Signaling Mechanisms Underlying Resistance Responses: What Have We Learned, and How Is It Being Applied?

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ABSTRACT

Plants have evolved highly specific mechanisms to resist pathogens including preformed barriers and the induction of elaborate signaling pathways. Induced signaling requires recognition of the pathogen either via conserved pathogen-derived factors or specific pathogen-encoded proteins called effectors. Recognition of these factors by host encoded receptor proteins can result in the elicitation of different tiers of resistance at the site of pathogen infection. In addition, plants induce a type of systemic immunity which is effective at the whole plant level and protects against a broad spectrum of pathogens. Advances in our understanding of pathogen-recognition mechanisms, identification of the underlying molecular components, and their significant conservation across diverse plant species has enabled the development of novel strategies to combat plant diseases. This review discusses key advances in plant defense signaling that have been adapted or have the potential to be adapted for plant protection against microbial diseases.

From mention of plant geminivirus infection in an ancient Japanese poem (Saunders et al. 2003), consumption of fungal-infected plant parts as food delicacy (Huitlacoche), to their devastating impacts on agriculture (Koeppel 2008; Singh et al. 2011; Yoshida et al. 2013), plant diseases have touched many aspects of human life. Plant diseases continue to pose a problem for crop production and the environment despite the use of cultural practices, chemicals, and resistant varieties. Combating a constant barrage of microbial pathogens is particularly an issue for plants due to their sessile nature and lack of a circulatory system. As a result, plants have evolved unique and effective modes to combat disease causing microbes by deploying sophisticated signaling mechanisms. Induced plant defense signaling results in the activation of antimicrobial compound production, cell wall reinforcement via the synthesis of lignin and callose, and the specific induction of elaborate defense signaling pathways. The various modes of induced defense provide species level resistance to nonhost pathogens, race-specific and basal resistance to virulent pathogens, and broad-spectrum systemic resistance (Fig. 1). Here, we discuss key advances in local and systemic plant defense signaling that have been/can be utilized to provide immunity against virulent microbial pathogens.

INDUCED IMMUNITY IN RESPONSE TO PATHOGEN-DERIVED ELICITORS/EFFECTORS

The first step in active plant defense involves the recognition of pathogen-derived factors, which is achieved via a two-tiered system involving extracellular and intracellular receptors. The first tier, which provides a low degree of general resistance, involves cell surface receptors termed pattern recognition receptors (PRR). PRRs recognize a diverse set of conserved microbial components designated pathogen/microbe-associated molecular patterns (P/MAMPs). Examples include bacterial flagellin and elongation factor Tu, chitin in fungal cell walls, and beta-glucans from oomycetes. Recognition of PAMPs by PRRs results in accumulation of reactive oxygen species (ROS) and calcium bursts. This is also accompanied by the activation of protein kinase cascades and substantial transcriptional reprogramming (Bigear et al. 2015; Monaghan and Zipfel 2012; Schwessinger and Ronald 2012; Zipfel 2009). Eventually, these enable restriction of pathogen colonization. This type of immunity is termed PAMP-triggered immunity (PTI) or basal resistance. Because PRRs recognize conserved microbial molecules, expressing them in heterologous hosts can be effective in combating a variety of related pathogens. For instance, expression of heterologous PRRs has been shown to confer bacterial resistance in banana, grapefruit, tomato, rice, and wheat (Lacombe et al. 2010; Schoonbeek et al. 2015, Schwessinger et al. 2015; Shi et al. 2016; Tripathi et al. 2014). Similarly, expression of a tomato PRR conferred fungal resistance in *Arabidopsis* (Fradin et al. 2011).

The second tier of resistance, which is species-specific in nature, is much more robust and effective in restricting pathogen

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proliferation. This type of resistance is triggered when specialized resistance (R) proteins in the plant recognize specific effector (Avr) proteins from the pathogen, and is termed R-mediated or effector-triggered (ETI) immunity (Flor 1971). An early hallmark of ETI is the induction of a hypersensitive response (HR) at the site of pathogen entry (Holliday et al. 1981). However, HR may not always be observed nor is it required for the onset of ETI (Jones and Dangl 2006). HR, a form of programmed cell death thought to help confine the pathogen to the dead cells, is generally absent in PTI.

RESISTANCE PROTEINS

R genes mediating defense against bacteria, fungi, viruses, oomycetes, nematodes, and insects have been identified from a variety of plants (reviewed in Césari et al. 2014; Kachroo and Kachroo 2007; Martin et al. 2003; Qi et al. 2013). Importantly, resistance signaling downstream of R protein activation is conserved across diverse plants making it possible to deploy *R* genes from heterologous sources in crop protection. For example, transfer of a pair of *R* genes from *Arabidopsis* to other Brassicaceae or Solanaceae members can confer resistance to bacterial and fungal pathogens, including the cucumber pathogen *Colletotrichum orbiculare* (Narusaka et al. 2013). Likewise, the barley *R* gene *MLA1* is fully functional in conferring resistance to powdery mildew fungi in *Arabidopsis* (Maekawa et al. 2012). Thus, *R* genes have been used for developing disease-resistant crops either via conventional breeding within sexually compatible gene pools or via genetically engineering genes from heterologous sources (Chisholm et al. 2006; Jones and Dangl 2006; Wally and Punja 2010). This approach has been especially relevant for pathosystems where major *R* loci are limited or unavailable within the crop germplasm (Kawashima et al. 2016). An

example of this was the successful engineering of resistance to the bacterial spot pathogen in tomato, a very destructive disease in warm, humid production areas. Robust levels of disease control were obtained in tomato plants under field conditions using a single *R* gene (*Bs2*) from pepper (Horvath et al. 2012; Tai et al. 1999). Other examples include, bacterial streak resistance in rice plants expressing the maize *Rxo1* gene, anthracnose resistance in alfalfa via expression of *Medicago truncatula* *RCT1*, late blight resistance in cultivated potato derived from *Rpi-blb2* of a wild potato relative, Asian soybean rust resistance in soybean plants expressing *CcRpp1* from pigeonpea, rice blast resistance in rice using *R* genes from multiple grass species, etc. (Kawashima et al. 2016; van der Vossen et al. 2005; Yang et al. 2008, 2013; Zhang et al. 2015). Pathogen-specificity and thereby efficacy against limited pathogen strains has been one drawback of deploying *R* genes, although pyramiding multiple *R* genes in the same background can provide resistance against multiple isolates of the same pathogen (Zhou et al. 2009). Pyramiding *R* genes via conventional breeding has also been used to increase the durability of field resistance (Vincelli 2016).

Interestingly, in some cases pathogen resistance requires complementary pairs of *R* genes. For instance, two *R* genes (*RPP2A* and *RPP2B*) are required for *Arabidopsis* resistance against *Hyaloperonospora arabidopsidis* (Sinapidou et al. 2004). Similarly, pairs of *R* genes confer resistance to *Puccinia graminis* in wheat and barley, and against *Magnaporthe grisea* in rice (Ashikawa et al. 2008; Brotman et al. 2012; Césari et al. 2013; Lee et al. 2009; Loutre et al. 2009; Narusaka et al. 2009; Okuyama et al. 2011; Sinapidou et al. 2004; Wang et al. 2013; Yuan et al. 2011). In some cases, the same set of paired *R* genes provide resistance to multiple diverse pathogens. For instance, the *R* genes *Prv* and *Fom-1* mediate resistance to *Fusarium oxysporum* and *Papaya ringspot virus* (PRSV) in

FIGURE 1

Types of local and systemic induced defense responses. Recognition of pathogen/microbe associated molecular patterns (PAMP) by plant pattern recognition receptors (PRR) induces signaling involving the accumulation of reactive oxygen species (ROS), induction of calcium (Ca^{+2}) bursts and mitogen associated protein kinase (MAPK) cascades, resulting in nuclear gene induction and eventually basal resistance in the infected tissue. This type of immunity is termed PAMP triggered immunity or PTI (blue arrows and boxes). Pathogen derived effectors can interfere with PTI (gray box). Plant resistance protein (R) mediated recognition of pathogen effector induces species-specific resistance in the infected tissue often via the phytohormone salicylic acid (SA). This type of immunity is termed effector-triggered immunity (ETI, green arrows and boxes). Induction of ETI can also trigger the accumulation of ROS, which help generate azelaic acid (AzA) via 18 carbon (C18) fatty acids (FA). AzA induces the accumulation of glycerol-3-phosphate (G3P). G3P-derived signaling together with SA-derived signaling can induce systemic broad-spectrum and trans-generational resistance.

melon (Brotman et al. 2012). In *Arabidopsis*, RPS4 and RRS1 are required for resistance to *Ralstonia solanacearum*, *Colletotrichum higginsianum*, and the *avrRps4* expressing strain of *Pseudomonas syringae* (Gassmann et al. 1999; Narusaka et al. 2009). Notably, in each of these cases the paired *R* genes are tightly linked, likely ensuring their cosegregation into progeny.

Based upon their structural characteristics and motifs, *R* proteins can be grouped into six classes (Kachroo and Kachroo 2007; Martin et al. 2003), with most belonging to the nucleotide-binding (NB) leucine-rich repeat (LRR) family of proteins (NLR) (Fig. 2). The NLR proteins contain LRR domains at the C-terminal and a central NB-ARC (domain shared by Apaf-1, Resistance, and CED-4 proteins) domain. The NB-ARC domain is thought to function as a molecular switch, which determines the dormant and active stages of the *R* protein, and this in turn is dependent on the binding of ADP or ATP, respectively, to this domain (Maekawa et al. 2011; Tameling et al. 2002; Tameling et al. 2006; Williams et al. 2011). NLR proteins are further subclassified based on the presence of the coiled coil (CC)- or toll-interleukin 1 receptor (TIR)-domains at their N-terminal. Homodimerization has been reported for several NLR proteins, including those that regulate resistance to bacteria, fungi, and viruses, and in at least two cases homodimerization of the respective CC or TIR domains is crucial for downstream signaling. Dimerization between paired NLRs can also be mediated via these domains, such as the rice RGA4/RGA5 pair which interact via their CC domains, and the *Arabidopsis* RPS4/RRS1 pair which interact via their TIR domains (Césari et al. 2014; Williams et al. 2014). *R* proteins also undergo intramolecular interactions, which are thought to be important for maintaining the protein in a dormant state. For example, in the NLR Rx (resistance

to *Potato virus X*), interactions have been detected between the LRR and CC-NB domains as well as the CC and NB-LRR domains (Moffett et al. 2002). The viral effector is known to disrupt these intramolecular interactions suggesting a role for these disruptions in Rx activation. In fact, coexpression of the LRR domain with the CC-NB domain or full length Rx induces HR.

R PROTEIN ACTIVATION

R proteins are activated upon direct or indirect association with the cognate pathogen effector(s). Direct interactions can be mediated by the CC, NB-ARC, or LRR domains of *R* proteins. For example, the *R* proteins L and RPP1, interact with their cognate effectors AvrL567 and ATR1, respectively, via their LRR domains (Dodds et al. 2006; Krasileva et al. 2010; Ravensdale et al. 2012), whereas the rice NLR Pik interacts with Avr-Pik from *M. grisea* via its CC domain (Kanzaki et al. 2012). Interestingly, in case of paired NLRs only one of the NLRs directly interacts with the cognate effector. The effector-interacting NLR represses its paired NLR, which functions as an activator of cell death and resistance. Effector binding relieves the repression to activate resistance signaling (Cesari et al. 2013; Kanzaki et al. 2012; Williams et al. 2014).

Although some *R* proteins directly interact with their cognate effectors, most others utilize indirect modes of pathogen recognition by “guarding” other plant proteins, which interact with and/or are modified by pathogen effectors (Innes 2004; Jones and Dangl 2006; Van der Biezen and Jones 1998). A classic example is the activation of *R*-mediated resistance to the *avrRpt2* strain of *P. syringae* in response to protease cleavage of the RIN4 (RPM1 interacting 4) protein by the bacterial effector (Axtell and Staskawicz 2003;

FIGURE 2

Types of cloned resistance proteins (*R*) based on structure. The different classes of *R* proteins are distinguished by colored boxes (pink, orange, blue, green, and purple). Examples for each class of *R* protein are indicated within the respective colored boxes and the corresponding organisms against which they provide resistance are indicated in brackets. The various structural domains are depicted in the key. Intracellular locations are indicated in italics. Note that although leucine-rich repeat family of proteins (NLR; purple boxes) are shown to be cytoplasmic (with the exception of the nuclear RRS1), many of these are peripherally attached to the membrane via posttranslational modifications and can alter localization from the cytoplasm to the nucleus during resistance signaling.

Mackey et al. 2003). RIN4 can undergo a different posttranslational modification (phosphorylation) in the presence of other bacterial effectors to induce resistance from the cognate R protein in diverse plants (Kim et al. 2005; Luo et al. 2009; Mackey et al. 2002; Selote and Kachroo 2010; Selote et al. 2013). Similarly, cleavage of the protein kinase PBS1 (AvrPphB susceptible 1) can activate bacterial resistance derived from another R protein in *Arabidopsis* (Shao et al. 2003). Notably, some pathogen effectors target multiple host proteins. For example, the *Cladosporium fulvum* effector Avr2 inhibits the activities of two apoplastic papain-like cysteine proteases (PIP1 and RCR3) in tomato (Shabab et al. 2008). Inhibition of RCR3 is associated with activation of resistance derived from the R protein Cf2 in tomato (Rooney et al. 2005). Similarly, the *P. syringae* effector AvrPto inhibits the kinase domains of multiple PRRs. In plants containing the Pto (protein kinase)-Pfr (R protein) combination, inhibition of Pto activity induces ETI via Pfr (Zipfel and Rathjen 2008). Such examples led to the suggestion that related host proteins interacting with the same pathogen effector may function as “decoys” by contributing to R protein activation, but not serving as pathogen virulence enhancers (van der Hoorn and Kamoun 2008). Engineering effector targets to promote perception of diverse pathogens could potentially provide a novel avenue for generating broad-spectrum resistance. For instance, a recent study showed that resistance could be engineered against multiple bacterial strains and viral pathogens simply by modifying the protease cleavage sites of PBS1 to serve as substrates for effectors from each of those pathogens (Kim et al. 2016).

Pathogen effector-dependent disruption of interactions between R proteins and other host proteins that promote R protein stability and/or resistance signaling, can also contribute to R protein activation. For example, the coat protein (CP) effector of TCV inhibits the interaction between the R protein HRT and double-stranded RNA-binding protein (DRB) 4, which is required for HRT stability and its derived resistance (Zhu et al. 2013). Likewise, the bacterial effector AvrRps4, inhibits the interaction between EDS1 (Enhanced Disease Susceptibility 1, Wiermer et al. 2005) and a repressor of AvrRps4-triggered immunity (Kwon et al. 2009; Bhattacharjee et al. 2011). EDS1 is a well-known regulator of signaling derived from TIR type of NLR proteins and the defense-related phytohormone salicylic acid (SA). EDS1 is also important for resistance signaling by some CC type of NLR proteins, where it functions redundantly with SA (Cui et al. 2017; Venugopal et al. 2009). Notably, EDS1 physically interacts with the CC type of NLR, HRT (HR to *Turnip crinkle virus*) and is involved in the potentiation of HRT-mediated HR (Zhu et al. 2011). Interestingly, despite physical association between soybean EDS1 orthologs (GmEDS1) and HRT, the GmEDS1 proteins cannot potentiate HRT-mediated HR (Wang et al. 2014b). This correlates with only partial complementation of the *Arabidopsis eds1* mutant phenotypes by GmEDS1 proteins. In addition to NLR proteins, EDS1 also interacts with pathogen effectors like AvrRPS4, HopA1, and AvrA1, and is required for the virulence function of AvrA1 (Bhattacharjee et al. 2011; Wang et al. 2014b).

Changes in intracellular localization can also be important for the activation of some NLR proteins. Unlike PRRs, the majority of the known R proteins are intracellular, with some exceptions. Notably, NLR proteins from different plants show diverse localizations and several NLR proteins relocate to another subcellular compartment in response to pathogen infection. For example, resistance signaling by barley MLA10 involves nuclear relocation in the presence of pathogen effector (Shen et al. 2007). Likewise, *Arabidopsis* RPS4 localizes to the nucleus in the presence of the cognate bacterial effector though both nuclear and cytoplasmic fractions of RPS4 are essential for complete resistance (Heidrich et al. 2011). The potato Rx NLR, which localizes to both nucleus and cytoplasm, is activated specifically in the cytoplasm, but not the nucleus (Sacco et al. 2007; Sliotweg et al. 2010). Intramolecular interactions and

folding states of Rx are thought to regulate the nucleocytoplasmic distribution of Rx (Sliotweg et al. 2010). Several *Arabidopsis* NLRs localize to the plasma membrane and this is essential for the activation of at least two of these proteins (Gao et al. 2011; Qi et al. 2012). These aspects of R protein activation may be important considerations when devising strategies to deploy these for long-term crop protection.

EFFECTOR TARGETS

Pathogens use sophisticated secretion systems to deliver effectors and other pathogenicity elicitors into plant cells. Prominent examples of bacterial secretion systems include the type II system used for translocating plant cell wall-degrading enzymes by *Erwinia* and *Xanthomonas* species (Korotkov et al. 2012), type III system used to deliver effector proteins by Gram-negative bacteria like *P. syringae* (Alfano and Collmer 2004), and the type IV system used by *Agrobacterium tumefaciens* to transfer T-DNA (Cascales and Christie 2003). Fungal and oomycete pathogens use general secretory pathway as well as specialized structures like haustoria and appressoria (Petre and Kamoun 2014). A single pathogen strain can express and deliver multiple effectors into its host. Unlike PAMPs, which are typically essential for pathogen survival, effectors are presumed to primarily serve as pathogen virulence enhancers; pathogen effectors include proteins that interfere with the host PTI response, promote nutrient acquisition, and enhance pathogen dispersal (Chen et al. 2004; Kim et al. 2005; Shan et al. 2008; van Esse et al. 2007; Xiang et al. 2008). Examples are, the transcription-activator-like (TAL) effectors encoded by the plant pathogenic *Xanthomonas* and *Ralstonia* species, and a phytopathogenic fungal-endosymbiont, *Burkholderia rhizoxinica* (Juillerat et al. 2014; Lange et al. 2014). TAL effectors bind specific DNA sequences in the promoters of host genes and induce host gene transcription to promote pathogen virulence and host susceptibility (Zhang et al. 2015). Examples of such host genes include the SWEET-family of sugar transporters, which function as susceptibility genes (Hutin et al. 2015). Plants counteract TAL effectors by expressing recessive alleles of substrate genes that lack TAL binding sites (Hutin et al. 2015), NLR genes that are independent of TAL activity (Bonas et al. 1993; Schornack et al. 2004), and terminator/executor genes that activate HR and thereby restrict pathogen growth in response to TAL activity (Bogdanove et al. 2010; Tian et al. 2014). Engineering executor genes to serve as targets for nonspecific TAL effectors has been successfully used to enhance resistance against multiple unrelated pathogens in pepper and rice (Hummel et al. 2012; Römer et al. 2007). A similar strategy was used to generate citrus canker resistance in grapefruit (Jia et al. 2016).

SUSCEPTIBILITY GENES

Whereas *R* and *PRR* genes activate resistance, some plant genes promote pathogen infection and colonization, and are thereby termed “susceptibility genes” (van Schie and Takken 2014). Changes to susceptibility genes can result in increased disease resistance (Dangl et al. 2013; Sun et al. 2016; van Schie and Takken 2014; Vincelli 2016; Wang et al. 2014c).

The *Mlo* genes, which encode plant-specific integral membrane proteins of unknown biochemical function, are classic examples (Devoto et al. 2003). Powdery mildew fungi are thought to utilize MLO proteins to enter host cells (Panstruga 2005). In addition, the MLO2 protein of *Arabidopsis* is targeted by the HopZ2 effector of *Pseudomonas syringae* and is required for the virulence function of HopZ2 (Lewis et al. 2012). Naturally occurring mutations in *Mlo* genes have been linked to powdery mildew resistance in barley, pea, and tomato (Bai et al. 2008; Pavan et al. 2011; Piffanelli et al. 2004) and mutant *mlo* alleles of barley have long been used for agriculture

in Europe (Lyngkjaer et al. 2000). Some *mlo* mutations have also been reported to generate broad-spectrum resistance to powdery mildew fungi in barley and *Arabidopsis* (Büschges et al. 1997; Consonni et al. 2006). Transcription activator-like effector nuclease (TALEN) induced mutations in three wheat *MLO* genes was also shown to confer broad-spectrum, heritable resistance to powdery mildew (Wang et al. 2014c).

Viral pathogens are particularly reliant on host proteins for survival, and co-opt numerous host proteins for proliferation. Plant translation factors serve as a case-in-point because most plant pathogenic viruses are RNA viruses and translation of the viral RNA is crucial for its replication. Examples include the eukaryotic translation initiation factors eIF4E and eIF4G (Machado et al. 2017; Sanfaçon 2015). These proteins are part of the translation initiation complex and are involved in cap binding during the mRNA-protein complex assembly. In case of potyviruses the VPg (genome-linked viral protein) protein is thought to recruit the host translation complex for viral genome translation via its interaction with eIF4E, and in some cases eIF4G (Robaglia and Caranta 2006). eIF4E is known to affect systemic spread of other viruses (Contreras-Paredes et al. 2013). Naturally occurring mutations in eIF4E/G have been linked to virus resistance in a range of plants and have been deployed for virus resistance in commercially important crops (Wang and Krishnaswamy 2012). Another example is eukaryotic elongation factor 1 alpha (eEF1A), which is recruited by the replication complexes of many RNA viruses (Li et al. 2009; Nishikiori et al. 2006; Thivierge et al. 2008; Yamaji et al. 2006). eEF1A interacts with different viral proteins and lack of eEF1A or the associated eEF1B can restrict viral replication and disease development (Luan et al. 2016; Sasvari et al. 2011).

The functional redundancy among multiple isoforms of these plant translation factors provides important avenues for developing virus resistant plants without repercussions to the host translation machinery. Altering susceptibility genes could create durable disease resistance because a plethora of host factors contribute to host-parasite compatibility in many pathosystems. This offers many potential gene targets that may require only modest genetic changes for engineering resistance. Furthermore, overcoming changes to susceptibility genes would require the pathogen to gain a new function to replace the lost host factor it was exploiting, a task that is unlikely to be easily accomplished (van Schie and Takken 2014).

PATHOGENICITY GENES

Besides altering plant genes or their expression, pathogen-derived genes have also been exploited to generate resistance. The strategy of using pathogen-derived transgenes is based on the concept of pathogen-derived defense (PDR) (Sanford and Johnston 1985), and involves transgenic expression of a pathogen gene in the host. For instance, expression of *Tobacco mosaic virus* (TMV) coat protein confers resistance against TMV in tobacco (Abel et al. 1986). The transgenic expression of viral coat protein blocks the disassembly of the infecting virus thereby preventing virus replication and movement. This mechanism of resistance is effective against virions but ineffective against the unencapsidated viral RNA or high inoculation titer. Coat protein-mediated resistance has been demonstrated against number of RNA viruses including *Potato virus X*, *Alfalfa mosaic virus*, *Cucumber mosaic virus*, *Tobacco etch virus*, *Potato mop-top virus*, PRSV, and more recently against *Tobacco ringspot virus* (Cillo and Palukaitis 2014). PDR can also be achieved by expressing defective movement protein, replicase subunits or symptom suppressing viral satellites (Baulcombe 1996; Lomonosoff 1995). Movement protein-mediated resistance is advantageous because it can confer broad-spectrum resistance. For example, expression of a defective TMV-movement protein conferred resistance to tobamovirus, cucumovirus, potyvirus, and tobamoviruses (Cooper et al. 1995). A peptide-mediated resistance strategy has

also been developed that involves expressing a 29-amino-acid-long peptide, which interacts with the nucleoprotein of tospoviruses. Transgenic tobacco plants expressing this peptide exhibited broad-spectrum resistance to *Tomato spotted wilt virus*, *Tomato chlorotic spot virus*, *Groundnut ring spot virus*, and *Chrysanthemum stem necrosis virus* (Rudolph et al. 2003).

There are several other examples where PDR is achieved at the transcript level, and this involves transgene-induced silencing of viral RNA by the host encoded RNA silencing machinery (Baulcombe 1996). This technology has been widely used to develop virus-resistant plants, many of which have been approved for commercial use in various countries (Khalid et al. 2017; Palukaitis 2011). While older technologies relied on expressing full-length/partial viral sequences, newer technologies use very short artificial sequences to knock down viral gene expression. This mitigates the risks associated with transgenic expression of longer viral sequences to some extent (Vincelli 2016). Notable examples include the release of PRSV resistant transgenic papaya expressing the coat protein (CP) of PRSV in Hawaii (Fitch et al. 1992; Ferreira et al. 2002; Gonsalves 2006), and the subsequent development of transgenic papaya with resistance specificity to Asian PRSV strains (Bau et al. 2003). Transgenic papaya varieties with commercial approval are now available in both United States and China (Khalid et al. 2017). Likewise, *Plum pox virus* (PPV)-resistant plum expressing the CP or hairpin structures targeting the CP of PPV have been developed (Hily et al. 2007; Ravelonandro et al. 2014; Scorza et al. 2001). The CP-expressing variety is approved for release in the United States (Khalid et al. 2017). Other proteins such as viral replicase or RNA silencing suppressors have also been used as targets in RNAi (RNA interference) approaches to develop viral resistance in various hosts including tomato, banana, citrus fruits, common bean, maize, rice, and wheat (Khalid et al. 2017). Some of the lines have been tested for resistance stability in the field over many generations (Cao et al. 2013; Shimizu et al. 2011; Wang et al. 2016). Potato, squash, bean, pepper, and tomato lines have been cleared or approved for release in the United States, Brazil, and China (Aragao et al. 2013; Khalid et al. 2017). The RNAi strategy has also been effectively used to develop resistance against a DNA virus in cassava (Vanderschuren et al. 2007). Increased resistance durability and broader spectrum efficacy has been achieved by targeting multiple viral proteins or using chimeric constructs to simultaneously target multiple pathogens (Gal-On et al. 2005; Lin et al. 2012; Wu et al. 2010).

Plant expressed RNAi constructs against pathogen-derived genes have also been used to enhance resistance against fungal and oomycete pathogens. However, unlike viruses, efficacy of this strategy against fungi or oomycetes requires transport/uptake of host miRNA (microRNA) across the pathogen cell membrane. Indeed, a recent study showed that cotton plants export miRNA into fungal hyphae and specifically target genes that are essential for fungal virulence in the plant (Zhang et al. 2016). Successful examples of resistance induced against fungi and oomycete include, wheat plants expressing RNAi constructs targeting fungal chitin synthase or β -1,3-glucan synthase that exhibit resistance to *Fusarium* species (Chen et al. 2016; Cheng et al. 2015). Host-induced silencing of predicted pathogenicity genes or haustorial-enriched genes from the rust fungus *Puccinia triticina* suppressed rust symptoms in wheat (Panwar et al. 2013; Yin et al. 2015). Notably, host-induced silencing of a *Blumeria graminis* Avr effector reduced haustoria formation in barley plants lacking the cognate *R* gene (Nowara et al. 2010).

SYSTEMIC ACQUIRED RESISTANCE

In addition to local responses, plants also induce systemic responses that provide pathogen resistance at the whole plant level. One such mechanism, which is induced in response to primary infection by a pathogen, is referred to as systemic acquired resistance

(SAR). SAR involves the generation of signal(s) in the local tissue (site of primary infection), and this occurs very rapidly; within 4 to 6 h of primary infection. The signal(s) then translocate acropetally likely via the phloem, where they arm the distal uninfected tissue against subsequent secondary pathogen infections (Fu and Dong 2013; Gao et al. 2015; Kachroo and Robin 2013; Shah and Zeier 2013; Wendehenne et al. 2014). This requires careful and balanced cross-talk between various phytohormones, metabolites, and proteins (Pieterse et al. 2012). SAR can also be retained as a memory to be passed on to the next generation of progeny (Luna et al. 2012; Slaughter et al. 2012). Thus, SAR is highly desirable for crop protection because it involves the generation of long-lasting, broad-spectrum resistance at the whole plant level. Remarkably, SAR has been reported to confer a fitness advantage under conditions of high disease pressure even though the induction of SAR is associated with negative growth repercussions (Traw et al. 2007).

Several crucial aspects of SAR signaling have been elucidated in the last decade, although much also remains unknown. Several chemical inducers of SAR have been identified; some of which are known to translocate systemically. These include, SA and its methylated derivative MeSA (Durrant and Dong 2004; Park et al. 2007), azelaic acid (AzA) (Jung et al. 2009), glycerol-3-phosphate (G3P) (Chanda et al. 2011), pipecolic acid (Pip) (Návarova et al. 2012), dehydroabietinal (DA) (Chaturvedi et al. 2012), and the free radicals nitric oxide (NO) and reactive oxygen species (ROS) (Wang et al. 2014a). Recent studies show that AzA, G3P, NO, and ROS function in a linear, but feedback-regulated branch, which functions parallel to a second SA-regulated branch, to activate SAR. DA and Pip likely feed into the SA-dependent branch of the SAR pathway because they induce SA accumulation (Bernsdorff et al. 2016; Chaturvedi et al. 2012; Návarova et al. 2012). The SAR-inducing abilities of many of these chemicals require the nonspecific lipid transfer-like protein (LTP), DIR1 (defective in induced resistance) (Maldonado et al. 2002) and the hybrid proline-rich protein, AZI1 (AzA insensitive) (Cecchini et al. 2015; Jung et al. 2009). SAR induction also requires “perception” of the mobile signal(s) in the distal tissue. Though some factors essential for signal perception have been identified, this aspect of SAR is not yet well understood. For instance, SAR induction is dependent on the distal tissue having an intact cuticle, a hydrophobic barrier comprising wax and cutin monomers that surrounds all aerial surfaces of the plant (Gao et al. 2015; Lim et al. 2016; Xia et al. 2009, 2010). Plants that are defective in cuticle biosynthesis can generate the SAR signal but are unable to perceive it. In addition, some cuticular components also contribute to SAR mobile signal generation (Xia et al. 2012). This is also true of the major plant lipid, digalactosyl diacylglycerol (DGDG), which contributes to both signal generation and perception. A hallmark of SAR signaling is the significant amount of cross-regulation among the various SAR signaling components. For example, the parallel functioning of the SA- and AzA/G3P-derived branches, the feedback regulatory loop between G3P and DIR1/AZI1, the involvement of DGDG in signal generation and perception, and the inhibition of intracellular movement of AzA and G3P by SA (Lim et al. 2016). All these mechanisms likely promote a finer control of SAR induction to reduce its implications on normal growth particularly since many of the signaling molecules are conserved and essential primary metabolites.

Despite its obviously desirable traits, SAR has not been used in crop protection likely because key advances in our understanding SAR have only been made more recently. It is important to note that although exogenous SA application is widely marketed as an SAR inducer, whole plant chemical applications technically induce local, rather than systemic resistance. SA (and its functional analogs), which is well known to induce broad-spectrum resistance, is marketed commercially as both a pesticide (e.g., Actigard) and a growth stimulant (e.g., AgriGro Ultra). However, SA application typically negatively affects plant productivity due to constitutive

reallocation of growth resources to defense responses. In addition to SA, transgenic expression of NPR1 (nonexpressor of pathogenesis related 1), the SA receptor and central regulator of SA responses, is well known to induce broad-spectrum resistance (Fu and Dong 2013; Yan and Dong 2014). Expression of NPR1 was shown to confer resistance to multiple diverse pathogens in *Arabidopsis* and has been subsequently applied in countless species like wheat, cotton, rice, brassicas, peanut, citrus, strawberry, apple, etc. (Cao et al. 1998; Chen et al. 2012; Dutt et al. 2015; Joshi et al. 2017; Makandar et al. 2006; Molla et al. 2016; Sadumpati et al. 2013; Silva et al. 2015). However, NPR1-expressing transgenic plants have not yet been used in commercial agriculture. Further understanding of the nuances of SAR signaling is key for its applicability in crop production because constitutive induction of SAR or indeed any type of defense is undesirable.

CONCLUSIONS

Significant advances in our understanding of how plants perceive pathogens and the elucidation of key molecular events underlying defense activation present several novel avenues for generating pathogen resistance in the field. Despite these advances, commercial adaptation of research-based strategies has been limited to the deployment of *R* genes, natural variants in susceptibility genes, and transgene-induced silencing of pathogen-derived factors. The durability and applicability of usable strategies is constantly challenged by the emergence of resistance breaking pathogen strains, negative repercussions to agronomic traits and yield potential, endurance under adverse environmental conditions, impact to the environment, and public acceptance of strategies involving genetic manipulations. While the use of elite genome editing tools could help alleviate concerns associated with genetic manipulations, further dissection of plant defense pathways is needed to identify factors that are not under evolutionary pressure for change and can be altered to enhance resistance without affecting growth, yield, nutritional value, etc. Understanding how pathogen defense responses interface with primary metabolism, growth and development, abiotic stress responses, and interactions with beneficial organisms, would also be important for developing long-lasting and sustainable plant protection strategies.

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