

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 phytotoxins 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

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notion that plants possess a two-tiered immune system comprising pattern-triggered immunity (PTI) and effector-triggered immunity (ETI) (Dodds and Rathjen, 2010). PTI is based on the perception of conserved foreign (non-self) molecules known as microbe-associated molecular patterns or pathogen-associated molecular patterns (PAMPs) by members of a large family of pattern-recognition receptors (PRRs), or on the perception of endogenous plant-derived signals arising from damage caused by pathogen infection (modified-self) known as damage-associated molecular patterns (DAMPs) (Boller and Felix, 2009; Boutrot and Zipfel, 2017; Li et al., 2020). Successful pathogens have evolved so-called effector molecules to breach this first line of defense, either by suppressing PTI signaling or by preventing host detection of their PAMPs (De Jonge et al., 2010; Bardoel et al., 2011). In this ongoing arms race, some plants have acquired a second line of defense in which intracellular NLR immune receptors mediate the recognition of these attacker-specific effectors, resulting in ETI (Jones and Dangl, 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).

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 Tsuda, 2010). Salicylic acid (SA) and jasmonic acid (JA) constitute major defense-related phytohormones (Shigenaga and Argueso, 2016). Other phytohormones, such as ethylene (ET), ABA, gibberellins (GAs), auxin, and cytokinins (CKs), may also function as plant immunity modulators and have specific roles in resistance to different types of pathogens (Robert-Seilanian et al., 2011; Shigenaga et al., 2017).

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-

tions between plants and pathogens. Most of the discussed work involves the model plant *Arabidopsis thaliana* (*Arabidopsis*); where appropriate, we have also included examples from other species. We first address discoveries regarding the ambivalence effect in the two-layered immune system comprising PTI and ETI, followed by discoveries that further our understanding of the molecular players involved in the ambivalence effect. Second, we review the signal transduction pathways of two major defense hormones, SA and JA, which function in the plant defense signaling network; we then consider the crosstalk among individual hormone pathways and how such interactions may have ambivalent roles in pathological outcomes. Third, we assess the roles of other plant hormones in the ambivalence effect, focusing on modulation of the SA–JA backbone of the plant immune signaling network. Fourth, we emphasize how plant pathogens hijack non-immunity-based factors to suppress host defense and establish an ambivalent association with the host. Finally, we explore detailed information on the ambivalence effect that can overcome the limitations of conventional breeding approaches in recognizing the factors and removing the roadblocks that cause persistent losses in crop production or in editing crop plants for the engineering of durable disease resistance (Chen et al., 2019).

MOLECULAR PLAYERS IN THE PTI-MEDIATED AMBIVALENCE EFFECT

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 Ca²⁺ 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.

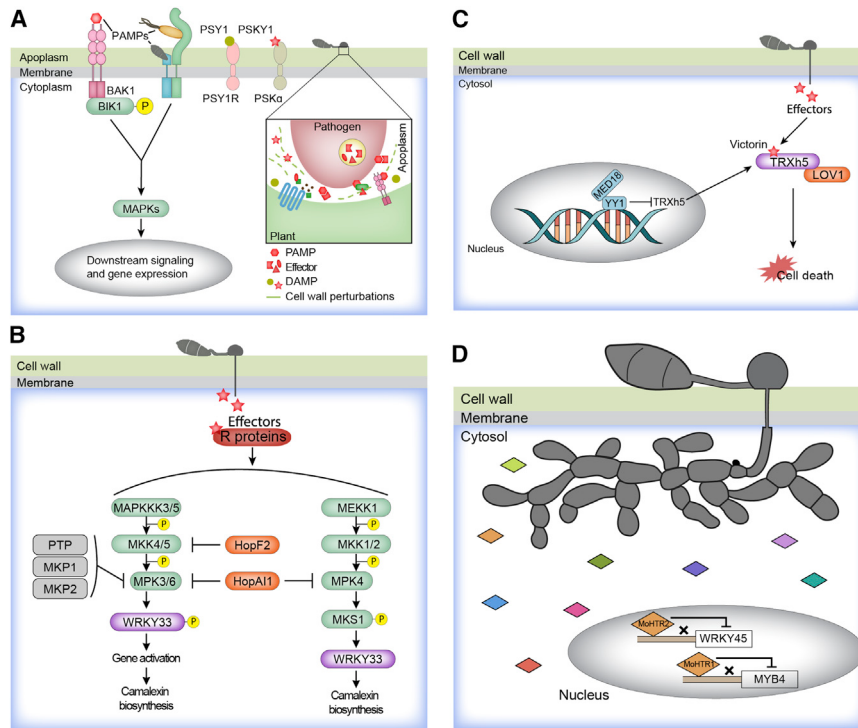


Figure 1. Schematic representation of the molecular components involved in the ambivalence effect in plants.

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 PSK α 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 MEKK3–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 *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 *Co-chliobolus victoriae*. The transcription of *Trx-h5* is regulated by the transcription factor YY1 through its interaction with the mediator MED18 **(C)**. The fungus *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 *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.

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 PSK α (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). PSK α and PSY1 negatively regulate PAMP-mediated defense. The *pskr1* and *psy1r* mutants exhibited enhanced defense gene expression and heightened resistance against the biotrophic pathogen *Pseudomonas syringae* and the fungus *Fusarium oxysporum*. Conversely, *pskr1* mutants exhibited enhanced susceptibility to the necrotrophic fungus *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 *P. syringae* pv. *tomato* (*Pst*). Furthermore, *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 α -D-galacturonic acid and helps with the maintenance of cell wall integrity. Fragments of this polymer are known as OGs; these are derived from the degradation of a major component of pectin in plant cell walls, either by pathogen-encoded hydrolytic enzymes (polygalacturonases) during an infection or by the action of mechanical damage-induced endogenous polygalacturonases (Cervone et al., 1989; Orozco-Cardenas and Ryan, 1999). OGs elicit a wide range of defense responses, including the accumulation of phytoalexins (Davis et al., 1986), oxidative bursts (Galletti et al., 2008), increased chitinase and glucanase activities (Davis and Hahlbrock, 1987; Broekaert and Peumans, 1988), increased hormone biosynthesis (Denoux et al., 2008), callose deposition (Bellincampi et al., 2000), and enhanced resistance against the fungus *Botrytis*

Protein function	Gene	Gene product	Plant species	Pathogen species
				Pleiotropic effect
Transcription factor	WRKY33	WRKY transcription factor	Arabidopsis	<i>Pseudomonas syringae</i>
				increased susceptibility to <i>Botrytis cinerea</i> and <i>Alternaria brassicicola</i>
	WRKY45	WRKY transcription factor	rice	<i>Cochliobolus miyabeanus</i>
				increased susceptibility to <i>Magnaporthe oryzae</i> and <i>Xanthomonas oryzae</i> pv. <i>oryzae</i> in MoHTR2 (<i>Magnaporthe oryzae</i> effector that represses OsWRKY45 expression) overexpression (OX) transgenic rice
	WRKY70	WRKY transcription factor	Arabidopsis	<i>Alternaria brassicicola</i>
				increased resistance to <i>Erysiphe cichoracearum</i>
	WRKY50, WRKY51	WRKY transcription factor	Arabidopsis	<i>Pseudomonas syringae</i>
				increased susceptibility to <i>Botrytis cinerea</i>
	MYB4	MYB transcription factor	rice	<i>Cochliobolus miyabeanus</i>
				increased susceptibility to <i>Magnaporthe oryzae</i> and <i>Xanthomonas oryzae</i> pv. <i>oryzae</i> in MoHTR1 (<i>Magnaporthe oryzae</i> effector that represses OsMYB4 expression) OX transgenic rice
Kinase	PSY1R, PSKR1	leucine-rich repeat receptor kinase (LRR-RK)	Arabidopsis	<i>Fusarium oxysporum</i> / <i>Pseudomonas syringae</i>
				increased susceptibility to <i>Alternaria brassicicola</i>
	BIK1	plasma membrane-localized ser/thr protein kinase involved in early PTI signaling	Arabidopsis	<i>Pseudomonas syringae</i>
				increased susceptibility to <i>Botrytis cinerea</i> and <i>Alternaria brassicicola</i>
	MPK4	MAP kinase	Arabidopsis	<i>Pseudomonas syringae</i>
				increased susceptibility to <i>Alternaria brassicicola</i>
DELLA protein	Sln1c	DELLA protein	barley	<i>Blumeria graminis</i>
				increased susceptibility to <i>Oculimacula</i> spp. (eyespot)
	Sln1d	DELLA protein	barley	<i>Oculimacula</i> spp.
				increased susceptibility to <i>Blumeria graminis</i>

Table 1. Genes that contribute to the ambivalence effect.

(Continued on next page)

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

Table 1. Continued

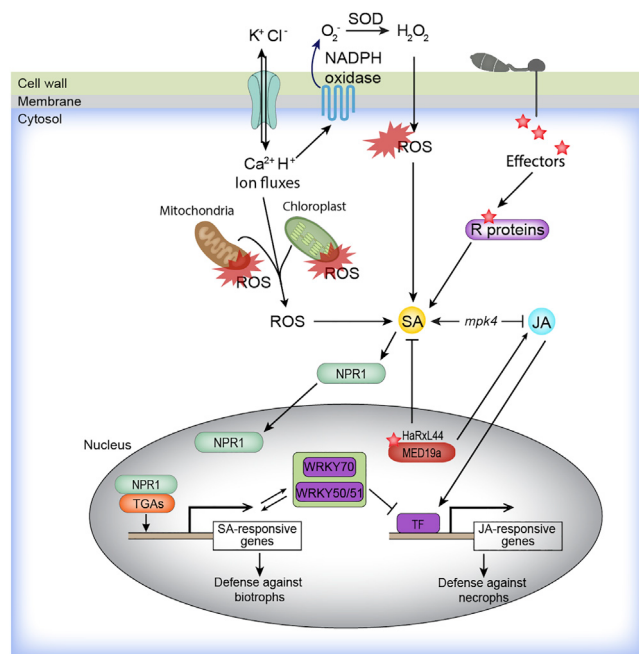


Figure 2. A basic framework for the ambivalence effect in plants.

The perception of a pathogen by plants occurs through cytoplasmic R proteins that recognize pathogen effectors. As a result of pathogen recognition, a cascade of signaling events is initiated. Ion fluxes lead to increased intracellular Ca^{2+} and H^{+} concentrations, which activate Ca^{2+} -dependent protein kinases that phosphorylate and activate NADPH oxidases present in the membrane. NADPH oxidase complexes, together with mitochondria and chloroplasts, act as sources of reactive oxygen species (ROS) production. The increase in ROS production signals for the synthesis of salicylic acid (SA) in the chloroplast, which in turn leads to the generation of more ROS, leading to a cycle of continuous amplification of both molecules. The accumulation of SA causes a change in the redox state of the cell that triggers the separation of oligomers of the regulatory protein NPR1 into monomers. Several transcriptional (co)activators, such as NPR1, TGA, and WRKY, play a role in SA-mediated suppression of jasmonic acid (JA)-responsive genes. Nuclear localization of NPR1 is essential for SA-responsive defense gene expression, and it is required for SA-mediated suppression of the JA-mediated pathway. TGAs, which interact with NPR1, act as important regulators of SA-induced expression by binding to SA-responsive promoters. WRKY50 and WRKY51 are essential for SA-mediated suppression of JA signaling. WRKY70 is an important node of convergence between SA and JA signaling. The green frame highlights components whose expression has been shown to be responsive to SA. Arrows and lines with bars indicate positive and negative regulatory actions, respectively. See the text and Table 1 for further details.

cinerea (Ferrari et al., 2007). A recent study demonstrated the release of OGs *in vivo* during interactions between *A. thaliana* and *B. cinerea* (Voxeur et al., 2019). However, considering the general complexity and availability of pectic polysaccharides, other pectin-derived DAMPs may also contribute to the ambivalence effect. Notably, cell wall fractions from plants carrying mutations in ARABIDOPSIS RESPONSE REGULATOR 6 (ARR6) (implicated in CK perception) reportedly triggered enhanced resistance and susceptibility, respectively, to the necrotrophic fungus *Plectosphaerella cucumerina* and the biotrophic bacterial wilt pathogen *Ralstonia solanacearum* (Table 1) (Bacete et al., 2020).

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 cause 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-SENSITIVE 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 (Jagodzick 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/MKK2-MPK4, which negatively regulates immune responses (Petersen et al., 2000; Berriri 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*, *MKP2*, *EDR1*, and *AtWRKY4/8/18/33/40/60*, exhibit enhanced biotroph resistance but reduced necrotroph 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

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 antimicrobial effects (Zhou et al., 1999; Mao et al., 2011). Moreover, MPK4 is targeted by *P. syringae* bacterial type III effector HopAI1, 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 autoimmunity of *mpk4* (Takagi et al., 2022). As a result, the MPK4 cascade is proposed to be a “guardee” 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).

AMBIVALENCE 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 (Sweat 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; Sweat and Wolpert, 2007; Sweat 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; Litzenger, 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 hijack 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 arabidopsidis* (*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-Seilanianantz 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-Seilanianantz et al., 2011).

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

SA is a natural phenolic 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 rice 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 Vleeschauwer 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 DELLA proteins 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 DELLA proteins in response to pathogens is also generally conserved in the monocots wheat and barley; experiments on the effects of differential DELLA 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, *Sln1d*, 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, *Oculimacula* 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 (hemi) 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., 2008). In addition, auxins can negatively impact plant defense by interfering with other hormone signaling

pathways or with PTI (Robert-Seilaniantz et al., 2011). The bacterial PAMP flg22, a peptide from flagellin protein (Boller 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 developmental 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 transcription. 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 immune 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* (Bessire 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 (Bessire 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 (Hückelhoven, 2004; Watanabe and Lam, 2009). BI-1 is localized to the endoplasmic reticulum; it is conserved in both plants and animals (Hückelhoven, 2004). BI-1 controls the hypersensitive response, a well-characterized form of plant defense against pathogens (Iakimova 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 pustule 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) (Imani 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 (Büschges 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 (Büschges 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* (Jarosch 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 (Gimenez-Ibanez and Solano, 2013): recent reports show that NPR3 and NPR4, which are SA receptors, interact directly with several JAZ 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.

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 (Rodríguez-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 a solution 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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