *B. cinerea* targets host’s signaling pathways (Weilberg et al., 2013), the coverage of this term should probably be extended to any pathogen-produced molecule that contributes to disease development.

In addition to relatively well-characterized MAMPs and many virulence factors, pathogen genomes seem to encode a large number of uncharacterized effectors, and potential plant targets have been reported for only a few of these effectors to date. Most effectors make only subtle contributions to overall pathogen virulence, and these small effects may be difficult to detect using pathogen knockouts. It is also becoming increasingly evident that a single pathogen species can produce a large number of effectors that can simultaneously target multiple host processes, including phytohormone pathways that regulate both defense and development. Numerous studies have suggested a tradeoff between plant growth and development and defense. Effector-mediated manipulation of host hormone biology to promote plant growth may benefit pathogens by reducing resources available for the plant to mount an effective defense response (Kazan and Manners, 2009; De Bruyne et al., 2014; Huot et al., 2014). Furthermore, the versatility of pathogen effectors is evidenced by the demonstration that a single effector can interfere with multiple host targets (Cui et al., 2010; Lindeberg et al., 2012; Raffaele and Rivas, 2013; Zhou et al., 2014). A more complete understanding of the complex interactions of phytohormone signaling networks triggered by pathogen effectors may require the adoption of systems biology approaches (Kim et al., 2014; Naseem et al., 2014).

Identification of conserved protein motifs for nuclear localization, gene suppression, cellular entry, and subcellular targeting would certainly be helpful for future studies examining effector mode of action. The biosynthesis of many phytohormones takes place in the chloroplast. Therefore, interfering with chloroplast function may be a common strategy used by many pathogens. As reviewed here, the *P. syringae* effector Hop1 targets chloroplasts to reduce SA biosynthesis (Jelenska et al., 2007). More recently, two type III effectors, HopK1 and AvrRps4 from *P. syringae*, were also found to be localized to *Arabidopsis* chloroplasts, and this seems to be mediated by a cleavable transit peptide found in these effectors (G. Li et al., 2014). Loss of chloroplast function can also lead to chlorosis that contributes to disease symptom development. For instance, host-selective toxins, produced by the necrotrophic pathogen *Alternaria alternata*, disrupt chloroplast function to promote disease development (reviewed in Tsuge et al., 2013).

Given the importance of transcription factors in the regulation of genes involved in plant hormone biosynthesis and signaling, it is plausible that pathogen effectors target members of plant transcription factor gene families, although so far only few such transcription factors directly targeted by pathogen effectors...
have been identified. It is expected that future research will identify new pathogen effectors that either directly or indirectly target transcriptional activators and repressors of the host’s hormone signaling pathways.

A number of secreted pathogen effectors contain nuclear localization signals indicating that they may interfere with transcription (Canonne and Rivas, 2012; Stamm et al., 2013), although direct targets of these effectors remain to be determined. Bacterial effectors that act as plant transcription factors, such as those belonging to the TAL family, activate host target genes, but their precise mode of action remains unclear (Boch and Bonas, 2010). Computational analyses to identify TAL targets in plant genomes may go some way toward uncovering this question (Nöl et al., 2013; Pereira et al., 2014). Synthetic TAL or TAL-EAR effectors designed to modulate the expression of TFs involved in defense-associated phytohormone pathways should also have utility in biotechnological applications (Mahfouz et al., 2012).

To date, effector targets have been mainly investigated for bacterial, biotrophic, and hemibiotrophic fungal pathogens and oomycetes. Necrotrophic fungal pathogens potentially secrete large numbers of effectors that affect a variety of cellular targets. Host-specific toxins secreted by necrotrophic pathogens (Friesen et al., 2008) can activate a variety of cellular responses, including phytohormone pathways. Host-selective toxins (ToxA and ToxB) of Pyrenophora tritici-repentis, the necrotrophic fungal pathogen that causes tan spot disease in wheat, activate the JA pathway (Pandelova et al., 2012). More recently PR1-5, a wheat PR1-like protein, which physically interacts with ToxA from Stagonospora nodorum, another necrotrophic wheat pathogen, has been identified as a potential ToxA target, suggesting that this interaction may be responsible for ToxA-induced necrosis on wheat (Lu et al., 2014). Other mycotoxins such as oxalic acid and necrosis and ethylene-inducing peptide (NEP1) secreted by S. sclerotiorum and various pathogenic fungi, respectively, act as effectors to alter phytohormone-regulated host defenses (Qutob et al., 2006; Liang et al., 2009). Similarly, the fungal toxin deoxynivalenol (DON) produced by the wheat pathogen F. graminearum acts as an effector, eliciting plant host defenses and cell death (Desmond et al., 2008), although exact cellular targets of DON remain elusive.

The role of herbivore- or microbial-induced plant volatiles as elicitors of plant defense and pathogen protection have been relatively well studied (reviewed in Arimura et al., 2011). These compounds can have antimicrobial and/or defense-inducing effects and can also attract enemies of predatory insects (Leroy et al., 2011). However, one relatively unexplored area is the effect of microbially produced volatiles as effectors. Indeed, there is evidence that certain volatiles, such as 1-hexanol released by several plant-infecting bacteria, suppress the fig22-induced production of ET and reactive oxygen species, suggesting that pathogen produced volatiles can manipulate hormone defense signaling pathways (Blom et al., 2011).

In conclusion, recent studies reviewed here reveal diverse mechanisms used by pathogens to target phytohormone signaling pathways. Host phytohormone signaling hubs and their associated networks directly or indirectly targeted by pathogen effectors constitute “susceptibility factors.” A better understanding of effector mode of action would enable us to engineer susceptibility factors so that vulnerability to pathogens in crop plants could be reduced without causing unintended effects on plant growth and development.

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