Ambivalent response in pathogen defense: A double-edged sword?

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ABSTRACT

Plants possess effective immune systems that defend against most microbial attackers. Recent plant immunity research has focused on the classic binary defense model involving the pivotal role of small-molecule hormones in regulating the plant defense signaling network. Although most of our current understanding comes from studies that relied on information derived from a limited number of pathosystems, newer studies concerning the incredibly diverse interactions between plants and microbes are providing additional insights into other novel mechanisms. Here, we review the roles of both classical and more recently identified components of defense signaling pathways and stress hormones in regulating the ambivalence effect during responses to diverse pathogens. Because of their different lifestyles, effective defense against biotrophic pathogens normally leads to increased susceptibility to necrotrophs, and vice versa. Given these opposing forces, the plant potentially faces a trade-off when it mounts resistance to a specific pathogen, a phenomenon referred to here as the ambivalence effect. We also highlight a novel mechanism by which translational control of the proteins involved in the ambivalence effect can be used to engineer durable and broad-spectrum disease resistance, regardless of the lifestyle of the invading pathogen.

Key words: ambivalence effect, crop protection, hormone crosstalk, pathogen, plant defense, susceptibility (S) gene

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INTRODUCTION

In nature, plants encounter a vast array of insects and pathogenic microorganisms, including fungi, bacteria, oomycetes, viruses, and nematodes (Jones and Dangl, 2006; Howe and Jander, 2008). Despite the large number of microorganisms that inhabit the surroundings of plants, only a few taxa constitute pathogens that are able to attack specific plant species. Plants protect themselves well against microbes, such that disease is the exception rather than the rule. Based on their lifestyles, plant pathogens are classified as biotrophs, necrotrophs, and hemibiotrophs. Biotrophic pathogens feed on living cells and cause limited injury, mainly at the cell wall during penetration. Necrotrophs first destroy host cells, often through the production of phytoxins and cell wall-degrading enzymes, and then feed on the contents; by contrast, hemibiotrophs have an initial biotrophic phase that is followed by a necrotrophic phase (Thaler et al., 2004). Insect pests also cause mechanical damage to plants, which also triggers a specific defense response. Plants produce volatile organic compounds in response to insect feeding; these may repel harmful insects or attract predatory insects that prey on the harmful pests.

Studies focusing on plants under pathogen attack have improved our knowledge of plant–pathogen interactions. Pathogens prefer host cells as a source of the nutrients required for their growth. Plants possess an innate ability to sense and recognize potential invading microorganisms and to mount successful defenses (Pandey et al., 2017). After pathogen recognition, plant cells broadly reprogram their metabolic activities and switch on their defense mode. Substantial evidence supports the prevailing
Phytohormones are small molecules produced within plants that govern diverse physiological processes and act as central players in triggering the plant immune signaling network (Howe and Jander, 2008; Bari and Jones, 2009; Pieterse et al., 2009; Katagiri and Zipfel et al., 2006). Activated immune responses (e.g., production of reactive oxygen species [ROS], callose deposition, activation of mitogen-activated protein kinases [MAPKs], transcriptional reprogramming, and production of phytohormones) occur in both PTI and ETI; however, they exhibit temporal and quantitative differences (Cui et al., 2015).

Antagonistic or synergistic interactions among diverse hormone signal transduction pathways enable a plant to finely regulate its immune response to any invader encountered. However, a concept that has received increasing interest over the past few years is the complex crosstalk among different classes of hormones that may enhance resistance against a particular pathogen but could also have a strong negative effect on resistance; the overall effects depend on the lifestyle and overall infection biology of the invading pathogen, as well as the specialized features of each interaction. Furthermore, emerging evidence shows that these complex pleiotropic effects that arise from a plant’s defense response are caused by hormone signaling and multiple genes (Jarosch et al., 1999; Bacete et al., 2020; Kim et al., 2022). Hereafter, we use the term “ambivalence effect” to refer to phenomena in which gene/hormone relationships result in both positive and negative effects from immune responses because of the diversity of plant pathogen lifestyles; we contrast such phenomena with “trade-off,” which refers to growth defects modulated by hormonal pathways that may or may not be accompanied by a resistance-enhancing effect.

In this review, we have surveyed recent advances in deciphering the ambivalent outcomes of immune signaling network interac-

DAMP molecules regulate the ambivalence effect

DAMPs in both mammals and plants are recognized by a diverse set of germline-encoded PRRs and trigger early immunity-related signals, including MAPK activation, cytosolic Ca^{2+} influx, ROS production, and various phenotypic resistance responses (Heil and Land, 2014; Tanaka et al., 2014; Acevedo et al., 2015; Choi and Klessig, 2016; Duran-Flores and Heil, 2016; Gust et al., 2017; Li et al., 2020). In contrast to the large number of known mammalian tissue injury-derived danger signals, surprisingly few plant DAMPs have been identified thus far. These include proteins and small peptides (Choi et al., 2016; Souza et al., 2017), extracellular DNA (Duran-Flores and Heil, 2016; Vega-Muñoz et al., 2018), nucleotides such as extracellular adenosine triphosphate (Tanaka et al., 2014; Chen et al., 2017), and carbohydrates such as extracellular sucrose (Cooksey et al., 1983; Duran-Flores and Heil, 2016). In plants, the responses triggered by endogenous elicitors or DAMPs largely overlap with responses activated by PAMPs/effectors, similar to the findings in other eukaryotic organisms (Hein et al., 2009; Heil and Land, 2014). For instance, different PAMP- and DAMP-induced signaling pathways converge at early stages by sharing their main signaling components, such as NADPH oxidase, MAPK cascades, several defense genes (Navarro et al., 2004; Zipfel et al., 2006; Denoux et al., 2008), and ion channels (Krol et al., 2010). Collectively, the discovery and characterization of diverse immunogenic triggers and their receptors have revealed that plant-derived oligogalacturonides (OGs) and microbial PAMPs induce largely overlapping patterns of plant defenses and prime the plant immune system against pathogens. Emerging evidence indicates that DAMP-mediated signaling may modulate disease resistance, with outcomes dependent on the pathogen’s lifestyle and the genetic constitution of the host.
Phytosulfokines (PSKs), which were purified from plant cell culture media, are secreted sulfated pentapeptides (Matsubayashi and Sakagami, 1996). PSY1 (an 18-amino-acid sulfated and glycosylated peptide) and PSKα (a bisulfated 5-amino-acid peptide) are perceived by the LRR-receptor kinases PSY1R and PSKR1 (PSK receptors (Figure 1A), respectively; both reactions generate a feedback loop that opposes immunity and promotes growth (Matsubayashi et al., 2002; Mosher et al., 2013). PSKα and PSY1 negatively regulate PAMP-mediated defense. The pskr1 and psy1r mutants exhibited enhanced defense gene expression and heightened resistance against the biotrophic pathogen \textit{Pseudomonas syringae} and the fungus \textit{Fusarium oxysporum}. Conversely, \textit{pskr1} mutants exhibited enhanced susceptibility to the necrotrophic fungus \textit{Alternaria brassicicola} (Table 1) (Mosher et al., 2013; Shen and Diener, 2013). Earlier studies have shown that PSK attenuates the pathogen-triggered immune response induced upon detection of \textit{P. syringae pv. tomato} (Pst). Furthermore, \textit{pskr1} mutations led to the suppression of seedling growth and enhanced defense gene expression (Igarashi et al., 2012). Taken together, these results suggest that PSK has a role in balancing the trade-off between the maintenance of growth and the induction of costly pathogen defense systems, considering the wide range of pathogen lifestyles.

Other intracellular or extracellular matrix-derived DAMPs that are passively released upon wounding or microbial infection also exist. Homogalacturonan is the main component of pectins. It consists of a linear polymer of 1,4-linked \(\alpha\)-galacturonic acid and \(\alpha\)-D-galacturonic acid and passively released upon wounding or microbial infection. Homogalacturonan is the main component of pectins, which often attack and propagate in apoplastic spaces within plant tissues. (A) The perception of pathogen-derived, non-self, pathogen-associated molecular patterns (PAMPs; flagellin, elongation factor-Tu, and chitin) by pattern-recognition receptors (PRRs) such as BAK1 activates several signaling events, which include signaling pathways mediated by mitogen-activated protein kinases (MAPKs). Plant-derived damage-associated molecular patterns (DAMPs) such as PSKα and PSY1 are perceived by PSKR1 and PSY1R, respectively. DAMP and PRR recognition can trigger immune responses and may overlap with PTI. (B) Plant MAPK cascades in signaling effector-triggered defense response. Pathogens use effectors that are delivered to the plant cell to suppress plant immunity. Plants utilize resistance (R) proteins to sense the presence of these effectors, thereby triggering effector-triggered immunity (ETI). The activation of pathogen-responsive MAPK cascades is one of the earliest signaling events in ETI. Perception of PAMPs/MAMPs by cell surface-localized PRRs activates two branches of MAPK cascades in plants, the MEKK1–MKK1/MKK2–MPK4 and MEKK7–MKK4/MKK5–MPK3/MPK6 cascades. The MKK4/MKK5–MPK3/MPK6 branch contributes to PTI, whereas the MEKK1–MKK1/MKK2–MPK4 branch is guarded by SUMM2 through monitoring of MPK4 substrates. The \textit{Pseudomonas syringae} type III effector HopA1 inactivates MPK3/4/6 through dephosphorylation of the activation loop. Inhibition of MPK3/MPK6 causes impaired PTI, whereas inhibition of MPK4 induces SUMM2 activation and ETI. Through phosphorylation of target proteins, including the transcription factor WRKY33, MAPKs control the synthesis and/or activation of defense genes and the synthesis of antimicrobial metabolites, among other defense responses. (C and D) Some effectors specifically bind to the promoter regions of target genes, inducing and/or decreasing their expression. The effector victorin binds to the host virulence target Trx-h5 and activates LOV1 (a nucleotide-binding leucine-rich repeat protein)-mediated susceptibility to \textit{Colletotrichum graminicola}. The transcription of \textit{Trx-h5} is regulated by the transcription factor YY1 through its interaction with the mediator MED18 (Q). The fungus \textit{Magnaporthe oryzae} delivers hundreds of effector proteins into the plant cytoplasm during infection. The effectors MoHTR1 and MoHTR2 target the nucleus and reprogram the transcription of immunity-associated genes, such as MYB4 and WRKY45, respectively, to promote \textit{M. oryzae} infection (D). Arrows and lines with bars indicate positive and negative regulatory actions, respectively. “X” indicates blocked processes. See the text and Table 1 for further details.

**Figure 1.** Schematic representation of the molecular components involved in the ambivalence effect in plants. Plants face continuous challenges from several biotrophic, hemibiotrophic, and necrotrophic pathogens, which often attack and propagate in apoplastic spaces within plant tissues. (A) The perception of pathogen-derived, non-self, pathogen-associated molecular patterns (PAMPs; flagellin, elongation factor-Tu, and chitin) by pattern-recognition receptors (PRRs) such as BAK1 activates several signaling events, which include signaling pathways mediated by mitogen-activated protein kinases (MAPKs). Plant-derived damage-associated molecular patterns (DAMPs) such as PSKα and PSY1 are perceived by PSKR1 and PSY1R, respectively. DAMP and PRR recognition can trigger immune responses and may overlap with PTI. (B) Plant MAPK cascades in signaling effector-triggered defense response. Pathogens use effectors that are delivered to the plant cell to suppress plant immunity. Plants utilize resistance (R) proteins to sense the presence of these effectors, thereby triggering effector-triggered immunity (ETI). The activation of pathogen-responsive MAPK cascades is one of the earliest signaling events in ETI. Perception of PAMPs/MAMPs by cell surface-localized PRRs activates two branches of MAPK cascades in plants, the MEKK1–MKK1/MKK2–MPK4 and MEKK7–MKK4/MKK5–MPK3/MPK6 cascades. The MKK4/MKK5–MPK3/MPK6 branch contributes to PTI, whereas the MEKK1–MKK1/MKK2–MPK4 branch is guarded by SUMM2 through monitoring of MPK4 substrates. The \textit{Pseudomonas syringae} type III effector HopA1 inactivates MPK3/4/6 through dephosphorylation of the activation loop. Inhibition of MPK3/MPK6 causes impaired PTI, whereas inhibition of MPK4 induces SUMM2 activation and ETI. Through phosphorylation of target proteins, including the transcription factor WRKY33, MAPKs control the synthesis and/or activation of defense genes and the synthesis of antimicrobial metabolites, among other defense responses. (C and D) Some effectors specifically bind to the promoter regions of target genes, inducing and/or decreasing their expression. The effector victorin binds to the host virulence target Trx-h5 and activates LOV1 (a nucleotide-binding leucine-rich repeat protein)-mediated susceptibility to \textit{Colletotrichum graminicola}. The transcription of \textit{Trx-h5} is regulated by the transcription factor YY1 through its interaction with the mediator MED18 (Q). The fungus \textit{Magnaporthe oryzae} delivers hundreds of effector proteins into the plant cytoplasm during infection. The effectors MoHTR1 and MoHTR2 target the nucleus and reprogram the transcription of immunity-associated genes, such as MYB4 and WRKY45, respectively, to promote \textit{M. oryzae} infection (D). Arrows and lines with bars indicate positive and negative regulatory actions, respectively. “X” indicates blocked processes. See the text and Table 1 for further details.
| Protein function | Gene | Gene product | Plant species | Pathogen species | Pleiotropic effect |
|------------------|------|--------------|---------------|------------------|-------------------|
| Transcription factor | WRKY33 | WRKY transcription factor | Arabidopsis | Pseudomonas syringae | increased susceptibility to Botrytis cinerea and Alternaria brassicicola |
| | WRKY45 | WRKY transcription factor | rice | Cochliobolus miyabeanus | increased susceptibility to Magnaporthe oryzae and Xanthomonas oryzae pv. oryzae in MoHTR2 (Magnaporthe oryzae effector that represses OsWRKY45 expression) overexpression (OX) transgenic rice |
| | WRKY70 | WRKY transcription factor | Arabidopsis | Alternaria brassicicola | increased resistance to Erysiphe cichoracearum |
| | WRKY50, WRKY51 | WRKY transcription factor | Arabidopsis | Pseudomonas syringae | increased susceptibility to Botrytis cinerea |
| | MYB4 | MYB transcription factor | rice | Cochliobolus miyabeanus | increased susceptibility to Magnaporthe oryzae and Xanthomonas oryzae pv. oryzae in MoHTR1 (Magnaporthe oryzae effector that represses OsMYB4 expression) OX transgenic rice |
| Kinase | PSY1R, PSKR1 | leucine-rich repeat receptor kinase (LRR-RK) | Arabidopsis | Fusarium oxysporum/Pseudomonas syringae | increased susceptibility to Alternaria brassicicola |
| | BIK1 | plasma membrane-localized ser/thr protein kinase involved in early PTI signaling | Arabidopsis | Pseudomonas syringae | increased susceptibility to Botrytis cinerea and Alternaria brassicicola |
| | MPK4 | MAP kinase | Arabidopsis | Pseudomonas syringae | increased susceptibility to Alternaria brassicicola |
| DELLA protein | Sin1c | DELLA protein | barley | Blumeria graminis | increased susceptibility to Oculimacula spp. (eyespot) |
| | Sin1d | DELLA protein | barley | Oculimacula spp. | increased susceptibility to Blumeria graminis |

Table 1. Genes that contribute to the ambivalence effect.
| Protein function                              | Gene | Gene product                                        | Plant species | Pathogen species                                      | Pleiotropic effect                                                                 |
|----------------------------------------------|------|-----------------------------------------------------|---------------|-------------------------------------------------------|------------------------------------------------------------------------------------|
| Hypersensitive response-based programmed cell death and cell wall-based defense | BI-1 | transmembrane protein, Bax inhibitor-1              | barley/carrot | *Blumeria graminis/Thielaviopsis basicola*            | increased susceptibility to *Botrytis cinerea* in carrots, reduced *Chalara elegans* root symptoms |
|                                              | HvMLO| membrane-anchored protein                           | barley        | *Blumeria graminis*                                    | increased susceptibility to *Bipolaris* and *Cochliobolus*                         |
| Resistance protein                           | Pc-2 | NBS-LRR (nucleotide binding leucine rich repeat) resistance gene | oats          | confers resistance to the rust fungus *Puccinia coronata* in oats | increased susceptibility to *Cochliobolus victoriae*                                 |
| Others                                       | ARR6 | type-A response regulator                           | Arabidopsis   | *Plectosphaerella cucumerina*                          | increased susceptibility to the bacterial wilt *Ralstonia solanacearum*            |
|                                              | MKP2 | MAP kinase phosphatase                               | Arabidopsis   | *Ralstonia solanacearum*                               | increased susceptibility to *Botrytis cinerea*                                     |
|                                              | MED19a| mediator of RNA polymerase II transcription subunit 19a-like protein | Arabidopsis   | *Hyaloperonospora arabidopsidis*                       | increased resistance to *Botrytis cinerea* in *HaRxL44* (*Hyaloperonospora arabidopsidis* effector that interacts with MED19a) OX plants |
|                                              | LACS2| Acyl-CoA synthetase for cutin synthesis              | Arabidopsis   | *Botrytis cinerea*                                     | increased susceptibility to *Pseudomonas syringae*                                 |

Table 1. Continued
Adenosine-5’-triphosphate (ATP) is an energy-rich metabolite of fundamental importance in all organisms. It is a key substrate and cofactor in a wide range of intracellular biochemical processes. Surprisingly, given its value as a biochemical intermediate, ATP is secreted by plant, animal, and microbial cells. This extracellular ATP (eATP) can act as a signal in response to various biotic and abiotic stresses (Dark et al., 2011; Ramachandran et al., 2019). Pathogen infection, wounding, or insect infestation also causes plants to release high levels of ATP (approximately 40 μM) into the extracellular matrix, where it is recognized as a DAMP to initiate plant resistance responses (Chivasa et al., 2009; Choi et al., 2014a,b; Medina-Castellanos et al., 2014). Indeed, eATP induces various defense responses in parallel with plant defense hormones and through an independent mechanism (Jewell et al., 2019). Some of these responses are involved in enhancing resistance against the necrotroph B. cinerea mediated by eATP-JA-mediated synergistic signaling that requires ROS as well as other second messengers, nitrous oxide, and calcium (Tripathi et al., 2018; Tripathi and Tanaka, 2018). Moreover, eATP also regulates gene expression through pathways independent of CORONATINE-INSENSITIVE 1 (COI1) but reliant on MYC transcription factors and CALMODULIN-BINDING TRANSCRIPTION ACTIVATOR 3 (CAMTA3) (Jewell et al., 2019). SA is also involved in eATP-induced intracellular responses. A complex relationship appears to exist between eATP, SA, and the signaling pathways that they control (Chivasa et al., 2009). Application of exogenous ATP into leaves caused a decrease in basal SA levels, whereas SA treatment of tobacco cell cultures caused a collapse in the concentration of ATP in the medium (Chivasa et al., 2009). Conversely, under appropriate illumination conditions, enzymatic depletion of eATP by apyrase induced pathogenesis-related gene expression and increased resistance to Pseudomonas syringae pv. tabaci and tobacco mosaic virus (Chivasa et al., 2009). Thus, eATP may suppress pathogenesis-related responses by inhibiting intracellular SA signaling.

Ambivalence effect with mutations in PTI components

Phosphorylation is central to defense in signal transduction (Jagodzik et al., 2018); the activation of the MAPKs MPK3, MPK4, and MPK6 (MPK3/4/6) is a hallmark of immune system activation and is crucial for establishing disease resistance (Bi et al., 2018). All known PRRs activate two MAPK cascades consisting of MAPK kinase kinase (MAPKKK), MAPK kinase (MKK), and MAPKs: MAPKKK3/MAPKKK5-MKK4/MKK5-MPK3/MPK6, which positively regulates defense, and MEKK1-MKK1/MPK2-MPK4, which negatively regulates immune responses (Petersen et al., 2000; Berrieri et al., 2012; Kong et al., 2012; Genot et al., 2017; Bi et al., 2018). Plants with mutations in signal transduction pathway genes, for example, BIK1, MPK4, MPK2, EDR1, and AtWRKY4/8/18/33/40/60, exhibit enhanced biotrophic resistance but reduced necrotrophic resistance. For instance, mutations in WRKY33, which is targeted by MPK4 in Arabidopsis (Figure 1B), caused enhanced susceptibility to B. cinerea together with decreased PDF1.2 expression (Table 1). Conversely, the overexpression of WRKY33 increased the level of resistance against two necrotrophic fungal pathogens. The wrky33 mutants did not exhibit changes in their response to a virulent strain of the bacterial pathogen P. syringae, although the ectopic expression of WRKY33 resulted in enhanced susceptibility to this pathogen (Table 1) (Petersen et al., 2008; Birkenbihl et al., 2012). WRKY33 is a substrate of
The ambivalence effect

MPK3/6 that activates transcription of PHYTOALEXIN DEFICIENT 3 (PAD3); PAD3 encodes a cytochrome P450 enzyme (CYP 71B15) that carries out the last step of camalexin biosynthesis, causing induction of camalexin, which has anticrobial effects (Zhou et al., 1999; Mao et al., 2011). Moreover, MPK4 is targeted by P. syringae bacterial type III effector HopA1, and the MPK4 cascade was originally considered to be a negative regulatory pathway of defense responses because its disruption leads to autoimmune phenotypes characterized by spontaneous cell death, constitutive defense responses, and dwarf morphology (Petersen et al., 2000; Ichimura et al., 2006; Qiu et al., 2008). However, it was discovered that the autoimmune responses in the MPK4 cascade mutants are caused by ETI activation mediated by SUPPRESSOR OF MKK1/MKK2 2 (SUMM2), an NLR protein (Zhang et al., 2012). Mutations in SUMM2 almost completely suppress the autoimmune phenotypes in mpk4, mkk1/mkk2, and mekk1 mutants. In addition to SUMM2, the TIR-type NLR protein RPS6 can also partially suppress the autoimmune phenotypes of mekk1 and mpk4 plants (Takagi et al., 2019). Interestingly, a recent study showed that disruption of both SUMM2 and RPS2 fully suppresses the autoimmune response of mpk4 mutants (Takagi et al., 2022). As a result, the MPK4 cascade is proposed to be a “guardian” of SUMM2 (Zhang et al., 2017).

BOTRYTIS CINEREA-INDUCED KINASE 1 (BIK1), a kinase involved in early PTI signaling, is a positive regulator of resistance against B. cinerea (Veronese et al., 2006). The inactivation of BIK1 (bik1) resulted in susceptibility to B. cinerea and A. brassicicola, although it enhanced resistance against P. syringae (Table 1) (Veronese et al., 2006). However, during the initiation of immune signaling after pathogen recognition, loss of BIK1, like that of MPK4, results in autoimmune responses and resistance rather than a lack of immune activation (Couto and Zipfel, 2016). These results are consistent with the hypothesis that crucial components in the initiation of immune signaling may be “guarded” by NLRs. The autoimmune phenotype of bik1 mutants may thus reflect the consequence of an improper activation of an NLR, rather than resulting from loss of BIK1 kinase activity. bik1 plants were also reported to have a higher basal SA level than wild-type plants (Veronese et al., 2006; Lei et al., 2014), suggesting that this ambivalent effect may be attributable to the SA pathway and other unknown pathways.

Another example of the ambivalence effect involves the gene encoding MAPK PHOSPHATASE 2 (MKP2), which dephosphorylates phospho-MPK3 and phospho-MPK6 in vitro (Figure 1B) (Lee and Ellis, 2007; Lumbreras et al., 2010). Mutant plants in which MKP2 was disrupted exhibited a delay in the development of wilt symptoms after infection with R. solanacearum, whereas more prominent disease symptoms were observed after infection with B. cinerea (Table 1) (Lumbreras et al., 2010).

AMBIGUITY EFFECT OF THE HOST PROTEINS TARGETED BY EFFECTORS

Effectors modulate S genes

Plant genes that facilitate pathogen infection and contribute to susceptibility are termed susceptibility genes (S genes) (Zaidi et al., 2018). Loss-of-function mutations in S genes substantially reduce the compatibility between hosts and pathogens; such mutations enable resistance against a diverse array of pathogens. Pathogens transmit effector proteins to the host to manipulate host processes that are important for plant–pathogen interactions. Filamentous pathogens are predicted to secrete up to several hundred effectors, whereas bacteria produce a few dozen (Bozkurt et al., 2012; Donofrio and Raman, 2012; Xin and He, 2013). After secreting effectors, filamentous pathogens require the effectors to be taken up by host cells (Bozkurt et al., 2012; Donofrio and Raman, 2012), and most effectors appear to act inside the host cell; bacteria can inject effectors using a type III secretion system (Xin and He, 2013). The identification of effector–target interactions in the host is thus essential for fully understanding the interactions between plant susceptibility and pathogen virulence. To increase virulence, many pathogen effectors suppress host factors involved in resistance (Deslandes and Rivas, 2012). Some effectors, such as members of the transcription activator-like effector family secreted by the bacterial pathogen Xanthomonas, bind to specific genomic sequences in their host plant and manipulate the expression of susceptibility factors encoded by S genes (Kay et al., 2007; Chen et al., 2010; Römer et al., 2010; Noel et al., 2013; Streubel et al., 2013).

The alteration of S gene expression appears to be a preferred and viable strategy, particularly in Xanthomonas bacteria. Other pathogen effectors also target S genes and contribute to the ambivalence effect in the host. Victorin, a fungal effector of the necrotrophic fungus Cochliobolus victoriae, the pathogen responsible for Victoria blight in oats, specifically targets Arabidopsis TRXh5 (Lorang et al., 2004, 2007). Victorin binds to TRXh5 via the first Cys of its active site (Cys39), resulting in inhibition of TRXh5 activity (Sweet and Wolpert, 2007). This is recognized by LOCUS ORCHESTRATING VICTORIN EFFECTS1 (LOV1), an NB-LRR that guards TRXh5, and in turn activates programmed cell death (PCD) (Lorang et al., 2007, 2012; Sweet and Wolpert, 2007; Sweet et al., 2008). As necrotrophs kill host cells before feeding, TRXh5-victorin-induced cell death promotes disease susceptibility to C. victoriae. Consequently, victorin inhibits TRXh5 activity and can cause susceptibility to biotrophic pathogens, providing a clue as to why LOV1 guards TRXh5 and demonstrating that C. victoriae hijacks a redox-dependent immune response to biotrophs to promote its own virulence (Figure 1C and Table 1) (Lorang et al., 2012). Victorin sensitivity in oats is conferred by a single dominant gene named Vb (Wolpert et al., 1985). Interestingly, the oat Pc-2 gene confers disease resistance against the biotrophic crown rust fungus Puccinia coronata and is tightly linked to the Vb gene, complicating breeding efforts against both rust and blight diseases (Meehan and Murphy, 1946; Litzenberger, 1949). Pc-2 and Vb genes are now considered to be the same gene, which confers resistance to P. coronata but susceptibility to C. victoriae (Wolpert et al., 2002; Lorang et al., 2012). This is a remarkable example of how necrotrophs can evolve mechanisms to highjack R genes against biotrophs for their own benefit. In conclusion, although effectors are usually known for their suppression of resistance, a substantial number of effectors activate S genes and sometimes regulate the ambivalence effect.

Effectors targeting phytohormone crosstalk

Hormonal signaling pathways in plant immunity are often interconnected, and this can lead to antagonistic or synergistic
interactions (Weiss and Ori, 2007; Choi et al., 2010; Jiang et al., 2010; Argueso et al., 2012; Pieterse et al., 2012; Naseem et al., 2014, 2015; Berens et al., 2017). An example is the antagonism between the SA and JA pathways (Pieterse et al., 2009; Tsuda et al., 2009). Within this context, we describe our current understanding of effector proteins that directly influence SA/JA-mediated pathways. The effects of other hormones (including hormones in the SA and JA response pathways) on the ambivalence effect are discussed below.

The downy mildew pathogen of Arabidopsis, Hyaloperonospora arabidopsisidis (Hpa), employs an intriguing tactic to combat host SA-mediated immune responses. The Hpa effector HaRxL44 specifically interacts with Arabidopsis MEDIATOR COMPLEX SUBUNIT 19a (MED19a), resulting in the degradation of MED19a in a proteasome-dependent manner in host cell nucleoplasm. By degrading MED19a, HaRxL44 shifts the defense balance between the SA and JA/ET pathways while inducing JA/ET-responsive genes and suppressing SA-responsive PR1 gene expression (Figure 2). Thus, HaRxL44-elicited MED19a degradation provides immunity against necrotrophs by means of an enhanced JA/ET response but favors the growth of biotrophs (such as Hpa) through suppression of the SA response (Table 1) (Caillaud et al., 2013).

The ambivalence effect was also observed upon the expression of pathogen effector genes in transgenic plants (Kim et al., 2020). Recently, we described two M. oryzae-specific nuclear effectors, MoHTR1 and MoHTR2, that modulate the expression of the target genes OsMYB4 and OsWRKY45, respectively (Figure 1D and Table 1) (Kim et al., 2020). The overexpression of these effectors in rice conferred protection only against the necrotrophic fungus C. miyabeanus while increasing susceptibility to M. oryzae and Xanthomonas oryzae pv. oryzae (Xoo) (Kim et al., 2020).

CONSERVED ROLES OF PHYTOHORMONES IN PLANT DEFENSE

In the model plant A. thaliana, with some exceptions, SA is predominantly associated with resistance against biotrophic and hemibiotrophic pathogens, whereas JA- and ET-driven defenses positively regulate immunity against necrotrophic pathogens (Glazebrook, 2005; Pieterse et al., 2009; Robert-Seilianiitz et al., 2011). Other hormones, such as ABA, GAs, auxin, and CKs, modulate the ambivalence effect in hormone signaling networks mainly through interactions with SA and JA (Pieterse et al., 2009; Robert-Seilianiitz et al., 2011).

SA, JA, and ET as conserved regulators of the ambivalence effect in plant defense

SA is a natural phenol compound (synthesized by plants in response to a wide range of pathogens) that is well known for its roles in thermogenesis, flowering, plant-defense signaling, and systemic acquired resistance (Loake and Grant, 2007; Vlot et al., 2009). JA is an oxygenated fatty acid (oxylipin) involved in resistance against necrotrophic pathogens and insect infestation (Thaler et al., 2004). JA and its structurally related metabolites, collectively known as jasmonates, are lipid-derived regulators that fulfill essential roles in numerous physiological processes (e.g., biotic and abiotic stress defenses, wound responses, and secondary metabolite syntheses). The small gaseous hormone ET controls diverse developmental processes, as well as responses to environmental stimuli (Johnson and Ecker, 1998; Wang et al., 2002). In plant immunity, ET is generally presumed to act in concert with JA to induce resistance against necrotrophs while antagonizing SA-mediated resistance against biotrophs (Derksen et al., 2013). However, there is increasing evidence that ET can interact both positively and negatively with SA, depending on the lifestyle of the invading pathogen (Van der Ent and Pieterse, 2012; Derksen et al., 2013).

The first indications of the antagonistic nature of the crosstalk between the SA and JA pathways came from studies in tomato; those studies revealed that SA and aspirin, its acetylated form, are potent suppressors of the JA-dependent wound response (Doherty et al., 1988; Peña-Cortés et al., 1993). Since its discovery in tomato, the antagonism between the SA and JA pathways has been demonstrated in many plant species, including Arabidopsis (Van Wees et al., 1999; Spoel et al., 2003). SA-JA crosstalk has been demonstrated in experiments in which inoculation with the hemibiotrophic pathogen Pst DC3000 rendered plants more susceptible to the necrotrophic pathogen A. brassicicola and led to decreased expression of the JA/ET markers PDF1.2, HEL, and CHI-B (Spoel et al., 2007). Similarly, prior inoculation with the SA-inducing biotrophic pathogen Hpa suppressed JA-mediated defenses that were activated upon feeding by caterpillars of Pieris rapae (Koornneef et al., 2008). This reciprocal antagonistic crosstalk between the SA and JA pathways, initially demonstrated in Arabidopsis, has also been observed in other plant species; phylogenetic studies indicate that it may have evolved with the development of angiosperms (Berens et al., 2017).

Several other proteins play roles in regulating SA-mediated suppression of the JA pathway, including NPR1, nuclear TGA and WRKY transcription factors, and MAPKs (Pieterse et al., 2012). Functional data (primarily based on gene expression analyses) revealed that NPR1 modulates the balance between the SA and JA response pathways in Arabidopsis, rice, and tomato, implying that this subfunction of NPR1 may have an ancient origin (e.g., in the common ancestor of monocots and eudicots) (Glazebrook et al., 2003; Spoel et al., 2003; Johansson et al., 2006; Mao et al., 2007; Yuan et al., 2007; Stein et al., 2008; Leon-Reyes et al., 2009; Ramirez et al., 2010).

Downstream of NPR1, several WRKY transcription factors have important roles in the regulation of SA-dependent defense responses; many of them are upregulated by SA (Rushton et al., 2010). Several WRKY transcription factors have been implicated in SA-JA crosstalk (Li et al., 2004, 2006). Arabidopsis WRKY33, a positive regulator of JA/ET-mediated defense response signaling and a negative regulator of SA-mediated defense response signaling, has an important role in plant defense against necrotrophs and biotrophs (Table 1) (Zheng et al., 2006). Gao et al. (2011) showed that WRKY50 and WRKY51 mediate SA- and low oleic acid (18:1)-dependent repression of JA signaling. Signaling induced by a decrease in oleic acid levels simultaneously upregulated SA-mediated responses and inhibited JA-inducible defenses (Figure 2), resulting in enhanced resistance against biotrophs and increased susceptibility to necrotrophs (Table 1) (Gao et al., 2011). Moreover, the overexpression of WRKY70
activated several SA-responsive genes (Figure 2) and compromised resistance against the necrotrophic fungus A. brassicicola, while enhancing SA-dependent resistance against the biotrophic fungus Erysiphe cichoracearum (Table 1) (Li et al., 2006; Ren et al., 2008).

In plant immunity, ET generally obstructs symptom development caused by necrotrophic pathogens while promoting cell death caused by biotrophic and hemibiotrophic pathogens (Bent et al., 1992; Hoffman et al., 1999; Thomma et al., 1999; Derksen et al., 2013). For example, ET-insensitive soybean mutants displayed less severe symptoms when infected with the hemibiotrophs P. syringae pv. glycinea and Phytophthora sojae; they exhibited more severe symptoms when infected with the necrotrophic fungi Septoria glycines and Rhizoctonia solani (Hoffman et al., 1999).

Similarly, Arabidopsis mutants with decreased ET sensitivity exhibited enhanced resistance against the hemibiotrophic pathogen Pst and the biotrophic pathogen Xanthomonas campestris pv. campestris; they demonstrated enhanced susceptibility to the necrotrophic fungus B. cinerea (Bent et al., 1992; Thomma et al., 1999). These findings support the notion that JA- and ET-controlled responses have ambivalent roles in Arabidopsis resistance against diverse pathogens with different lifestyles.

Modulation of the ambivalence effect by other plant hormones
In contrast to the classic defense hormones SA, JA, and ET, other hormones (e.g., ABA, GAs, auxins, and CKs) have historically been studied primarily because of their roles in regulating major physiological processes, abiotic stress, growth, and development (Schwartz et al., 2003; Aloni et al., 2005; Sakakibara, 2006; Adie et al., 2007; Benjamins and Scheres, 2008; Sun, 2011); thus, they have only recently emerged as additional participants in plant–microbe interactions. Although their functions and precise roles in regulating plant defense have not yet been clarified, recent data are now beginning to reveal how these hormones modulate the ambivalence effect.

In addition to its role in plant development and adaptation to abiotic stress, particularly salinity and drought stress, ABA has emerged as an important modulator of the plant immune signaling network (Asselbergh et al., 2008; Ton et al., 2009; Cao et al., 2011). In rice, the application of ABA suppressed basal immunity against both blast and bacterial blight (Koga et al., 2004; Jiang et al., 2010; Xu et al., 2013) while inducing resistance against the brown spot fungus (De Vleesschauwer et al., 2010). Moreover, successful infection with these pathogens is commonly associated with extensive reprogramming of ABA-responsive and -biosynthesis genes, implying that these pathogens hijack the rice ABA pathway to cause disease (Koga et al., 2004; Jiang et al., 2010; Yazawa et al., 2012; Xu et al., 2013). Therefore, similar to ET, ABA appears to have an ambivalent role in rice immunity, acting as either a positive or negative regulator of disease resistance by interfering at multiple levels with biotic and abiotic stress signaling cascades.

Although they were first discovered in a fungal plant pathogen, GAs and their signaling components have only recently been implicated in plant responses to pathogen attack. According to current concepts, GAs promote plant growth by inducing the degradation of a class of nuclear proteins known as DELLAs (Sun, 2011). Research with Arabidopsis has indicated that DELLAs may have ambivalence effects, including the alteration of responses to pathogens. Arabidopsis mutants lacking four of the five DELLAs exhibited increased levels of resistance against the hemibiotrophic bacterium Pst, together with elevated levels of SA (Navarro et al., 2008). By contrast, a correlation between attenuated induction of the JA marker gene PDF1.2 and enhanced susceptibility to the necrotrophic fungus A. brassicicola was observed in the same quadruple mutants (Navarro et al., 2008). The role of DELLAs in response to pathogens is also generally conserved in the monocots wheat and barley; experiments on the effects of differential DELLAs status have revealed similar resistance ambivalence involving increased susceptibility to biotrophs and enhanced resistance against necrotrophs (Saville et al., 2012). In barley cv. Himalaya, a gain-of-function, GA-insensitive allele at the DELLA-encoding Slender 1 locus, Sn1d, exerted similar effects to Rht genes in wheat: enhanced susceptibility to the biotrophic fungus Blumeria graminis mildew, as well as reduced susceptibility to a necrotrophic pathogen of the stem base, Oculilmaucula spp. (eyespot), and to Fusarium graminearum head blight. A loss-of-function allele, sln1c, had opposite effects, increasing resistance against mildew associated with the spread of necrotic lesions while enhancing susceptibility to eyespot (Table 1). Importantly, DELLA proteins modulate plant immunity via competitive binding to JAZ proteins (Jasmonate, Zim Domain), a family of JA-signaling repressors (Hou et al., 2010; Wild et al., 2012; Yang et al., 2012). JAZ proteins bind to and inhibit the activities of a wide array of transcription factors, including the key JA transcriptional activator MYC2 (Kazan and Manners, 2012, 2013). DELLA proteins close off JAZ1 by binding to it, thereby reducing JAZ–MYC2 interactions and releasing free MYC2, which then activates JA-responsive gene expression and enhances resistance against necrotrophic pathogens (Navarro et al., 2008; Hou et al., 2010; Wild et al., 2012; Yang et al., 2012). On the basis of these findings, GAs are presumed to suppress cellular competence in response to jasmonates and thus to shift the balance between SA- and JA-dependent signaling, resulting in resistance ambivalence in the response to pathogens with different lifestyles.

In Arabidopsis, auxins, such as indole-3-acetic acid, have been shown to interact antagonistically with SA, thereby increasing the susceptibility to biotrophic pathogens (Kazan and Manners, 2009). Thus far, auxin attenuates resistance against (hem) biotrophs but enhances plant defenses against necrotrophic pathogens (Fu and Wang, 2011). Accordingly, a rice transgenic line with reduced levels of free indole-3-acetic acid, caused by overexpression of the auxin-conjugating GRETCHEN HAGEN 3 (GH3) protein, exhibited enhanced resistance against M. oryzae and Xoo (Ding et al., 2008; Domingo et al., 2009; Fu et al., 2011); however, it was susceptible to C. miyabeanus (Fonteyne, 2011). However, in contrast to Arabidopsis, in which auxin is presumed to repress SA levels and signaling, auxin-induced susceptibility to biotrophs in rice is not associated with changes in SA or JA signaling. Instead, it has been proposed that pathogen-induced auxin triggers the expression of cell wall-loosening expansins, thereby facilitating pathogen entry and causing increased nutrient leakage (Ding et al., 2009). In addition, auxins can negatively impact plant defense by interfering with other hormone signaling
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pathways or with PTI (Robert-Seilaniantz et al., 2011). The bacterial PAMP flg22, a peptide from flagellin protein (Boiler and Felix, 2009; Pel and Pieterse, 2012), induces an Arabidopsis microRNA (miR393) that targets the auxin receptors TRANSPORT INHIBITOR RESPONSE1 (TIR1), AUXIN SIGNALING F-BOX 2 (AFB2), and AFB3, leading to repressed auxin signaling (Jones-Rhoades and Bartel, 2004; Sunkar and Zhu, 2004; Navarro et al., 2006; Huot et al., 2014). Plants constitutively expressing MIR393 are less susceptible to the bacterial pathogen Pst DC3000. By contrast, activation of auxin signaling through overexpression of an auxin receptor that is partially refractory to miR393-mediated transcript cleavage enhanced susceptibility to Pst DC3000 (Navarro et al., 2006). Collectively, these data demonstrate that auxins play a central role in balancing plant resistance responses.

CKs are some of the most recent development hormones to be linked to plant immunity. Together with SA, plant-derived CKs stimulate defense responses to biotrophs. In Arabidopsis, CKs activate the transcriptional regulator ARR2, which positively modulates SA signaling by interacting with TGA1A-RELATED GENE 3 (TGA3), a transcription factor critical for defense gene activation (Choi et al., 2010). Indeed, ARR2 binds directly to the promoters of PR1 and PR2 to induce their expression. The anti-biotrophic effect of CKs largely depends on SA biosynthesis and is probably dose-dependent (Argueso et al., 2012). Argueso et al. (2012) proposed a model of plant defense in which high concentrations of CKs increase SA-mediated resistance against biotrophic pathogens, whereas lower concentrations of CKs result in increased susceptibility to biotrophs, which is partially regulated by type-A ARRs (ARR3, ARR4, ARR5, ARR6, ARR8, and ARR9).

OVERLAPPING AMBIVALENT IMMUNE RESPONSES IN PTI AND ETI

PTI and ETI were traditionally considered to be independent immunity sectors contributing to pathogen resistance and converging on transcriptional defenses (Tao et al., 2003; Cui et al., 2015). However, PTI and ETI are interconnected and play synergistic roles to induce a set of downstream responses, such as the generation of ROS and global transcriptional reprogramming, for pathogen defense (Lu and Tsuda, 2021; Ngou et al., 2021; Yuan et al., 2021). PTI components are necessary for mounting an efficient ETI response, and, vice versa, ETI components are required for PTI; the interlink between PTI and ETI is crucial for the overall plant immune network (Ngou et al., 2021; Pruitt et al., 2021; Tian et al., 2021; Yuan et al., 2021). However, to date, evidence of PTI-ETI connectivity is mainly limited to Arabidopsis, and the underlying mechanisms remain unclear.

ROS function as key defense and signaling molecules and are induced in both PTI and ETI. ROS may function as signaling molecules, triggering plant immune and cell death responses (Tenhaken et al., 1995; Jabs, 1999; Torres, 2010). As major early signaling products, through activation of NADPH oxidases as well as peroxidases, ROS have been proposed to act as defense molecules that kill pathogens, as well as signaling molecules that activate additional immune responses (Figure 2) (Qi et al., 2017; Yuan et al., 2021). Recognition of a pathogen expressing an effector that is recognized by an R protein elicits biphasic ROS accumulation with an initial low-amplitude, transient phase (probably triggered by PAMPs), followed by a sustained phase of much higher magnitude, which is triggered based on effector recognition by the R protein (Torres et al., 2006). Plants resist invading pathogenic fungi, often biotrophs, by induction of the hypersensitive response, a PCD that results from pathogen recognition and is generally associated with the induction of ROS. Cell death increases resistance against biotrophic pathogens but helps necrotrophs, such as B. cinerea and Sclerotinia sclerotiorum, proliferate (Govrin and Levine, 2000). Recently, we reported that ROS are detected in the host plant during infection by M. oryzae and Xoo hemibiotrophs. Whereas ROS-mediated plant cell death is detrimental for hemibiotrophic pathogens, generation of ROS seems advantageous for a necrotrophic pathogen such as C. miyabeanus (Kim et al., 2022).

CELL WALL-ASSOCIATED AMBIVALENT RESPONSES TO PATHOGENS

The resistance conferred by R genes is based on pathogen recognition, followed by the induction of defense responses. Another type of resistance, based on the loss of function of S genes, has recently been identified (Eckardt, 2002; Pavan et al., 2011). S genes are a promising, emerging research focus because they are strong determinants of disease outcomes from plant–pathogen interactions (Van Schie and Takken, 2014). They can modulate core plant processes; in some instances, attenuation of these genes can lead to ambivalent immune responses that are dependent on pathogen lifestyles. An example of host genes that support the ambivalence effect is the SWEET genes; SWEET sugar transporters transport sucrose out of plant cells for sugar reallocation. SWEETs are S genes because they can be overexpressed in pathogen interactions and function in providing nutrients for the pathogen (Chandran, 2015). In summary, host cellular processes support certain demands of pathogens that feed from live tissue, and the components of these processes can be S genes.

Cuticle and cell wall structure

The cuticle and cell wall constitute the first layers of defense against microbial pathogens. They serve as physical barriers against pathogen penetration, as well as sensitive sensors for the timely activation of intracellular and systemic defense responses; the leaf cuticle contains components that are used by filamentous pathogens as essential developmental cues for pathogenicity (Hansjakob et al., 2011; Uppalapati et al., 2012; Wang et al., 2012). Plant genes encoding enzymes and other compounds involved in the synthesis of such components contribute to susceptibility and can also be regarded as S genes. Cutin-deficient Arabidopsis mutants bearing mutations in LONG-CHAIN ACYL-COA SYNTHETASE 2 (LACS2), a gene involved in cuticle biosynthesis, exhibited enhanced resistance against B. cinerea (Bessiere et al., 2007). In this situation, increased cuticular permeability appeared to enhance the diffusion of inoculum-derived elicitors that induced the production of small, polar antifungal compounds; these compounds inhibited B. cinerea growth (Bessiere et al., 2007). Conversely, the lacs2 mutation resulted in increased susceptibility to avirulent strains of P. syringae (Table 1) (Tang et al., 2007), indicating
that cutin has an important role as a physical barrier against hemibiotrophic pathogens. However, the cutinase transgenic lines form a defective cuticle in *Arabidopsis* and can result in increased resistance against necrotrophic fungal pathogens through a secondary (but poorly understood) mechanism involved in the ambivalence effect (Tang et al., 2007).

**Negative regulators of cell death are involved in the ambivalence effect**

PCD plays an important role in a wide range of developmental processes and in responses to biotic and abiotic stresses in plants (Dickman and Fluhr, 2013). PCD is essential for growth and development of multicellular organisms as well as for proper response to the environment, including the hypersensitive response to biotrophic pathogens (Gadjev et al., 2008). On the other hand, necrotrophs can also cause disease symptoms and trigger PCD in plant tissues by producing phytotoxins (Coffeen and Wolpert, 2004). The ambivalence effect toward diseases caused by biotrophic and necrotrophic pathogens has been observed in experiments with BAX INHIBITOR-1 (BI-1), which is a PCD suppressor in eukaryotes (Huckelhoven, 2004; Watanabe and Lam, 2009). BI-1 is localized to the endoplasmic reticulum; it is conserved in both plants and animals (Huckelhoven, 2004). BI-1 controls the hypersensitive response, a well-characterized form of plant defense against pathogens (Jakimova et al., 2005); it is also involved in susceptibility to penetration by powdery mildew (*Blumeria graminis*) in barley (Eichmann et al., 2004, 2010). BI-1 is considered a candidate susceptibility factor because its transient or stable overexpression favored the penetration of the biotrophic pathogen *Blumeria graminis* f. sp. *hordei* (*Bgh*) into host epidermal cells, thereby weakening the oxidative defense response and allowing consequent putrol development (Eichmann et al., 2004, 2006; Babaeizad et al., 2009). Moreover, BI-1 was expressed in carrots susceptible to the necrotroph *B. cinerea*, mediated resistance against fungal-induced leaf cell death, and decreased root symptoms and fungal sporulation after infection with the hemibiotrophic pathogen *Chalara elegans* (Thielaviopsis basicola) (Table 1) (Irani et al., 2006). In addition, stable expression of a green fluorescent protein-BI-1 fusion protein in barley leaves corresponded with limited development of the necrotroph *F. graminearum* and less severe infection (Babaeizad et al., 2009). These findings indicate that BI-1 has an ambivalent role in plant strategies against pathogen infection.

One of the best-known S genes is **MILDEW RESISTANCE LOCUS O** (*mlo*) in barley, which is required for powdery mildew penetration of epidermal cells and encodes a protein with seven transmembrane domains (Büsches et al., 1997). The *mlo* mutant bearing a loss-of-function mutation at the *MLO* locus exhibits broad-spectrum resistance against *Bgh*; thus, it has been widely used in European countries to protect barley from powdery mildew for almost four decades (Büsches et al., 1997; Kusch and Panstruga, 2017). However, the greatest limitation to its use is the ambivalence effect that comprises both resistance against powdery mildew and susceptibility to non-biotrophic pathogens. For instance, a new *mlo* allele of the S genes was precisely controlled in wheat through genome editing, and a new germplasm with broad-spectrum powdery mildew resistance and high yield was obtained (Li et al., 2022). However, such genes may inadvertently become a double-edged sword for plant health by creating unintended susceptibility to non-target pathogens.

Plants containing the *mlo* allele were more susceptible to diseases with necrotrophic stages, such as rice blast caused by *M. oryzae* (Jaroch et al., 1999), spot blotch disease caused by *Bipolaris sorokiniana* (Table 1) (Kumar et al., 2001), head blight caused by *F. graminearum* (Jansen et al., 2005), and Ramularia leaf spot caused by *Ramularia collo-cygni* (McGrann et al., 2014). In particular, the incidence of Ramularia leaf spot epidemics has increased over the past few decades in all major barley-growing regions, and the disease has become a major threat to barley production (Havis et al., 2015); this phenomenon highlights the existence of a pleiotropic effect that differentially regulates the manifestation of disease symptoms in barley upon infection by a facultative fungal pathogen. *MLO* is a well-known S gene, but its fundamental biochemical activity remains unknown. Studies of *MLO* will improve our understanding of the mechanisms underlying the ambivalence effect as it relates to host cell death and disease development in plants, enhancing the development of disease-resistance strategies in plant breeding programs.

**CONCLUDING REMARKS AND PERSPECTIVES**

It is critical to understand the fundamental mechanisms underlying plant disease resistance—this understanding will promote sustainable agriculture and aid in the maintenance of human health. Fueled by the advent of large-scale “omics” technologies and advances in computational biology for investigations of the model plant *Arabidopsis*, our understanding of the plant immune signaling network has improved greatly over the past decade. The tight coregulation of phytohormones, at least in the case of SA–JA antagonism, is widely evolutionarily conserved across land plant species (Thaler et al., 2012). Antagonistic effects between SA and JA signaling pathways are considered to provide plants with the regulatory potential to survive in their complex biological environments in a resource cost-effective manner (Thaler et al., 2012). This can be realized by shifting defense responses to either the SA- or JA-signaling pathway according to the lifestyle of the particular invading pathogen (Pieterse et al., 2012), referred to here as the ambivalence effect. Interestingly, attackers have evolved to manipulate JA–SA antagonism; hormone pathways not only protect against pathogen invasion but also can be utilized by pathogens to facilitate disease. Coronatine, which is produced by *P. syringae*, is a functional mimic of jasmonoyl-L-isoleucine (JA-Ile; one of the conjugated forms of JA) and therefore induces the JA pathway to suppress the SA pathway for bacterial infection (Geng et al., 2014). Several aspects of the ambivalence effect that contribute to JA–SA antagonism have been reported (Jimenez-Lizana and Solano, 2013): recent reports show that NPR3 and NPR4, which are SA receptors, interact directly with several JA proteins to trigger JAZ degradation in a COI1-independent manner (Liu et al., 2016) and that JA activates a signaling cascade that inhibits SA accumulation (Zheng et al., 2012). Thus, more strategies by which pathogens trick host plants within hormone pathways require further study to better help with the improvement of plant resistance.
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Several S genes appear to regulate the ambivalence effect. For the optimal exploitation of S genes, future research should focus on further clarifying the molecular mechanisms that underlie S-gene-modulated resistance. This is essential for the identification of novel susceptibility factors that can increase the capabilities of plant breeding programs. Furthermore, intensive research is required to control (or diminish, if possible) pleiotropic effects, such that S genes can be fully exploited. One approach would be to identify partial S gene mutants. Such mutations may provide low levels of resistance that remain sufficient to mitigate any pleiotropic effect on immunity while conferring resistance against pathogens. Recently, quantitative regulation of gene expression was achieved by genome editing of cis-regulatory elements (Rodrı´gu ez-Leal et al., 2017; Bisht et al., 2019). This may be a strategy for limiting the negative impacts associated with reduced S gene function through modifications of the timing, pattern, and/or level of S gene expression. Another way to engineer resistance without causing such pleiotropic side effects is to tightly control the timing and location of gene expression. One recent study tested this approach in rice, in which AtNPR1 expression was controlled by two pathogen-responsive upstream open reading frames of the TL1-BINDING FACTOR 1 (TBF1) gene, thereby providing pathogen-induced translational increases in NPR1. The combined effects of transcriptional and translational control produced resistance to Xoo/Xanthomonas oryzae pv. oryzicola as assessed by disease lesion symptoms in both field and greenhouse conditions without a notable yield penalty (Xu et al., 2017). Therefore, the timely and tissue-localized induction of immunity is a potential strategy for engineering resistance if pleiotropic effects on yield can be avoided.

In conclusion, despite substantial recent progress, there is a considerable lack of understanding regarding the regulation of the ambivalence effect and its impacts. Deepening our knowledge in this area will advance our overall understanding of how plants integrate and balance immune system function in response to diverse pathogens. It will also be instrumental in developing novel strategies for the establishment of durable, environmentally friendly, and biologically based disease resistance in various agricultural settings.

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AUTHOR CONTRIBUTIONS
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