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Review

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Message in a Bottle: Chemical Biology of Induced Disease Resistance in Plants

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The outcome of plant-pathogen interactions is influenced significantly by endogenous small molecules that coordinate plant defence responses. There is currently tremendous scientific and commercial interest in identifying chemicals whose exogenous application activates plant defences and affords protection from pathogen infection. In this review, we provide a survey of compounds known to induce disease resistance in plants, with particular emphasis on how each compound was originally identified, its putative or demonstrated mechanism of defence induction, and the known biological target(s) of each chemical. Larger polymeric structures and peptides/proteins are also discussed in this context. The quest for novel defence-inducing molecules would be aided by the capability for high-throughput analysis of candidate compounds, and we describe some issues associated with the development of these types of screens. Subsequent characterization of hits can be a formidable challenge, especially in terms of identifying chemical targets in plant cells. A variety of powerful molecular tools are available for this characterization, not only to provide insight into methods of plant defence activation, but also to probe fundamental biological processes. Furthermore, these investigations can reveal molecules with significant commercial potential as crop protectants, although a number of factors must be considered for this potential to be realized. By highlighting recent progress in the application of chemical biology techniques for the modulation of plant-pathogen interactions, we provide some perspective on the exciting opportunities for future progress in this field of research.

When faced with pathogen attack, plants do not have the option to physically escape. Instead, all threats must be confronted and effectively mitigated using the plant's available resources. The coordination of these defensive resources involves a number of small molecules with various physiological activities. Salicylic acid (SA) is a key regulator of plant defence that primarily mediates responses to biotrophic pathogens (Glazebrook, 2005; Thomma et al., 1998). The detection of an invading pathogen by host resistance (R) proteins initiates a cascade of events that culminate in programmed cell death at the site of infection, known as the hypersensitive response (HR). This cell death response is facilitated by local accumulations of nitric oxide and reactive oxygen species (ROS) as well as SA. Following the HR, uninfected tissues become more resistant to subsequent pathogen infections. This systemic acquired resistance (SAR) is SA-dependent and provides protection from attacks by a broad range of pathogens (Gaffney et al., 1993; Ryals et al., 1996). When plants encounter necrotrophic pathogens, their responses generally rely on jasmonic acid (JA) and ethylene (ET) signaling. Both JA and ET are also implicated in the control of induced systemic resistance (ISR), which is stimulated by the infection of plant roots with certain strains of nonpathogenic plant growth-promoting rhizobacteria (van Loon et al., 1998). Recently, additional molecules have been found to modulate disease resistance, including abscisic acid (ABA), brassinosteroids, gibberellin, cytokinin, and auxin (Mauch-Mani and Mauch, 2005; Nakashita et al., 2003a; Navarro et al., 2006; Robert-Seilaniantz et al., 2007; Wang et al., 2007). There is significant cross-talk among these signaling molecules which helps coordinate responses appropriate for the invading pathogen (Robert-Seilaniantz et al., 2007; Spoel and Dong, 2008).

Given the diversity of endogenous molecules known to influence plant disease resistance, there is considerable interest in the activation or enhancement of these immune responses by the exogenous application of chemicals. Indeed, White (1979) noted that treatment of tobacco (*Nicotiana tabacum* cv. Xanthi-nc) with SA significantly reduced its susceptibility to infection by tobacco mosaic virus (TMV). Similarly, applications of JA or ET can induce resistance to pathogens such as *Botrytis cinerea* and *Erysiphe graminis* (Diaz et al., 2002; Schweizer et al., 1993). There are, however, critical limitations on the widespread use of these specific compounds in a field or greenhouse setting. For example, at the concentrations required to induce resistance, SA displays phytotoxicity in some plant species (Friedrich et al., 1996). As a gas, large-scale application of ET is impractical. Some of these endogenous

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signals may also only have transient activity due to their conversion to biologically inactive conjugates for storage (Chen et al., 1995). The search for novel chemicals for the induction of disease resistance was initiated in part to address these technical issues, while at the same time generating additional tools for probing the signaling pathways that control resistance. Here, we summarize the current products of this research, both in terms of historical background and subsequent mechanistic characterization. We focus only on those molecules that, when applied as a single, purified entity, result in a measurable, significant increase in resistance to a given pathogen. We exclude those compounds that have only been demonstrated to activate a specific marker of plant defence, as well as those with direct antimicrobial activity. In addition, we have not sought to exhaustively catalogue all of the plant-pathogen combinations whose interaction is influenced by a given chemical, but rather provide examples that illustrate this activity. This review was prompted in part by the emergence of new, high-throughput approaches for the study of host-pathogen interactions and their modulation by exogenously-applied molecules. As such, we discuss some of the issues associated with high-throughput screening for novel inducers of defence, particularly with regards to defining the goals and setup of a screen, as well as the extensive downstream analyses required to characterize the activity of a molecule of interest.

Known Inducers of Plant Disease Resistance

Small Molecules (<500 Da)

Synthetic/Inorganic Compounds. The established role of SA in modulating disease resistance made this molecule a popular starting point for testing structural derivatives. One such compound, 2,6-dichloroisonicotinic acid (INA), was identified in an industrial screening program (Ciba-Geigy AG, now Novartis) as capable of inducing resistance to anthracnose disease (*Colletotrichum lagenarium*) in cucumber and TMV in tobacco (Table 1; Metraux et al., 1991; Ward et al., 1991). This chemical is both structurally and functionally similar to SA, as both compounds induce the expression of similar sets of pathogenesis-related (PR) proteins concomitant with the development of SAR (Uknes et al., 1992; Ward et al., 1991). Further, both bind to and inhibit the ROS scavenging enzymes catalase (salicylic acid-binding protein, SABP) and ascorbate peroxidase (Conrath et al., 1995; Durner and Klessig, 1995). Modulation of ROS levels appears to be a key aspect of SA/INA activity, because co-application of INA and an antioxidant blocked the induction of PR gene expression. Notably, however, INA does not induce SA accumulation, and INA still confers resistance upon both tobacco and Arabidopsis plants expressing the *nahG* gene, which encodes a bacterial salicylate hydroxylase that degrades salicylic acid to biologically inactive catechol (Delaney et al., 1994; Vernooij et al., 1995). This indicates that INA acts downstream of SA accumulation to induce disease resistance.

Further screening led to the identification of additional compounds that, although more structurally diverse, still mimicked SA function. In a screen of various benzothiadiazole derivatives, benzo-1,2,3-thiadiazole-7-carbothioic acid S-methyl ester (BTH, acibenzolar-*S*-methyl) emerged as a strong inducer of SAR in numerous plant-pathogen combinations, with much lower phytotoxicity than either SA or INA (Friedrich et al., 1996; Schurter et al., 1987). Like SA, BTH inactivated catalase, ascorbate peroxidase, and a mitochondrial NADH:ubiquinone oxidoreductase (van der Merwe and Dubery, 2006; Wendehenne et al., 1998). Treatment of barley (*Hordeum vulgare* L.) with BTH did not immediately induce ROS production, but conditioned the plants for a faster and stronger response upon infection with the powdery mildew fungus *Blumeria graminis* (Faoro et al., 2008). This potentiated, or "primed" (Conrath et al., 2006) response included a more intense HR-associated oxidative burst and more extensive formation of cell wall appositions (papillae), coupled with greater accumulation of phenolic compounds at sites of attempted fungal penetration (Faoro et al., 2008). The activity of BTH varies between different pathosystems though, as BTH-induced resistance of bean (*Phaeseolus vulgaris*) to the rust fungus *Uromyces appendiculatus* involves an oxidative burst but no HR-related cell death (Iriti and Faoro, 2003). With regards to SA signaling, BTH acts downstream of SA accumulation (Friedrich et al., 1996) and may contribute to the establishment of SAR through an interaction with SABP2, a methyl salicylate esterase that is critical for the perception of defence-inducing signals in systemic tissues (Du and Klessig, 1997; Forouhar et al., 2005; Park et al., 2007).

A number of other SAR inducers also act downstream of SA accumulation, although their activity has been less thoroughly characterized. Based on the efficacy of BTH, a screen of variant benzothiadiazole structures was conducted at Nihon Nohyaku Co., Ltd. (Japan) on the rice (*Oryza sativa*)-rice blast (*Magnaporthe grisea*) pathosystem. This screen yielded 3,4-dichloro-*N*-(2-cyanophenyl)-1,2-thiazole-5-carboxamide (tiadinil, TDL), which has activity not only against fungal pathogens of rice but also bacterial and viral pathogens of tobacco (Tsubata et al., 2006; Yasuda et al., 2004). A metabolite of TDL, termed SV-03, was subsequently found to be equally effective in the stimulation of disease resistance (Yasuda et al., 2006). In a different screen, 3-chloro-1-methyl-1H-pyrazole-5-carboxylic acid (CMPA) was identified from a survey of pyrazolecarbox-

Table 1. Small molecules (<500 Da) known to induce disease resistance in plants

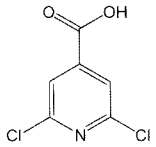
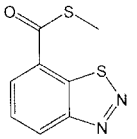
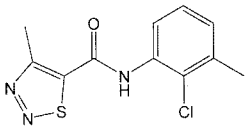
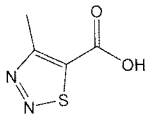
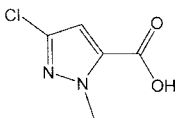
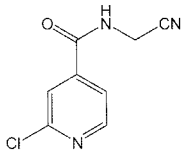
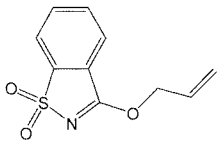
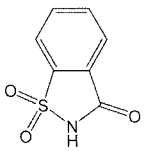
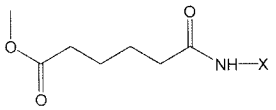
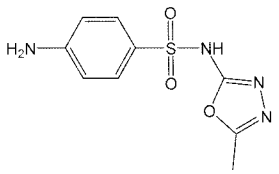
Name	Structure	Original Source-Molecules Screened	Reference
2,6-dichloroisonicotinic acid (INA)		SA analogues	Metraux et al., 1991; Ward et al., 1991
benzo(1,2,3)thiadiazole-7-carbothioic acid S-methyl ester (BTH)		Benzothiadiazole derivatives	Friedrich et al., 1996; Schurter et al., 1987
3,4-dichloro-N-(2-cyanophenyl)-1,2-thiazole-5-carboxamide (tiadinil)		Benzothiadiazole derivatives	Tsubata et al., 2006; Yasuda et al., 2004
SV-03		(Tiadinil metabolite)	Yasuda et al., 2006
3-chloro-1-methyl-1*H*-pyrazole-5-carboxylic acid (CMPA)		Pyrazolecarboxylic acid derivatives	Nakashita et al., 2003
N-cyanomethyl-2-chloroisonicotinamide (NCI)		Cyanoalkylisonicotinamide derivatives	Yoshida et al., 1987; Yoshida et al., 1990
probenazole (PBZ)		Benzothiadiazole derivatives	Watanabe et al., 1977
benzisothiazole (BIT)		(Probenazole metabolite)	Yoshioka et al., 2001
Adipic acid derivatives		Adipic acid derivatives	Flors et al., 2003 PMPP
Sulfamethoxazole		Arabidopsis-bioactive compounds	Schreiber et al., 2008
Phosphates	XPO_4	Potassium and phosphate salts	Gottstein and Kuc, 1989

Table 1. Continued

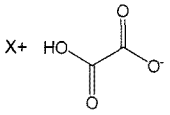
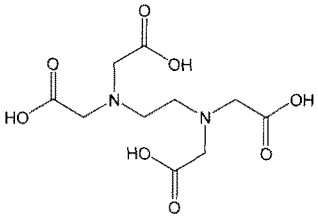
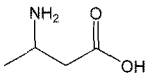
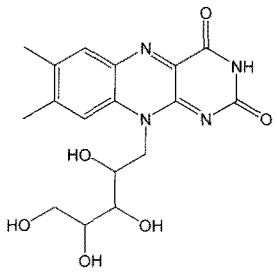
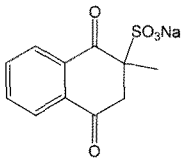
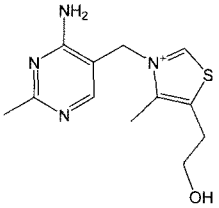
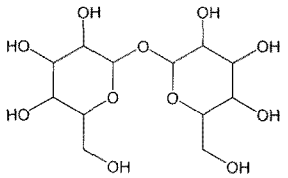
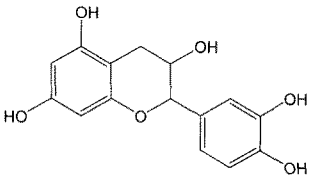
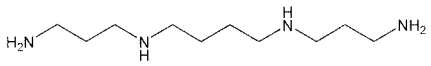
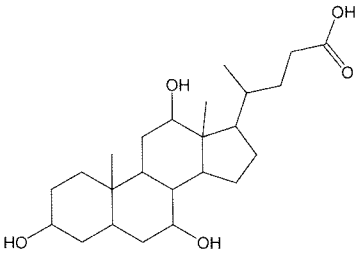
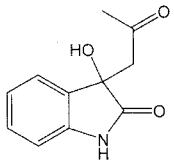
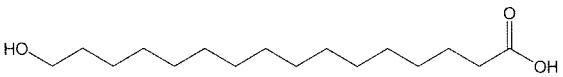
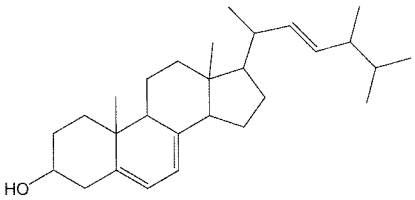
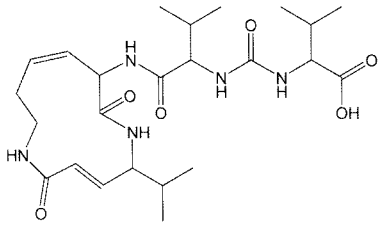
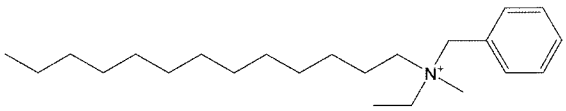
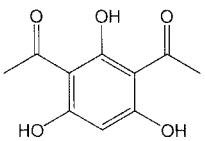
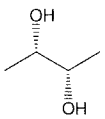
Name	Structure	Original Source-Molecules Screened	Reference
Oxalates		Chemical extracts from spinach and rhubarb	Doubrava et al., 1988
Ethylenediaminetetraacetic acid		Specifically tested as a calcium chelator	Walters and Murray, 1992
Silicon	Si, H_4SiO_4	–	reviewed in Epstein, 1994
Cadmium	Cd	Specifically tested	Ghoshroy et al., 1998
β-aminobutyric acid (BABA)		Variant amino acids	Papavizas, 1964
Riboflavin (Vitamin B_2)		Collection of plant metabolites	Emmanouil and Wood, 1981
Menadione sodium bisulfite (Vitamin K_3 addition compound)		Specifically tested	Borges et al., 2003
Thiamine (Vitamin B_1)		Compounds shown to induce PR-1 gene expression	Malamy et al., 1996
Trehalose		Natural product collection	Reignault et al., 2001
Catechin		Specifically tested	Prithiviraj et al., 2007

Table 1. Continued

Name	Structure	Original Source-Molecules Screened	Reference
Spermine		Chemical extract from the intercellular fluid of TMV-infected tobacco leaves	Yamakawa et al., 1998
Cholic acid		Chemical extract from human feces	Koga et al., 2006
3-acetonyl-3-hydroxyoxindole (AHO)		Chemical extract from *Strobilanthes cusia*	Li et al., 2008
Cutin monomers (16-hydroxypalmitic acid shown)		Collection of cutin monomers	Schweizer et al., 1996
Ergosterol		Specifically tested	Laquitane et al., 2006
Syringolin		Growth media from cultures of *Pseudomonas syringae* pv. *syringae* strain B 301D-R	Waspi et al., 1998
N-alkylated benzylamine derivatives		Growth media from cultures of *Pseudomonas putida* BTP1	Ongena et al., 2005
2,4-diacetylphloroglucinol		Selected mutants of *Pseudomonas fluorescens* CHA0 (i.e. genetic screen)	Iavicoli et al., 2003
2R, 3R-butanediol		Volatiles from *Bacillus subtilis* GB03 and *Bacillus amyloliquefaciens* IN937a	Ryu et al., 2004

[a]Refers to initial observations of induced disease resistance in plants
[b]Note: some microbial fatty acids also induce disease resistance (see text).

ylic acid derivatives as capable of protecting rice from infection by rice blast (*Pyricuraria oryzae*) and bacterial blight (*Xanthomonas oryzae* pv. *oryzae*) (Nakashita et al., 2003b; Nishioka et al., 2005). The resistance of tobacco to *Pseudomonas syringae* pv. *tabaci* and *Oidium* sp. was also enhanced by treatment with CMPA (Yasuda et al., 2003). Finally, among several cyanoalkylisonicotinamide structures screened for their ability to control *M. grisea* infection, *N*-cyanomethyl-2-chloroisonicotinamide (NCI) was especially effective (Yoshida et al., 1990; Yoshida et al., 1987). This compound also reduced the growth of a virulent strain of *P. syringae* on Arabidopsis, as well as TMV, *P. syringae* pv. *tabaci*, and *O. lycopersici* on tobacco (Nakashita et al., 2003a; Yasuda et al., 2003). Yasuda (2007) noted that TDL, SV-03, CMPA, and NCI all induced the expression of the same set of PR genes, all acted independently of SA accumulation and JA/ET perception, and all required the SA signaling regulatory protein NONEXPRESSER OF PR GENES1 (NPR1). Evidently, it is possible to stimulate the pathway between SA production and NPR1 activity with a variety of different chemical structures, although the cellular ligand(s) for each compound remain to be identified.

Other compounds are also closely tied to SA signaling, but at different points in the pathway. Researchers at Meiji Seika Kaisha, Ltd. (Japan) also drew inspiration from BTH as a starting point for screening benzothiadiazole derivatives for novel inducers of resistance. This investigation produced 3-allyloxy-1,2-benzothiazole 1,1-dioxide, which has been widely used under the name probenazole for the control of *M. grisea* in rice (Watanabe et al., 1977). Probenazole and its metabolite 1,2-benzisothiazole-1,1-dioxide (BIT, saccharin) both stimulated the expression of PR genes and the development of SAR against a range of pathogens (Nakashita et al., 2002; Yoshioka et al., 2001). In contrast to the compounds discussed above, however, probenazole and BIT do induce SA accumulation, they do not bind either catalase or SABP2, and their ability to confer SAR is blocked in plants expressing the *nahG* gene. Efforts to understand the mechanism of probenazole-induced resistance resulted in the isolation of a probenazole-responsive gene termed *PBZ1* (Midoh and Iwata, 1996). Interestingly, PBZ1 is also induced by NCI, but not BIT, indicating that the induced resistance is not necessarily PBZ1-dependent (Nakashita et al., 2001). The lack of PBZ1 induction by SA also suggests that probenazole does not function by exclusively stimulating SA accumulation. The sequence of PBZ1 shows some similarity to that of PR-10 (Midoh and Iwata, 1996), which may be a ribonuclease (Bantignies et al., 2000). Kim et al. (2008a) observed the accumulation of PBZ1 in tissues undergoing programmed cell death, although the exact function of PBZ1 in this context remains to be fully elucidated. Additional probenazole-induced genes include phenylalanine ammonia lyase (PAL) and caffeic acid 3-O-methyltransferase, which may be responsible for the production of flavonoid-type phytoalexins and/or lignin or, in the case of PAL, SA biosynthesis (Lin et al., 2008).

Some compounds have been discovered as part of a search for bioactive synthetic molecules with general effects on plant metabolism. Flors et al. (2001) hypothesized that synthetic growth regulators may enhance disease resistance by delaying senescence and stimulating biosynthetic pathways with potential defence-related end-products. This was tested by synthesizing derivatives of adipic acid, a six-carbon dicarboxylic acid, and screening for compounds that reduced the growth of *Phytophthora citrophthora*, *Phytophthora capsici*, or *Alternaria solani* on tomato (*Solanum lycopersicum* L.) or pepper (*Capsicum annuum* L.). While many compounds were most effective when used as a mixture, three novel amide derivatives of adipic acid provided significant protection when used on their own (Flors et al., 2001; Flors et al., 2003a; Flors et al., 2003b). These compounds stimulated plant growth, increased total protein content, reduced protease activity, increased photosynthetic rate, and improved water use efficiency, indicative of an overall antisenescence effect. The chemicals also upregulated PAL and chalcone isomerase (CHI) activities for increased output of phenylpropanoids and flavanones potentially bound for isoflavonoid phytoalexins. No direct antimicrobial activity was observed for the three compounds.

In some cases, even molecules with ostensible antibiotic activity can specifically stimulate plant defence responses. A collection of compounds known to be bioactive in Arabidopsis was screened to identify chemicals that protect Arabidopsis seedlings from infection by *P. syringae* (Schreiber et al., 2008). A group of sulfanilamide compounds was identified that provided varying levels of protection, with sulfamethoxazole (Smex) being the most effective. At the concentration used for screening, this compound did not directly inhibit bacterial growth. Analysis of various Arabidopsis signaling mutants indicated that Smex-mediated protection is manifested independently of SA, JA, ET, and ABA signaling, and does not require an oxidative burst. Both the physical target of Smex and its mechanism of activity are currently unknown.

Inorganic compounds can also be applied to enhance disease resistance in plants. Gottstein and Kuc (1989) first noted that phosphate salts induced systemic resistance to anthracnose in cucumber. The activation of broad-spectrum, systemic disease resistance by phosphates has since been observed in several other plant species (Reignault and Walters, 2007). This activity may involve the sequestration of calcium ions, which could disrupt the cell wall and cause

the release of defence-inducing cell wall fragments (Gottstein and Kuc, 1989). Notably, Ca^{2+}-binding organic acids such as oxalates and ethylenediaminetetraacetic acid also induced resistance to anthracnose in cucumber (Doubrava et al., 1988; Walters and Murray, 1992). Tissues treated with phosphates also exhibited ROS production, cell death, and both local and systemic accumulations of SA (Orober et al., 2002). In addition, phosphates stimulated increases in the activity of PAL, peroxidase, and lipoxygenase enzymes, which could contribute to cell wall reinforcement and further defence induction (Mitchell and Walters, 2004).

Although it is the second most abundant element in soils, silicon has long been known to alleviate biotic stress in plants (reviewed in Epstein, 1994). Dioga and Wydra (2007) suggested that pathogen spread was inhibited by silicon-induced modifications to pectic polysaccharides that help maintain cell wall integrity. Indeed, silicon treatment upregulated the activity of PAL, polyphenol oxidase, and peroxidase enzymes, all of which could influence cell wall structure (Qin and Tian, 2005). Transcriptomic analysis of silicon-treated Arabidopsis plants revealed that, while this element had essentially no effect on plants in the absence of pathogen infection, it dramatically enhanced host defence responses upon perception of a fungal invader (Fauteux et al., 2006).

Various metal ions are also capable of inducing both defence gene expression and resistance to pathogen infection (Asselin et al., 1985; Sinha and Giri, 1979; White et al., 1986). A mechanism of action has not been elucidated for most of these ions, but frequently, a direct antimicrobial effect at some level cannot be excluded (Poschenrieder et al., 2006). On the other hand, non-toxic concentrations of cadmium eliminated the disease symptoms caused by turnip vein clearing virus, apparently by interfering with systemic viral movement in a SA-independent manner (Citovsky et al., 1998; Ghoshroy et al., 1998). When applied as a seed treatment, this metal also protected wheat seedlings from infection by *Fusarium oxysporum* (Mittra et al., 2004), in the absence of direct antifungal activity.

Inducers from Biotic Sources

Amino acids and β-aminobutryic acid: In consideration of the selective pressures placed on plants for the evolution of effective defence mechanisms, the vast pool of naturally produced compounds seems to be an obvious source for molecules that influence disease resistance. One of the first "natural products" with such demonstrated activity was phenylalanine, which significantly reduced the susceptibility of apple leaves to infection by the fungal pathogen *Venturia inequalis* (Kuc et al., 1957). This finding fuelled a period of extensive investigation into the relationship between amino acids and disease resistance in which a variety of structures were tested in several different pathosystems (van Andel, 1966). The modes of action for these compounds were not fully ascertained, but it was evident that most amino acids did not have antimicrobial activity at the concentrations required for activation of plant defence responses. While the potential use of amino acids as prophylactic plant protectants has been revisited occasionally (Asselin et al., 1985; Emmanouil and Wood, 1981; Sinha and Giri, 1979), mechanistic explanations for this activity are mostly still lacking.

One notable exception to this situation is the nonprotein amino acid β-aminobutyric acid (BABA), which has provided tremendous insight into defence-related signaling pathways in plants. As the relevance of common amino acids to plant defence was becoming apparent, Papavizas (1964) identified BABA from a set of variant amino acid structures as a compound that significantly reduced the severity of root rot on peas (*Pisum sativum*) caused by the fungal pathogen *Aphanomyces euteiches*. The efficacy of BABA as an inducer of disease resistance was subsequently demonstrated in numerous plant-pathogen combinations (Cohen, 2002). Importantly, this activity occurs in the absence of direct antimicrobial effects. The signaling pathways required for BABA-induced resistance (BABA-IR) seem to vary for different types of pathogens. In Arabidopsis, the resistance induced against *P. syringae* and *B. cinerea* is SA-dependent but JA and ET-independent, while resistance to the oomycete *Hyaloperonospora parasitica* is independent of all three pathways (Zimmerli et al., 2000; Zimmerli et al., 2001). BABA does not directly activate defence responses, but rather primes the plant to respond more rapidly after pathogen attack, as demonstrated by the enhanced *PR-1* gene induction following *P. syringae* infection, and the earlier and greater callose deposition upon infection of BABA-treated Arabidopsis with the necrotrophic pathogens *Alternaria brassicicola* and *Plectosphaerella cucumerina* (Ton and Mauch-Mani, 2004). Inhibition of callose formation by 2-deoxy-D-glucose eliminated BABA-IR to *A. brassicicola*. Interestingly, treatment with ABA mimics the response to BABA, both in terms of primed callose accumulation and subsequent resistance to *A. brassicicola* and *P. cucumerina*. Furthermore, BABA-IR to *P. cucumerina* is blocked in the ABA biosynthetic mutant *aba1-5*, the ABA-insensitive mutant *abi4-1*, and the callose synthase mutant *pmr4-1*.

The connection between callose, ABA, and BABA was addressed through more detailed genetic studies. High concentrations of BABA induce sterility in Arabidopsis (Jakab et al., 2001), which allowed the identification of IBS (impaired in BABA-induced sterility) lines from a T-DNA insertion collection (Ton et al., 2005). One of the products of this screen was *IBS3*, which encodes a zeaxanthin

epoxidase with an important role in ABA biosynthesis. The *ibs3* mutant displayed reduced BABA-IR to *H. parasitica* coincident with deficiencies in priming for callose deposition and ABA-inducible gene expression. Disruption of *IBS2*, a polyphosphoinositide phosphatase, also reduced primed callose deposition, but only compromised BABA-IR to salt stress. Another mutant, *ibs1*, affected BABA-IR against *H. parasitica* and *P. syringae*, although the susceptibility of untreated plants was not altered. *IBS1* encodes a cyclin-dependent kinase that influences the SA-dependent component of BABA priming. These results suggest that BABA activity against different pathogens and stresses may be mediated by multiple pathways. Indeed, the callose-deficient *pmr4-1* mutant is compromised for BABA-IR against *A. brassicicola* but not *P. syringae* (Flors et al., 2008). This mutant is actually more resistant to *P. syringae*, owing to the negative crosstalk between callose synthesis and SA signaling (Nishimura et al., 2003). Treatment with BABA further enhances resistance to *P. syringae* (Flors et al., 2008). *A. brassicicola* downregulates ABA accumulation in Arabidopsis, which does not occur in BABA-treated plants. In this case, BABA appears to confer resistance by sensitizing tissues for ABA perception and priming callose deposition at some point upstream of PMR4.

Vitamins: As critical components of many physiological processes, vitamins may also influence the outcome of plant-pathogen interactions. Emmanouil and Wood (1981) observed that treating the leaves of pepper, tomato, or eggplant with riboflavin (vitamin B_2) prior to inoculation of roots with *Verticillium dahliae* significantly reduced the fungal load and overall disease symptoms of these plants. Riboflavin was later shown to protect various hosts from viral, bacterial, fungal, and oomycete pathogens, with little or no phytotoxicity (Aver'yanov et al., 2000; Dong and Beer, 2000; Pushpalatha et al., 2007). This systemic induced resistance required protein kinase signaling and a functional *NPR1* gene, but did not depend on SA accumulation. As a cofactor of enzyme flavoproteins, riboflavin may influence plant defence responses by catalyzing the production or metabolism of ROS. The accumulation of active oxygen molecules may also underlie the activity of menadione (vitamin K_3), which was first studied as a plant growth regulator (Rao et al., 1985). The water-soluble addition compound menadione sodium bisulphite (MSB) showed strong activity against *Fusarium oxysporum* on banana and *Leptosphaeria maculans* on *Brassica napus* (Borges et al., 2004; Borges et al., 2003). Menadione is a naphthoquinone that functions as an electron carrier in the plasma membrane (Oldenburg et al., 2008). It is possible that exogenous menadione increases the pool of naphthoquinone, leading to an accumulation of superoxide ions and H_2O_2 that could stimulate plant defence responses (Borges et al., 2003).

Another recently characterized vitamin with resistance-inducing activity is thiamine (vitamin B_1). Some early experiments demonstrated that thiamine can activate *PR-1* gene expression in tobacco (Asselin et al., 1985) and stimulate resistance to TMV in a SA-dependent manner (Malamy et al., 1996). Subsequent investigations indicated that the resistance induced by thiamine is systemic, broad-spectrum, and long-lasting (Ahn et al., 2005). In Arabidopsis, thiamine primes the pathogen-induced expression of PR-1 and PAL as well as callose deposition and an oxidative burst associated with the HR (Ahn et al., 2007). All of these responses were abolished when catalase, a H_2O_2 scavenger, was co-infiltrated with a virulent bacterial pathogen, thus indicating the key role of ROS in the activity of thiamine. The primed response was also found to be independent of ABA, JA, and ET signaling, but required both SA accumulation and a functional *NPR1* gene. Finally, thiamine primes the expression of a Ca^{2+}-dependent protein kinase gene, suggesting that this compound acts upstream of Ca^{2+} signaling to activate a set of responses mediated by the SA pathway (Ahn et al., 2005).

Sugars: A number of sugars have also demonstrated a capability for plant defence induction. A screen of various sugars revealed that cellobiose, mannose, arabinose, and sucrose significantly reduced the colonization of pepper and eggplant leaves by *V. dahliae* (Emmanouil and Wood, 1981). Trehalose, previously shown to be important for plant responses to abiotic stress (Drennan et al., 1993), protected wheat from infection by the powdery mildew fungus *B. graminis* (Reignault et al., 2001). Tissues treated with trehalose exhibited enhanced papillae formation at sites of attempted fungal penetration, increased expression of the phenlypropanoid pathway enzymes PAL and peroxidase, as well as accumulations of H_2O_2 and phenolic compounds (Reignault et al., 2001; Renard-Merlier et al., 2007).

Catechin: The observation that high concentrations of the allelochemical catechin stimulated extensive ROS production and cell death in plants (Bais et al., 2003) spurred an investigation into the contribution of this molecule to plant defence responses. Intriguingly, lower concentrations of (±)-catechin stimulated growth in Arabidopsis and reduced its susceptibility to infection by a virulent strain of *P. syringae* (Prithiviraj et al., 2007). This level of exposure resulted in moderate accumulations of ROS, significant callose deposition in leaves, and the SA/NPR1-dependent induction of PR-1. Overall, these findings illustrate the phenomenon of hormesis, in which sublethal concentrations of a toxin actually promote the growth and survival

of an organism (Calabrese and Baldwin, 2003).

Polyamines: Although there is strong evidence that polyamines are associated with plant defence responses (Walters, 2003), they have only received brief attention as potential exogenous inducers of disease resistance. Polyamines are known to accumulate in necrotic lesions during the HR (Torrigiani et al., 1997) and in intercellular spaces of TMV-infected tissue (Yamakawa et al., 1998). Treatment of tobacco plants with the polyamine spermine induced the expression of several PR genes and resulted in significantly reduced lesion sizes in leaves inoculated with TMV. Spermine did not induce SA accumulation, nor did SA increase spermine levels. The activity of polyamines in the context of defence remains to be fully characterized, but these compounds could be components of the programmed cell death signaling machinery that facilitate the accumulation of ROS and other defence-related molecules (Kusano et al., 2008; Walters, 2003).

Cholic Acid: Based on observations that the application of manure-based fertilizers can suppress disease in plants (Zinati, 2005), Koga et al. (2006) postulated that compounds present in animal feces would be capable of inducing defence responses in plants. To test this theory, fractions from a chemical extract of human feces were applied to rice leaves, followed by assessments of phytoalexin accumulation. Cholic acid, a primary bile acid in animals, was identified as a strong inducer of phytocassane phytoalexins. This acid was subsequently shown to increase the resistance of rice to infection by *M. grisea* through a cell death-associated response. There appeared to be significant specificity in the activity of cholic acid, because no other bile acid derivatives elicited this response with the same strength as cholic acid, and other known microbial elicitors induced the accumulation of different combinations of phytoalexins (Shimizu et al., 2008). The mechanism of cholic acid-induced resistance in plants in unclear, and while natural ligands of other bile acids have been identified in animals, a receptor for cholic acid has yet to be identified.

3-acetonyl-3-hydroxyindole (AHO): Some resistance-inducing compounds have been isolated from surveys of non-agricultural plants. By screening chemical extracts from the ornamental *Strobilanthes cusia* for the induction of resistance to TMV in tobacco, Li et al. (2008) identified and purified the bioactive compound 3-acetonyl-3-hydroxyindole (AHO). This indole-type compound is a derivative of isatin, an auxin precursor (Applewhite et al., 1994). In addition to TMV, AHO protects tobacco from infection by the powdery mildew fungus *Erysiphe cichoracearum* (Li et al., 2008). The mode of action of AHO remains to be fully characterized, but this chemical is known to induce *PR-1* gene expression, PAL activity, and resistance to TMV in a SA-dependent manner. Furthermore, AHO induces SA accumulation as well as the expression of other proteins associated with SA signaling, such as mitogen-activated protein kinases (MAPKs) and SA-induced protein kinases (SIPKs).

Cutin: In some cases, plant-derived defence elicitors are liberated as a consequence of pathogen invasion. Upon contact with leaf tissue, many phytopathogenic fungi produce an exudate that contains cutinase enzymes (Schafer, 1993). The activity of these enzymes releases cutin monomers from the plant cuticle which, if perceived by the host plant, could betray the presence of an invading pathogen. With this in mind, a variety of cutin monomers were tested on barley for their effectiveness in eliciting resistance to the powdery mildew fungus *Erysiphe graminis* (Schweizer et al., 1996). A number of monomers provided partial protection from infection and also displayed activity against *M. grisea* on rice. Later studies indicated that cutin monomers stimulate ROS production (Kauss et al., 1999) and induce the expression of lipid transfer proteins (LTPs) (Kim et al., 2008b). A cutin receptor has yet to be identified, but it is possible that cutin monomers may be perceived by affecting membrane structure and/or certain membrane-associated proteins (Douliez, 2004). Transduction of a cutin-induced signal may involve LTPs, some of which are known to be involved in long-distance signaling for the establishment of SAR (Maldonado et al., 2002). This mechanism is, however, purely speculative.

Large Molecules (>500 Da)
Synthetic/Inorganic.

Polyacrylic Acid (PA): There are significant parallels between the immune systems of plants and animals (Iriti and Faoro, 2007; Nurnberger et al., 2004) which may be exploited for the discovery of plant defence-inducing compounds. Given that certain synthetic polyanions stimulate the production of antiviral interferons (Declercq et al., 1970), Gianinazzi and Kassanis (1974) hypothesized that these compounds might also induce virus resistance in plants. Of various polymers tested, only polyacrylic acid (PA) was capable of enhancing resistance to TMV and tobacco necrosis virus in tobacco (Table 2). Resistance was not induced by polyacrylamide which, notably, did not stimulate interferon production in animal cells (Declercq et al., 1970). Later studies indicated that small polymers (1,500-2,000 Da) also provided effective protection against *Colletotrichum lagenarium* in cucumber, pelargonium leaf curl virus in *Datura stramonium*, as well as *P. syringae* pv.

Table 2. Large molecules (>500 Da) known to induce disease resistance in plants

Name	Reference[a]
Polyacrylic acid	Gianinazzi and Kassanis, 1974
Plant-derived oligosaccharides	
Oligogalacturonides	Aziz et al., 2004
Cellodextrins	Aziz et al., 2007
Galactoglucomannan-derived oligosaccharides	Slovakova et al., 2000
Plant proteins	
Lipid transfer protein 1-jasmonic acid complex	Buhot et al., 2004
Microbe-associated molecular patterns	
Chitin/chitosan	Hadwiger, 1979
Glucans	Hodgson, 1969
Lipids	Cohen et al., 1991
Lipopolysaccharide	Graham et al., 1977
Peptides/Proteins	
flg22 (flagellin)	Zipfel et al., 2004
elf18 (elongation factor Tu)	Kunze et al., 2004
elicitins	Bonnet et al., 1996
cellulose-binding elicitor lectin	Gaulin et al., 2006
harpin	Dong et al., 1999
peptaibols	Kim et al., 2000
Sm1 (small protein 1)	Djonovic et al., 2006
Epl1	Vargas et al., 2008

[a]Refers to initial observations of induced disease resistance in plants

porri and tobacco ringspot virus in tobacco (Ahl et al., 1985; Mills and Wood, 1984). In all cases, PA did not exhibit antimicrobial activity. With regards to the characterization of PA activity, analysis of crosses between different *Nicotiana* species revealed that PA responsiveness was inherited as a dominant trait distinct from the *N* gene, which encodes an R protein that determines TMV resistance (Dumas et al., 1985). PA stimulates the production of SA, and PA-induced resistance to TMV is blocked in *nahG* plants and at high temperature (Malamy et al., 1996). While PA has been tested in other pathosystems (Ortega-Ortiz et al., 2003), further mechanistic characterization has not been performed.

Inducers from Biotic Sources.

Plant-derived oligosaccharides: The elicitation of plant defence responses by oligosaccharides is well-established (Shibuya and Minami, 2001). Hahn et al. (1981) first identified "endogenous elicitors" as oligosaccharides from soybean, tobacco, sycamore, and wheat cell walls that induced the accumulation of phytoalexin. Aziz et al. (2004) specifically studied α-1,4-oligogalacturonides (OGA) as candidate plant protectants, and demonstrated that these molecules do increase the resistance of grapevine to *B. cinerea* infection. In treated leaves, OGA triggered the production of H_2O_2 and induced the expression of several defence-related genes including some PR genes. The induced resistance response was impaired in the presence of diphenylene iodonium, which is an inhibitor of NADPH oxidase, and the protein kinase inhibitor K252a, thus highlighting the importance of both the oxidative burst and protein phosphorylation for the protective effect. In Arabidopsis, OGA-induced resistance to *B. cinerea* is mediated by mechanisms independent of SA, JA, and ET signaling (Ferrari et al., 2007). Cellodextrins, which are water-soluble derivatives of cellulose (β-1,4-linked glucoside residues), also protect grapevine from *B. cinerea* (Aziz et al., 2007). Like OGA, cellodextrins stimulate an oxidative burst and induce a similar set of defence-related genes, although the dynamics of these responses differ between the two stimuli, suggesting that they may be differentially perceived. Finally, oligosaccharides derived from galactoglucomannan significantly reduce the severity of disease symptoms caused by tobacco necrosis virus on cucumber (Slovakova et al., 2000). This response was accompanied by the accumulation of peroxidase enzymes and PR proteins.

Plant proteins: It is evident that there are a vast number of endogenous proteins involved in the mediation of plant defence responses, but the activity of exogenously-applied proteins is largely unexplored. One fascinating exception is the tobacco lipid transfer protein LTP1 which, in a complex with JA, enhances the systemic resistance of tobacco to *P. parasitica* (Buhot et al., 2004). Treatment of plants with LTP1 or JA alone did not induce resistance. As another example, AtPep1 is an endogenous Arabidopsis peptide that may be part of a positive feedback loop for innate immune signaling (Huffaker and Ryan, 2007). Although the efficacy of exogenous AtPep1 treatment was not tested, ectopic expression of an AtPep1 propeptide in Arabidopsis provided significant protection from infection by *Pythium irregulare* (Huffaker et al., 2006).

Microbe-Associated Molecular Patterns

Over the course of an attempted infection, pathogens are in extremely close association with their hosts. This proximity provides the opportunity for pathogens to manipulate host metabolism for the release of nutrients, but at the same time brings the invader within range of the plant's surveillance system. This system can perceive a wide variety of microbe-associated molecular patterns (MAMPs, also known as pathogen-associated molecular patterns or PAMPs), which

are highly conserved structures that are essential for microbial fitness yet absent from potential hosts (Nurnberger et al., 2004). These features provide an evolutionarily stable mechanism for the detection of "nonself" molecules by pattern recognition receptor (PRR) proteins. The recognition of MAMPs activates a basal immune response, that generally includes MAP kinase signaling, callose deposition for cell wall reinforcement, ROS production, and the expression of defence-related genes (Chisholm et al., 2006; Nurnberger et al., 2002). We discuss MAMPs in a separate section to illustrate the diversity and overall preponderance of potential defence-inducing molecules that are presented by microbes themselves, both pathogenic and nonpathogenic.

Chitin/Chitosan. Fungal cell walls often contain chitin, a β-1,4-linked N-acetylglucosamine polymer, and its deacetylated derivative chitosan. The elicitor activity of chitosan was first demonstrated in a screen of fungal cell wall components that were assayed for their ability to induce phytoalexin accumulation in pea pods and induce resistance to the fungal pathogen *Fusarium solani* (Hadwiger, 1979). Chitosan does exhibit some antifungal activity (Hadwiger and Beckman, 1980), but does stimulate several defence responses in plants, including production of PR proteins (Agrawal et al., 2002), lignification (Barber et al., 1989), increased lipoxygenase activity, and upregulation of PAL (Trotel-Aziz et al., 2006). Chitin and chitosan are known to associate with plasma membranes (Baureithel et al., 1994), and a chitin-binding protein (CE-BiP) was recently identified in rice (Kaku et al., 2006). This protein contains two extracellular Lysin Motif (LysM) domains and a transmembrane region, but lacks an obvious intracellular domain for signal transduction. Chitin-responsiveness assays were conducted on Arabidopsis lines with T-DNA insertions in CE-BiP-related sequences, yielding a receptor-like kinase (CERK1/LysM1 RLK) whose knockout completely abolished chitin-induced responses (Miya et al., 2007; Wan et al., 2008). These knockouts also displayed increased susceptibility to *A. brassicicola* and *Erysiphe cichoracearum*, but not *P. syringae*, indicating the importance of chitin perception to resistance against fungal pathogens.

Glucans. Another group of oligosaccharides, the glucans (D-glucose polymers), can also activate plant immune responses. This was first observed with a β-1,3-linked D-glucan from *P. infestans*, which strongly inhibited the development of lesions in tobacco tissues inoculated with various viruses (Hodgson et al., 1969; Singh et al., 1970). It is interesting to note that tobacco was also protected from the soft rot pathogen *Erwinia carotovora* by laminarin, a linear β-1,3 glucan from the marine brown alga *Laminaria digitata* (Klarzynski et al., 2000). Laminarin also reduced the growth of *B. cinerea* and *Plasmopara viticola* on grapevine leaves (Aziz et al., 2003). Host perception of laminarin induced multiple responses, including ion fluxes, an oxidative burst, activation of a MAPK cascade, callose deposition, phytoalexin production, and the expression of PR genes (Aziz et al., 2003; Daxberger et al., 2007; Trouvelot et al., 2008). In both Arabidopsis and tobacco, sulfated laminarin (PS3) provided greater local protection from TMV infection than did laminarin, and these glucans acted synergistically when used in combination (Menard et al., 2004; Menard et al., 2005). Notably, PS3 induced SA accumulation and PR-1 expression, while laminarin did not. In terms of a mechanism of action, glucan-binding proteins (GBP) have previously been identified (Mithofer et al., 1996; Umemoto et al., 1997). These proteins are composed of two domains, one with glucan binding activity, and the other showing similarity to fungal glucan endoglucosidase enzymes (Fliegmann et al., 2004). This structural arrangement would facilitate the release of elicitor molecules in close proximity to the elicitor binding site for efficient MAMP detection. The GBP is likely part of a larger receptor complex, because GBP alone is essential but not sufficient for the glucan response.

Lipids. As a group, lipids are ubiquitous entities with diverse structural and biochemical roles. When applied exogenously to plants, certain lipids induce the accumulation of phytoalexins (Bostock et al., 1981). The induction of resistance was demonstrated by Cohen et al. (1991), who noted a significant reduction in the symptoms of *P. infestans* infection on potato leaves sprayed with eicosapentanoic acid (EPA) or arachidonic acid (AA). Pre-treatment of pearl millet seeds with EPA, AA, or docosahexanoic acid protected plants from the downy mildew pathogen *Sclerospora graminicola*, even at later developmental stages (Amruthesh et al., 2005). In addition to fatty acids, sphingolipids such as ceramides and cerebrosides induce resistance in a variety of plant-pathogen combinations (Deepak et al., 2003; Koga et al., 1998; Umemura et al., 2004). These compounds stimulate ROS production, and there is some evidence that the intracellular balance between ceramides and their phosphorylated derivatives modulates programmed cell death in plants (Liang et al., 2003).

Ergosterol/Syringolin. Aside from fatty acids, a limited number of small molecule elicitors are derived from pathogens. Ergosterol is a component of fungal cell membranes that triggers ROS production, ion fluxes, and phytoalexin accumulation in plants (Kasparovsky et al., 2003). Grape plantlets treated with ergosterol exhibited large reductions in the symptoms of disease caused by *B. cinerea* (Laquitaine

et al., 2006). Another elicitor, syringolin, was isolated from *P. syringae* pv. *syringae* and characterized as a small peptide containing non-protein amino acids and an unusual ring structure (Waspi et al., 1998). The virulence function of syringolin was recently found to involve inhibition of the host proteasome as a means of suppressing defence responses (Groll et al., 2008). In plants that are nonhosts for *P. syringae*, however, purified syringolin induced resistance to the fungal pathogens *B. graminis* and *Pyricularia oryzae* (Waspi et al., 1998; Waspi et al., 2001). In addition to a protective effect, syringolin also displayed curative activity in eliminating fungal populations from previously inoculated tissues. This dramatic efficacy was not due to antifungal activity, but was associated with the induction of cell death and sustained accumulation of PR proteins.

Rhizobacteria-derived small molecules. Bacteria in the rhizosphere produce a variety of signals that stimulate ISR in the host plant. Characterization of the media in which *Pseudomonas putida* BTP1 was cultured revealed that an N-alkylated benzylamine derivative from this organism conferred systemic resistance to *B. cinerea* in bean plants (Ongena et al., 2005). Preliminary analyses suggested that this compound induces the production of antifungal phytoalexins in treated plants. Iavicoli et al. (2003) used mutants of *Pseudomonas fluorescens* CHA0 to demonstrate that the compound 2,4-diacetylphloroglucinol (DAPG) is important for ISR in Arabidopsis. Interestingly, stimulation of ISR by *P. fluorescens* is dependent on a functional NPR1 protein as well as JA and ET signaling, while DAPG-induced resistance requires only ET signaling. Finally, the compound 2R, 3R-butanediol was isolated from a blend of volatiles collected from two rhizobacterial *Bacillus* species and shown to induce resistance to *Erwinia carotovora* subsp. *carotovora* SCC1 in Arabidopsis (Ryu et al., 2004). This chemical was also recovered from *Pseudomonas chlororaphis* O6 in a screen for resistance-inducing volatiles using tobacco as a host (Han et al., 2006). The protection provided by 2R, 3R-butanediol is specific to this stereoisomer and is dependent on ET signaling.

Lipolysaccharide. One MAMP that is specific to Gram-negative bacteria is the cell wall component lipopolysaccharide (LPS). A screen of *Pseudomonas solanacearum* cell fractions revealed that purified LPS conferred resistance to tobacco against *P. solanacearum* infection (Graham et al., 1977). Treatment with LPS may prime plants for a more rapid response to pathogen infection, as shown with *Xanthomonas axonopodis* on pepper plants, where the induced responses included PR gene expression and accumulation of phenolic compounds (Newman et al., 2002). In dicots, LPS prevents HR-associated programmed cell death during pathogen challenge, but appears to induce cell death in monocots even in the absence of a pathogen (Desaki et al., 2006; Newman et al., 2000). The functional significance of this difference remains to be clarified. With regards to LPS perception, the LPS receptor in animal cells is comprised of a plasma membrane-bound, multiprotein complex that is endocytosed upon binding LPS (Husebye et al., 2006; Miyake, 2006). Exogenous LPS binds to the plant cell wall and is internalized in a manner suggestive of receptor-mediated endocytosis (Gross et al., 2005), but no proteins with significant sequence similarity to the components of the LPS receptor are found in Arabidopsis (Newman et al., 2007). However plants do possess receptors such as the R protein RPS4 that are structurally homologous to an intracellular LPS receptor found in mammals (Inohara and Nunez, 2003). Overall, the machinery of LPS detection and signaling in plants remains undefined.

Peptides/Proteins. A large number of MAMPs are peptides, regions of proteins not only associated with pathogen virulence, but also with general metabolism. Two of the most well-characterized MAMPs are located within the bacterial flagellin (flg22) and translational elongation factor-Tu (elf18) proteins (Felix et al., 1999; Kunze et al., 2004). Infiltration of either peptide into the leaves of Arabidopsis plants greatly reduced their susceptibility to subsequent infection by a virulent strain of *P. syringae* (Kunze et al., 2004; Zipfel et al., 2004). Both peptides are perceived by receptor-like kinase proteins that initiate a MAPK cascade leading to ROS production and callose accumulation (Gomez-Gomez and Boller, 2000; Nurnberger et al., 2004; Zipfel et al., 2006).

Elicitins are small (98 amino acids, ~10 kDa) proteins secreted by *Phytophthora* and *Pythium* spp. that activate a broad-spectrum, systemic resistance response when applied to plants (Baillieul et al., 2003; Benhamou et al., 2001; Bonnet et al., 1996; Capasso et al., 1999). This response may include the induction of ion fluxes, callose deposition, and accumulation of a calcium pectate gel in the intercellular spaces of parenchyma cells (Lherminier et al., 2003). Upstream of these responses, elicitins bind sterols, acting as a type of LTP (Osman et al., 2001). Buhot et al. (2001) identified a plasma membrane receptor whose binding to a plant LTP can be competed out by elicitin, suggesting a possible elicitin receptor.

Another *Phytophthora* protein, a cellulose-binding elicitor lectin (CBEL), was shown to protect tobacco from infection by a virulent strain of *H. parasitica* (Gaulin et al., 2006). The ability of this 34 kDa protein to elicit necrosis and expression of defence-related genes in plants depends on two cellulose-binding domains within CBEL (Villaba-Mateos et al., 1997).

Originally identified in *Erwinia amylovora*, harpins are acidic, glycine-rich, heat-stable proteins that induce a HR in many plants (Wei et al., 1992). Exogenously applied harpin induces resistance in numerous pathosystems (Reignault and Walters, 2007). In Arabidopsis, harpin-induced resistance to *H. parasitica* and *P. syringae* is SA- and NPR1-dependent, but JA- and ET-independent (Dong et al., 1999). A harpin receptor is not known, but expression profiling of harpin-treated tobacco cell suspensions identified a harpin-responsive receptor-like kinase gene that may play a role in harpin perception (Sasabe et al., 2007).

In many fungi, non-ribosomal peptide synthetases generate peptaibols, short (20 amino acids) peptides which frequently contain α-amino isobutyric moieties and modified termini (Grigoriev et al., 2003). Although generally characterized as antibiotics (Szekeres et al., 2005), peptaibols can also induce resistance in plants independently of this activity. A 19-mer peptaibol from *Apiocrea chrosospermin* conferred resistance to TMV in tobacco (Kim et al., 2000), while *Trichoderma virens* produces an 18-mer peptaibol that significantly reduced the growth of *P. syringae* on cucumber seedlings (Viterbo et al., 2007). This systemic resistance response involved the induction of defence-related genes such as hydroperoxide lyase, PAL, and peroxidase, although the mechanism of activation remains unknown.

T. virens also produces Sm1 (small protein 1), a 12.6 kDa protein that belongs to the ceratoplatanin family (Djonovic et al., 2006). Sm1 triggers an oxidative burst but not cell death, and the treatment of cotton cotyledons with this protein provides significant protection from infection by a *Colleotrichum* sp. pathogen. An Sm1 homologue from *T. atroviride*, Epl1, induces systemic resistance to *Colletotrichum graminicola* in maize (Vargas et al., 2008).

Finally, it is worth noting the peptides and peptide-associated MAMPs that stimulate plant defence responses, but have not yet been shown to induce disease resistance when applied exogenously. These include peptidoglycan (Gust et al., 2007), Pep-13 from a transglutaminase (Brunner et al., 2002), cold-shock protein (Felix and Boller, 2003), xylanase (Ron and Avni, 2004), invertase (Basse et al., 1993), and necrosis-inducing peptides (Fellbrich et al., 2002; Qutob et al., 2006). Interestingly, ectopic expression of a yeast invertase in tobacco significantly reduced its susceptibility to potato virus Y (Herbers et al., 1996). Given the induction of resistance by a significant number of MAMPs, the molecules listed above would be prime candidates for testing exogenously in a model pathosystem.

High-Throughput Chemical Genetics in Plant Pathology

In a very general sense, the quest for novel sources of enhanced disease resistance in plants relies heavily on chemical and/or genetic variation. Classically, the genes responsible for pathogen defence have been interrogated in genetically variable populations of plants generated by techniques such as chemical mutagenesis, transposon insertion (for gene disruption and/or activation), fast neutron bombardment, and ion irradiation (Alonso et al., 2003; Li et al., 2001; Shikazono et al., 2005; Waugh et al., 2006). A relatively new approach is that of chemical genetics, in which small molecules are used as biological perturbants to modulate a phenotype of interest (Stockwell, 2000). As with classical genetics, there are two main approaches to screening small molecules. Forward chemical genetics involves screening through collections of small molecules and identifying those that cause a specific phenotype in the test population, eventually working towards identifying the biological ligand of that chemical. In contrast, reverse chemical genetic approaches endeavour to identify chemical ligands of a specific biological target, followed by analyses of the phenotype induced by those small molecules at the organismal level. It should be evident from this review that there is a long history of forward chemical genetic screening for inducers of disease resistance, although most of these studies have only evaluated small sets of selected compounds. Many "modern" forward chemical genetic screens utilize large numbers of compounds in an effort to modulate as many targets as possible, akin to the saturation of a classical genetic screen. Extensive small molecule collections are commercially available for such genome-wide surveys, and many of these libraries have been assembled from compounds with "drug-like" properties to maximize their potential biological activity (Baurin et al., 2004). The capability to screen such large numbers of chemicals depends on the development of a high-throughput pathology assay, which in turn requires the consideration of several important issues.

Design of a High-Throughput Screen. The experimental design of a high-throughput assay is strongly influenced by the objective of the screen. If the goal is to modify a specific plant signaling pathway, then the phenotype used for identifying positive results (hits) could be the expression of a certain reporter gene or the accumulation of a specific protein. For example, the ability of various chemicals to induce the expression of specific PR proteins has been surveyed in the past (Asselin et al., 1985). More recently, Serrano et al. (2007) employed the β-glucuronidase gene fused to the promoters of several known MAMP-responsive genes in order to identify small molecules that either activated or inhibited responses to MAMPs. Activity of the β-glucuronidase reporter gene could be monitored either histochemically or by quantitative fluorimetry. This type of

screen can yield valuable insight into the signaling pathways that coordinate defence responses, but it may not identify compounds with an immediate function in disease resistance. In order to incorporate all pathways leading to effective disease resistance, it may be more appropriate to assess the general phenotype of a whole organism. This approach has been successfully adopted to identify antifungal compounds in the *Caenorhabditis elegans-Candida albicans* pathosystem (Breger et al., 2007), and presumably could be extended to bacterial pathogens as well (Aballay and Ausubel, 2002). In addition, a number of other well-characterized hosts are amenable to studies of chemical interference with microbial pathogenesis (Mylonakis et al., 2007). In most cases, the phenotypic endpoint is the death or survival of the host, although assessments of microbial proliferation can supplement these observations.

For screening disease resistance in plants, defining the phenotype to be evaluated is of fundamental importance. If the screen is intended to generate a commercial crop protectant, then major consideration should be given to the most economically relevant characteristics such as yield and crop quality. On the other hand, high-throughput analyses prioritize economy of time and space, and the maintenance of vast populations of plants over their entire growth season is generally impractical. As such, the main challenge for this type of screen involves defining a phenotype that will serve as an accurate surrogate for final yield/product quality. This is not a trivial task because, although pathogen infection and yield loss are correlated in a general sense, the connection between disease symptoms and yield can be more difficult to establish (Gaunt, 1995). Complications arise from the variety of factors that contribute to yield as well as the many epidemiological variables influence disease progression. As such, single assessments of disease symptoms may provide insufficient predictive power for estimates of yield, especially if made at a relatively early developmental stage. In the end, a practical compromise may be to select an obvious infection phenotype for a primary screen, and subsequently assess yield benefits in a secondary screen. We have developed a high-throughput assay in which Arabidopsis seedlings are grown in liquid media in 96-well plates (Schreiber et al., 2008). Inoculation of seedlings with virulent *P. syringae* results in the eventual bleaching of cotyledons, while cotyledons remain green in the presence of non-virulent strains. Furthermore, molecules known to induce defence in Arabidopsis, such as SA and the flg22 peptide, also protect seedlings from bleaching. This phenotype is closely associated with the level of bacterial growth within seedling tissues. For screening purposes, cotyledonary bleaching is a relatively straightforward phenotype to evaluate, and is sensitive enough that compounds that confer partial protection from infection can be identified. We have not yet verified the correlation between bleaching and yield, but importantly, compounds that prevent bleaching in seedlings also significantly reduce bacterial growth in adult Arabidopsis plants.

The diversity of structures and potential activities of small molecules implies that compromises may need to be made in other aspects of the screen. Ideally, every compound would be tested at multiple concentrations to generate a dose-response curve for the screening phenotype. For libraries comprised of thousands of chemicals, this approach would necessitate significant automation of the screening process and the capacity for analyzing massive amounts of data. Where such resources are not available, one or two concentrations (usually in the low micromolar range) can be tested with the acceptance of a certain rate of false negatives. The timing of chemical application and pathogen inoculation is another variable to consider.. The activation or priming of plant defence may require some amount of time before plants are "ready" to combat infection (Conrath et al., 2006). Screening at multiple time-points after chemical treatment would be the most comprehensive approach in order to identify the optimal priming time. As an example, SA and SA analogues induce PR gene expression within four to twelve hours of treatment, concomitant with the induction of disease resistance (Ward et al., 1991; Lawton et al., 1996; Lebel et al., 1998). Finally, the manner in which chemicals are applied will influence the output of the screen. In this review, we have described screens that introduced compounds through seed soaking, soil drenches, supplementation of growth media, foliar sprays, and direct infiltration of tissues. While it may be desirable to screen compounds in a context similar to what occurs in the field, logistics and practicality may limit the screen to a particular plant developmental stage or specific growth conditions that in turn dictate the use of a different approach. Again, compounds yielding positive results in the primary screen could be analyzed in secondary screens that more closely mimic field conditions.

Having determined the inputs for a screen, it is also necessary to consider the output of this experiment. If the screen is based on the expression of a reporter gene, quantification of the reporter should be relatively straightforward. For a phenotype-based pathosystem screen, a chemical that induces resistance to infection would confer a phenotype that deviates significantly from an untreated control. The results of this type of screen are less simple to interpret, as hits will be defined by an arbitrary threshold of what constitutes a "significant" difference in the form of protection from pathogen infection. The reproducibility of results will strongly influence where this threshold can be set.

Characterization of Hits. Once hits are identified in a screen, numerous analyses can be performed in order to understand the mechanism of action of these chemicals. Alterations of pathosystem behaviour can arise from chemically-induced effects on either the plant or the pathogen (or possibly both), so it is important to first differentiate where a compound is acting. Direct antimicrobial activity can be assessed by a simple growth assay, although this may be difficult for some biotrophic fungi and oomycetes. In the absence of antimicrobial effects, a compound may be affecting some aspect of pathogen virulence. Interference with the secretion of virulence effector proteins could be evaluated in media that normally stimulate effector production, or by co-infiltrating plants with the compound and an avirulent pathogen that normally triggers an effector-dependent hypersensitive response HR. Microscopic analysis may reveal chemically-induced effects on pathogen motility, or morphological changes such as reduced germ tube or appresorium formation (Geissler and Katekar, 1983; Oh and Lee, 2000; Pontzen and Scheinpflug, 1989).

On the other side of the pathosystem, the chemical of interest may be inducing a response in the plant. The entry of pathogens into host tissues could be blocked if the compound stimulated the closure of stomata, which could be ascertained microscopically. If pathogen entry is unaffected, then resistance may arise from the stimulation of active plant defence mechanisms. Here, analyses could include the expression of PR and other defence-related genes, ROS production, and callose deposition. The dependence of chemically-induced resistance, and possibly specific defence responses, on certain signaling pathways can also be determined. A large number of Arabidopsis mutants have been identified that disrupt signaling mediated by specific molecules (Kazan and Schenk, 2007; Robert-Seilaniantz et al., 2007). While these mutants can provide valuable information on the pathways being manipulated by a defence-inducing chemical, they usually cannot reveal direct molecular targets. The assembly of a more precise functional picture requires the identification of cellular target(s) that is (are) directly affected by the chemical.

Target Identification. Several different tools are available to assist in the search for biological ligands of small molecules, generally assumed to be proteins. A biochemical approach may be taken, in which the compound of interest is covalently linked to a solid substrate for affinity purification of interacting proteins from a crude cell extract (Zheng et al., 2004). This requires the introduction of a reactive linker into the chemical, which must then be retested and possibly redesigned to ensure that the modification does not interfere with the compound's activity. The development of tagged libraries eliminates the need for these structure-activity optimization steps (Inverarity and Hulme, 2007; Kim and Chang, 2007), but most available libraries do not have this feature. Overall, affinity purification can demonstrate physical associations with potential physiological relevance, but the technique often suffers from the recovery of background contaminants, especially when the affinity of the chemical for its protein ligand is low (Zheng et al., 2004).

An alternative approach for target identification is based on genetic analyses. Assuming that the chemical of interest inhibits the activity of its protein ligand, then inactivation of the corresponding gene should phenocopy the effects of the chemical. If the chemical is phytotoxic at some concentration, loss-of-function mutants could be obtained from a mutagenized population of plants that is screened for insensitivity to the compound. These mutants would be expected to show enhanced resistance to pathogen infection even in the absence of the compound. Even if the chemical actually stimulates rather than inhibits protein activity, these mutants remain informative as susceptible hosts whose infection cannot be prevented by the selected small molecule. It is important to note that the mutations identified in either scenario may not represent actual ligands, but rather some component of a specific signaling pathway altered by the chemical. Nonetheless, this approach has proven extremely useful in characterizing the activity of compounds such as BABA and the herbicide DAS734 (Ton et al., 2005; Walsh et al., 2007). Another genetic approach could utilize microarray analysis of transcripts from chemically-treated versus untreated plants to indicate the global transcriptional response to the chemical. The inclusion of transcriptomic data from infected plants would further enhance this analysis by identifying genes whose expression is altered in opposite directions in treated versus infected plants. Again, a chemical target may not be made immediately apparent through this exercise, but the metabolic pathways and processes influenced by the compound will be clarified. Some more specific tools are available in other model organisms such as yeast, where large collections of hetero- and homozygous deletion mutants can be screened for increased sensitivity to a chemical (Giaever et al., 1999; Parsons et al., 2004). This avoids the task of mapping mutations in plants, but relies on the assumption that an ortholog of the plant target exists in yeast. The cumulative output of these approaches may be a small list of candidate targets which must be verified by additional biochemical and genetic tests.

General Issues for Induced Disease Resistance in Agriculture

The successful application of crop protectants in a field setting depends on an additional set of factors. While the vast majority of small molecules found in libraries have

been pre-selected for drug-like qualities, many natural products do not meet these criteria. A hydrophilic molecule like trehalose, for example, cannot easily penetrate the cuticle of plant leaves, thus requiring relatively high concentrations in order to have an effect on disease resistance (Reignault et al., 2001). Some of these natural products can be chemically modified to enhance their activity, as demonstrated by the efficacy of sulfated laminarins over their unmodified form (Menard et al., 2004). Other molecules, such as heavy metals, may display strong activity, but are ecologically unsafe for wide release into the environment.

In the transition of candidate compounds from the laboratory to the field, efficacy is certainly a central concern. Environment, plant genotype, and plant nutrition can dramatically affect the induction of disease resistance (Walters et al., 2005), and an ideal chemical should maintain its efficacy in plants cultivated under a range of growth conditions. Since agricultural equipment is often not perfectly calibrated, chemical activity should be relatively consistent within a certain margin of application error, especially for hormetic phytotoxins. Beyond agronomic practicality, defence-inducing compounds must ultimately be economically feasible options for crop protection, minimizing yield losses to an extent that would be judged favorably in cost-benefit analyses.

The costs and benefits of induced disease resistance should also be weighed at a biological level. The activation of plant defence machinery requires a reallocation of some resources, possibly to the detriment of processes such as seed production (Heil and Baldwin, 2002). In the presence of pathogen infection, this response provides a net benefit to plant fitness, but may be more punitive when pathogens are absent. This is vividly illustrated by the stunted phenotype of mutants that constitutively express defence-related genes (Bowling et al., 1994). Chemical induction of plant defences provides some temporal control over the deployment of resources, but there still may be fitness costs in the absence of significant infection (Cipollini, 2002; Heil et al., 2000). As such, chemicals that prime plant defences may provide the greatest overall fitness benefit (van Hulten et al., 2006). As an aside, Kover and Schaal (2002) observed that different ecotypes of Arabidopsis varied in the impact of bacterial infection on seed yield. This was attributed to variations in "tolerance" of infection, as a phenomenon separate from R gene-mediated resistance mechanisms. While virtually unexplored as a factor affecting fitness, the influence of small molecules on tolerance could be another mechanism for the prevention of disease-related yield losses.

Conclusions and Future Perspectives

In this review, we have described a structurally diverse array of molecules that are capable of inducing disease resistance in plants, likely through equally diverse mechanisms. A vast amount of chemical space remains to be explored, and high-throughput assays will feature prominently in this exploration. The design of such assays is not trivial, but it should be centered on a salient infection phenotype that is dependent on pathogen virulence and reversible by known inducers of plant defence. The identification of hits in this assay is only the beginning of a long path of discovery with regards to a molecule's biological target and mechanism of action.

Advances in this field have been, and will continue to be, derived from the introduction of additional analytical tools and resources. The activity of compounds in different ecotypes or cultivars can reveal pharmacogenomic variation, which not only provides another avenue for target identification, but also generates valuable data on the structural aspects that influence protein-ligand interactions (Zhao et al., 2007). Future screens may also move beyond small molecules to include searches for bioactive peptides. An immense number of possible sequences exist even for small peptides, and the introduction of modifications such as glycosylation or phosphorylation would expand this number further. The commercial release of Messenger® (Eden Bioscience Corp., USA; Jones, 2001), a formulation of harpin protein, illustrates the utility of proteinaceous elicitors as crop protectants. Overall, plants are amazingly well-equipped to combat pathogen attacks, but would be assisted by a message to prepare their defences in advance of these assaults. Chemicals and other molecules can deliver that message, working with the plant's own defensive resources to generate an effective resistance response.

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