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Function, Discovery, and Exploitation of Plant Pattern Recognition Receptors for Broad-Spectrum Disease Resistance

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Abstract

Plants are constantly exposed to would-be pathogens and pests, and thus have a sophisticated immune system to ward off these threats, which otherwise can have devastating ecological and economic consequences on ecosystems and agriculture. Plants employ receptor kinases (RKs) and receptor-like proteins (RLPs) as pattern recognition receptors (PRRs) to monitor their apoplastic environment and detect non-self and damaged-self patterns as signs of potential danger. Plant PRRs contribute to both basal and non-host resistances, and treatment with pathogen-/microbe-associated molecular patterns (PAMPs/MAMPs) or damage-associated molecular patterns (DAMPs) recognized by plant PRRs induces both local and systemic immunity. Here, we comprehensively review known PAMPs/DAMPs recognized by plants as well as the plant PRRs described to date. In particular, we describe the different methods that can be used to identify PAMPs/DAMPs and PRRs. Finally, we emphasize the emerging biotechnological potential use of PRRs to improve broad-spectrum, and potentially durable, disease resistance in crops.

INTRODUCTION

Plants rely solely on innate immunity to perceive and ward off potential pathogens. They employ cell surface–localized pattern recognition receptors (PRRs) to detect apoplastic elicitors and intracellular nucleotide-binding site–leucine-rich repeat (LRR) receptors (NLRs) to detect cytoplasmic effectors delivered into host cells. In this review, we focus on plant PRRs, and the reader is otherwise directed to comprehensive recent reviews on plant NLRs (36, 87, 116).

Plant PRRs are either plasma membrane–localized receptor kinases (RKs) or receptor-like proteins (RLPs) (249) (**Figure 1**). RKs contain a ligand-binding ectodomain, a single-pass transmembrane domain, and an intracellular kinase domain, whereas RLPs lack any obvious intracellular signaling domains. PRRs typically perceive pathogen- or microbe-associated molecular patterns (PAMPs/MAMPs; hereafter, referred to as PAMPs) (**Table 1**) as well as damage-associated molecular patterns (DAMPs) (**Table 2**), which are host-derived molecules released upon pathogen attack or cell damage (12). PAMPs are often highly conserved molecules with signatures characteristic of a whole class of microbes. However, it is now clear that specific patterns/epitopes recognized as PAMPs within otherwise conserved molecules are under selective pressure and are thus more polymorphic than previously thought (34). Interestingly, the perception of DAMPs (altered-self), in addition to the non-self surveillance enabled by PAMP recognition, allows plant cells to

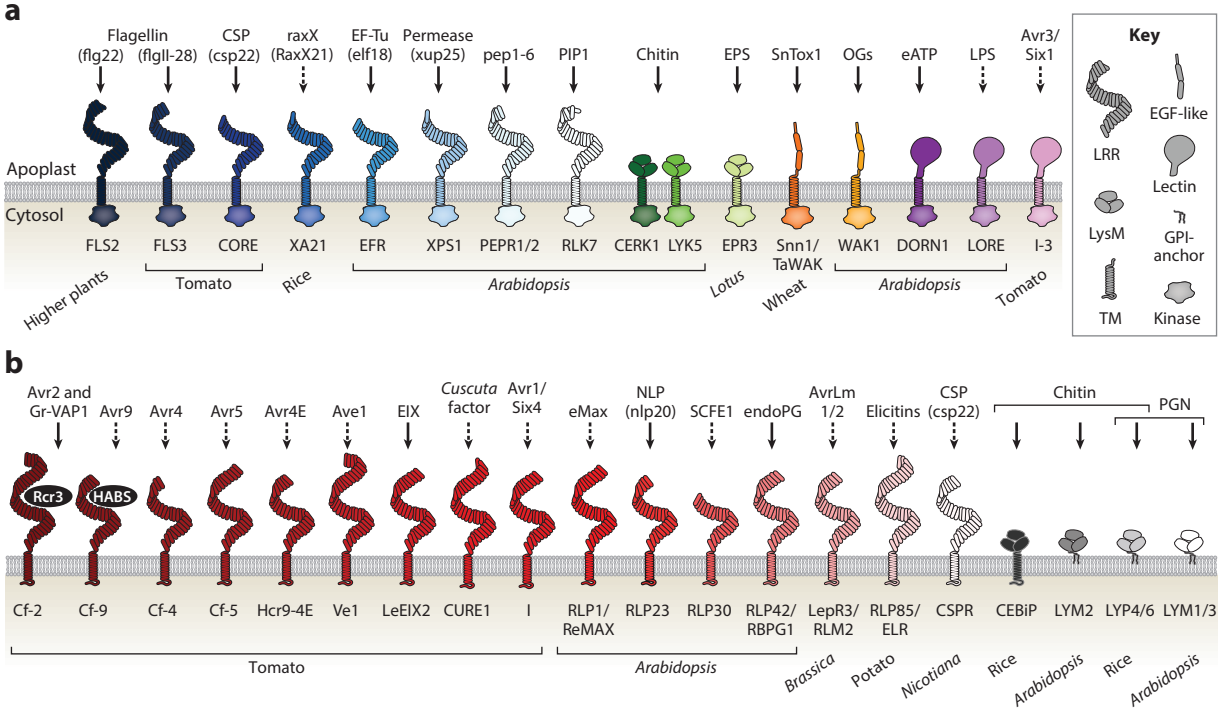

Figure 1

Proven and potential plant pattern recognition receptors (PRRs) with known ligands/agonists. (*a*) Receptor kinases (RKs). (*b*) Receptor-like proteins (RLPs). Ligands (*shown at the top of each panel*) are described in detail in **Tables 1** and **2**, and PRRs are described in detail in **Table 3**. Solid arrows indicate demonstrated direct binding; dashed arrows indicate a current lack of evidence for direct binding. Abbreviations: EGF, epidermal growth factor; EIX, ethylene-inducing xylanase; EPS, extracellular polysaccharides; GPI, glycophosphatidylinositol; LPS, lipopolysaccharide; LRR, leucine-rich repeat; OGs, oligogalacturonides; PGN, peptidoglycan; TM, transmembrane.

Table 1 Examples of apoplastic elicitors of plant immunity

Elicitor	Identification[a]	Origin[b]	Plant[c]	References
BACTERIA				
PROTEINS				
Harpin	Purification	*Erwinia amylovora*	*Nicotiana tabacum*, *Arabidopsis thaliana*	46, 226
Siderophore	Genetics	*Pseudomonas fluorescens*, *Pseudomonas putida*	*A. thaliana*, *Raphanus sativus*, *Solanum lycopersicum*, *Phaseolus vulgaris*	113, 139
Flagellin and epitopes: flg22 to flg15	Purification	*Pseudomonas syringae* pv. *tabaci*	*A. thaliana*, *S. lycopersicum*, *Solanum peruvianum*, *Solanum tuberosum*, *N. tabacum*	53
Flagellin epitope: flgII-28	Signature	*P. syringae* pv. *tomato*	*S. lycopersicum*, *Nicotiana benthamiana*	20
Flagellin epitope: CD2-1	Deletion series	*Acidovorax avenae*	*Oryza sativa*	94
Nep1-like protein (NLP) and epitope: nlp20	Sequence homology	*Streptomyces coelicolor*, *Bacillus halodurans*	*A. thaliana*, *N. benthamiana*	11, 152, 168
Cold shock protein (CSP) and epitopes: csp22 and csp15	Purification	*Staphylococcus aureus*	*N. tabacum*, *S. lycopersicum*	52
EF-Tu and epitopes: elf18 to elf26	Purification	*Escherichia coli*	*A. thaliana*, *Brassica oleracea*, *Brassica alboglabra*, *Sinapis alba*	107
EF-Tu epitope: EFa50	Purification	*A. avenae*	*O. sativa*	59
Superoxide dismutase (SOD)	Purification	*Xanthomonas campestris* pv. *campestris*, *E. coli*	*N. tabacum*	225
Acyl homoserine lactones (AHL)	Homology	*Serratia liquefaciens*, *P. putida*	*A. thaliana*, *S. lycopersicum*	155, 189
PeBL1	Purification	*Brevibacillus laterosporus*	*N. benthamiana*	221
RaxX and epitope RaxX21-sY	Genetics	*Xanthomonas oryzae* pv. *oryzae*	*O. sativa* (carrying XA21)	166
Xanthine/uracil permease and epitope xup25	Signature	*P. syringae*	*A. thaliana*	142
CARBOHYDRATES				
Extracellular polysaccharides (EPSs)	Abundance	*X. campestris* pv. *vesicatoria*	*Capsicum annuum*	176
LIPIDS				
Lipoteichoic acid (LTA)	Homology	*S. aureus*	*A. thaliana*	240
cis-11-methyl-2-dodecenoic acid (DSF)	Serendipity	*X. campestris* pv. *campestris*	*A. thaliana*, *N. benthamiana*, *O. sativa*	90
GLYCOPROTEINS				
Peptidoglycans (PGNs)	Homology	*S. aureus*	*A. thaliana*	65
LIPOPEPTIDES				
Cyclic lipopeptides	Serendipity/ abundance	*Bacillus subtilis*	*A. thaliana*, *P. vulgaris*, *S. lycopersicum*	68, 151

(*Continued*)

Table 1 (*Continued*)

Elicitor	Identification[a]	Origin[b]	Plant[c]	References
GLYCOLIPIDS				
Lipopolysaccharides (LPSs)	Homology	*P. fluorescens*	*A. thaliana*, *Dianthus caryophyllus*	47, 213
Rhamnolipids	Serendipity	*Pseudomonas aeruginosa*	*A. thaliana*, *Vitis vinifera*	181, 214
FUNGI				
PROTEINS				
Cellulase	Serendipity/ Abundance	*Trichoderma viridae*, *Rhizoctonia solani*	*A. thaliana*, *C. annum*	128, 224
Avr9	Purification	*Cladosporium fulvum*	*S. lycopersicum*	188
Ethylene-inducing xylanase (EIX)	Purification	*T. viride*	*A. thaliana*, *N. tabacum*	9, 57
Avr4	Purification	*C. fulvum*	*S. lycopersicum*	88
Necrosis- and ethylene-inducing protein 1 (Nep1)	Purification	*Fusarium oxysporum* f. sp. *erythroxyli*	*A. thaliana*, *Erythroxylum coca*	6, 97
Necrosis-inducing protein1 (NIP1)	Purification	*Rhynchosporium commune*	*Hordeum vulgare*	175
Ecp2	Purification	*C. fulvum*	*S. lycopersicum*	112
Cerato-platanin	Purification	*Ceratocystis fimbriata* f. sp. *platani*, *Magnaporthe grisea*	*A. thaliana*, *N. tabacum*, *Platanus* × *acerifolia*	155, 239
Ecp1, Ecp4, Ecp5	Purification	*C. fulvum*	*S. lycopersicum*	111
Avr2	cDNA	*C. fulvum*	*S. lycopersicum*	126
Endopolygalacturonase	Purification	*Botrytis cinerea*	*A. thaliana*, *V. vinifera*	165, 244
Avr3/Six1	Purification	*F. oxysporum* f. sp. *lycopersici*	*S. lycopersicum*	172
Avr4E	Purification	*C. fulvum*	*S. lycopersicum*	229
PemG1	Purification	*M. grisea*	*A. thaliana*, *Cucumis sativus*, *N. tabacum*, *O. sativa*, *Pisum sativum*, *S. lycopersicum*	162, 167
Nascent polypeptide-associated complex (NAC) α-polypeptide	Purification	*Alternaria tenuissima*, *B. cinerea*	*N. tabacum*	132, 246
Ave1	Genetics / Expression	*Verticillium dahlia*, *Verticillium albo-atrum*, *F. oxysporum* f. sp. *lycopersici*, *Cercospora beticola*	*S. lycopersicum*	40
PevD1	Purification	*V. dahliae*	*N. tabacum*	217
Hypersensitive response-inducing protein (HRIP)	Purification	*A. tenuissima*	*N. tabacum*	106
Serine protease (AsES)	Purification	*Acremonium strictum*	*Fragaria* × *ananassa*, *A. thaliana*	25
Avr5	Genetics	*C. fulvum*	*S. lycopersicum*	138

(*Continued*)

Table 1 (*Continued*)

Elicitor	Identification[a]	Origin[b]	Plant[c]	References
Cutinase	Serendipity	*Sclerotinia sclerotiorum*	*A. thaliana*, *Brassica napus*, *Glycine max*, *N. benthamiana*, *N. tabacum*, *O. sativa*, *Triticum aestivum*, *Zea mays*	243
Hydrophobin	Purification	*Trichoderma longibrachiatum* strain MK1	*S. lycopersicum*	179
Cyclodipeptides	Purification	*Eupenicillium brefeldianum*	*N. tabacum*	27
CS20EP[d]	Purification	*F. oxysporum* strain CS-20	*S. lycopersicum*	196
Rapid alkalinization factor (RALF)	Sequence homology	*F. oxysporum* f. sp. *lycopersici*	*N. benthamiana*, *S. lycopersicum*	209
Avr1/Six4	Purification	*F. oxysporum* f. sp. *lycopersici*	*S. lycopersicum*	76
SnTox1	Functional screening	*Stagonospora nodorum*	*T. aestivum*	119
AvrStb6	Genetics	*Zymoseptoria tritici*	*T. aestivum*	247
CARBOHYDRATES				
Chitin	Abundance	*Agaricus bisporus*	*A. thaliana*, *T. aestivum*	151, 212
Oligochitosan	Abundance	*Fusarium solani*	*A. thaliana*, *P. sativum*	19, 66
β-1,3-glucan	Purification	*M. grisea*	*O. sativa*	234
GLYCOPEPTIDES				
Invertase and epitope: gp8c	Abundance	*Saccharomyces cerevisiae*	*S. lycopersicum*	7
LIPIDS				
Ergosterol	Purification	*C. fulvum*	*S. lycopersicum*	64
SECONDARY METABOLITES				
Chrisophanol	Purification	*Trichoderma harzianum*	*Brassica oleracea* var. *capitata*	120
Cerebroside	Purification	*Magnaporthe oryzae*	*O. sativa*	102
OOMYCETES				
PROTEINS				
Elicitin	Purification	*Phytophthora cryptogea*, *Phytophthora capsici*	*N. tabacum*	173
Transglutaminase GP42 and epitopes: Pep-13 and Pep-25	Purification	*Phytophthora megasperma*	*Petroselinum crispum*	149
Cellulose-binding elicitor lectin (CBEL)/GP34	Purification	*Phytophthora parasitica* var. *nicotianae*	*N. tabacum*	194
CBEL epitope: CBD2synth	Deletion series	*P. parasitica* var. *nicotianae*	*A. thaliana*, *N. tabacum*	60
NLP	Purification	*Pythium aphanidermatum*	*A. thaliana*, *N. tabacum*	215

(*Continued*)

Table 1 (*Continued*)

Elicitor	Identification[a]	Origin[b]	Plant[c]	References
NLP epitopes: nlp11 and nlp24	Deletion series	*Hyaloperonospora arabidopsidis*	*A. thaliana*	152
NLP epitope: nlp20	Deletion series	*P. parasitica*	*A. thaliana*, *Arabids alpina*, *Thlaspi arvense*, *Draba rigida*, *Lactuca sativa*	11
PcF	Purification	*Phytophthora cactorum*	*S. lycopersicum*, *Fragaria vesca* × *ananassa*	153
Glycoside hydrolase (XEG1)	Purification	*Phytophthora sojae*	*G. max*, *S. lycopersicum*, *C. annum*, *N. benthamiana*	129
CARBOHYDRATES				
Heptaglucoside	Purification	*P. megasperma* f. sp. *glycinea*	*G. max*	195
Glucan-chitosaccharides	Purification	*Aphanomyces euteiches*	*Medicago truncatula*	145
LIPIDS				
Eicosapentaenoic acid (EPA)	Purification	*Phytophthora infestans*	*S. tuberosum*	13
Arachidonic acid (AA)	Purification	*P. infestans*	*A. thaliana*, *S. tuberosum*	13, 183
VIRUSES				
PROTEINS				
Coat protein (CP)	Purification	*Tobacco mosaic virus*	*N. tabacum*	5
NUCLEIC ACIDS				
dsRNA	Homology	*Oilseed rape mosaic virus*	*A. thaliana*	146
NEMATODES				
PROTEIN				
Gr-VAP1	Expression	*Globodera rostochiensis*	*S. lycopersicum*	123
GLYCOLIPIDS				
Ascarosides (ascr#18)	Purification	*Meloidogyne incognita*, *Meloidogyne javanica*, *Meloidogyne hapla*	*A. thaliana*, *S. lycopersicum*, *S. tuberosum*, *H. vulgare*	131
INSECTS				
CARBOHYDRATES				
β-galactofuranose polysaccharide	Purification	*Spodoptera littoralis*	*A. thaliana*	16
LIPOPEPTIDES				
Fatty acid–amino acid conjugates (FACs)	Purification	*Spodoptera exigua*, *Schistocerca americana*	*A. thaliana*, *Z. mays*	4, 186
PHOSPHOLIPIDS				
Phosphatidylcholine (DLOPC)	Purification	*Sogatella furcifera*	*O. sativa*	238

[a]Methods of identification. Functional characterization: serendipity, abundance, homology (active in other living organism/kingdom), and deletion series (minimal active epitope); Biochemistry: purification from extract; Sequence and genome analysis: forward genetics, sequence homology, functional screening of cDNA, functional screening of apoplastic effector, evolutionary signature, and expression profiling.
[b]Organisms in which they were first identified.
[c]Examples of plants in which they are recognized. Studies demonstrating recognition in the model plant *Arabidopsis thaliana* are also indicated.
[d]Recognition of the purified protein not tested.

indirectly monitor a greater diversity of pathogens and to amplify responses beyond those triggered solely by PAMP perception (72, 233).

Ligand recognition by PRRs leads to what is alternately called PAMP-, pattern-, or PRR-triggered immunity (PTI; a.k.a. surface immunity), which contributes to basal immunity to adapted pathogens as well as non-host resistance to non-adapted pathogens through the induction of both local and systemic immune responses (10, 12, 35, 231).

Although the hypersensitive response (HR), a form of programmed cell death, is often associated with NLR-triggered immunity (NTI; a.k.a. intracellular immunity) (36, 231), several PAMPs (e.g., bacterial flagellin and oomycete elicitins) can also induce HR (173, 206). Similarly, although PTI is often considered to confer only partial (quantitative) disease resistance, several PRRs lead to complete (qualitative) resistance in a way similar to the classical gene-for-gene relationship of disease resistance (55). For example, FLS2, the PRR for flagellin, plays a significant role in non-host resistance (56, 117), the tomato RK I-3 and RLP I-7 confer resistance to the fungus *Fusarium oxysporum* f. sp. *lycopersici* (24, 63), the tomato RLPs belonging to the Cf family confer complete resistance to the fungus *Cladosporium fulvum* (now *Passalora fulva*) (44, 45, 86, 125, 178, 208), and introgression of the RK XA21 from the wild rice species *Oryza longistaminata* into cultivated rice confers resistance to all races of bacterial blight tested (98, 202, 220). Furthermore, although most PRRs seem to perceive their ligands directly, examples of indirect recognition also exist. For example, tomato Cf-2 does not interact directly with the apoplastic elicitor Avr2 from *C. fulvum* or with the nematode elicitor Gr-VAP1 (123) but rather senses the inhibition imposed by these elicitor proteins on the host protease Rcr3 (43, 123, 178).

STRATEGIES FOR IDENTIFICATION OF PAMPs/DAMPs

PAMPs recognized by plants have been identified from all kingdoms of life, but the majority of currently known PAMPs are from bacteria, fungi, or oomycetes (**Table 1**). DAMPs from different plant species have also been characterized (**Table 2**). The major classes of biomolecules (proteins, carbohydrates, lipids, and nucleic acids) can all be PAMPs and DAMPs. Although many studies have relied on fractionation and purification of culture extracts by ion-exchange chromatography to characterize elicitors (**Table 1** and **Table 2**), the mining of genomic data has recently allowed the identification of conserved molecular patterns that could be tested as candidate PAMPs (134, 142).

In this review, we have attempted to list all of the elicitors that have been shown to induce PTI-like responses in plants and thus that may be recognized by PRRs. It is, however, still unclear whether some of these molecules instead act as toxins. Further, as in the case of Avr2 and Avr9 from *C. fulvum*, it is also possible that these elicitors are not directly recognized but rather that their action on host molecules/processes is sensed indirectly.

Functional Characterization of Known Molecules

Educated guesses based on prior knowledge have allowed the identification of many PAMPs active in plants.

Serendipity. Extracellular adenosine triphosphate (eATP) is one of the earliest DAMPs identified. While exploring the hypothesis that stomatal movement was energy consuming, Fujino and colleagues noticed that in the light stomata remained wide open in a medium containing 10-mM eATP, whereas stomata were primarily closed in the controls (58). Such eATP-induced stomatal opening is today somewhat surprising because exogenous application of DAMPs/PAMPs

Table 2 Examples of damage-associated molecular patterns (DAMPs) recognized by plants

Elicitor	Identification[a]	Origin[b]	Reference
PROTEINS			
Systemin	Purification	*Solanum lycopersicum*	159
Hydroxyproline-rich glycopeptide systemins (HypSys)	Purification	*Nicotiana tabacum*	157
Rapid alkalinization factors (RALFs)	Purification	*Arabidopsis thaliana*, *N. tabacum*, *S. lycopersicum*	158
AtPep1	Purification	*A. thaliana*	77
Subtilase (SubPep)	Purification	*Glycine max*	160
ATP synthase (inceptin)	Purification	*Vigna unguiculata*, *Zea mays*	185
GmPep914/GmPep890	Purification	*G. max*	235
PR-1b (CAP-derived peptide 1, CAPE1)	Purification	*A. thaliana*, *S. lycopersicum*	29
PAMP-induced secreted peptides (PIPs)	Expression	*A. thaliana*	75
High mobility group box 3 (*HMGB3*)	Homology	*A. thaliana*	30
CARBOHYDRATES			
Glucose (monosaccharide)	Serendipity	*N. tabacum*	85
D-allose (monosaccharide)	Serendipity	*Oryza sativa*	92
D-psicose (monosaccharide)	Serendipity	*O. sativa*	93
Sucrose (diholoside)	Serendipity	*A. thaliana*, *N. tabacum*	85, 232
Trehalose (diholoside)	Serendipity	*A. thaliana*, *Triticum aestivum*	171, 184
Galactinol (diholoside)	Expression	*N. tabacum*	99
Cellobiose, cellotetraose (β-1,4 glucans)	Serendipity	*Gracilaria conferta*	227
Oligoagar (DP>4, β-1,4;α-1,3 glucans)	Abundance	*G. conferta*	228
Oligogalacturonides (α-1,4 glucans)	Purification	*A. thaliana*, *G. max*, *N. tabacum*, *Acer pseudoplatanus*, *Triticum* spp.	67, 147
Xyloglucan (β-1,4 glucans)	Purification	*Rubus fruticosus*	89
Laminarin (β-1,3-1,6 glucans)	Serendipity	*A. thaliana*, *T. aestivum*	136, 161
Lichenan	Serendipity	*N. tabacum*, *Nicotiana benthamiana*, *Nicotiana glutinosa*	203
Galactoglucomannan	Serendipity	*Picea abies*	201
Carrageenan	Homology	*Tichocarpus crinitus*	144
Ulvan (β-1,4 glucans)	Purification	*A. thaliana*, *Medicago truncatula*	82
LIPIDS			
HESA (cutin monomer)	Abundance	*Hordeum vulgare*, *O. sativa*	192
NUCLEOTIDES			
Extracellular ATP	Serendipity	*A. thaliana*, *Commelina communis*	58, 114

[a]Methods of identification. Functional characterization: serendipity, abundance, and homology (active in other living organism/kingdom); Biochemistry: purification from extract; Sequence and genome analysis: genetics, and expression profiling.
[b]Plants in which they have been discovered to be active. Studies demonstrating an activity in the model plant Arabidopsis thaliana are also indicated.
Abbreviation: DP, degree of polymerization.

commonly induces stomatal closure, which can restrict pathogen entry into intercellular spaces (for review, see 135). These original observations were later clarified by demonstrating that the response to eATP treatment is biphasic, with lower concentrations inducing stomatal opening and higher concentrations inducing closure (32). Wound-induced cell damage is an obvious source of eATP, and a PRR for eATP was recently identified in *Arabidopsis thaliana* (31) (**Table 3**). The unsaturated fatty acid diffusible signal factor (DSF) used for quorum sensing in *Xanthomonas* was also recently fortuitously identified as a PAMP while Kakkar et al. (90) investigated its role in *Xanthomonas*–host plant interactions.

Abundant microbial surface components. Examination of elicitor candidates from within the most abundant compounds present in plant-pathogen interfaces has led to the identification of several PAMPs. For example, owing to its abundance in fungal cell walls, chitosan (a deacetylated derivative of chitin) was assayed, together with other carbohydrates, for the production of defense responses in pea pods and found to be a PAMP able to elicit the production of phytoalexins and induce resistance to *Fusarium solani* f. sp. *phaseoli* (66). Fungal chitin was also identified as a PAMP based on its high abundance and localization (161). To better define chitin-eliciting properties, purified oligomers were tested; heptamers and octamers were found to be the most active in eliciting gene expression in *A. thaliana* (242).

Homology with known PAMPs. Assaying compounds that have well-documented activities in other organisms is also an efficient strategy to identify elicitors that induce defense in plants. For example, lipopolysaccharides (LPSs) are the major cell surface components of Gram-negative bacteria and are endotoxins that activate innate immunity in mammals (for review, see 169). LPSs were also found to induce phytoalexin accumulation in carnation (*Dianthus caryophyllus*) (213). Perception of bacterial lipoteichoic acid (LTA) induces innate immunity in human cells (191), and its potential PAMP activity in plants was also later demonstrated in *Arabidopsis* (240). Peptidoglycans (PGNs) from the cell walls of both Gram-positive and Gram-negative bacteria are polymers, which are cross-linked by short peptides and consist of alternating β(1,4)-linked *N*-acetylmuramic acid and *N*-acetylglucosamine glycan. They are a classical PAMP perceived, for example, by both *Drosophila* (49) and plants where they activate PTI (65).

Biochemistry

Biochemical approaches have been the most successful approaches to identify many elicitors perceived by plant PRRs.

Purification from culture extracts. PAMPs and DAMPs have most often been identified using biochemical purification from culture extracts (**Tables 1** and **2**), principally using ion exchange chromatography and high-performance liquid chromatography (HPLC), which allow the physical separation of a mixture of compounds. These analytical tools are often coupled to mass spectrometry (MS) analyses to provide structural elucidation of organic compounds or the sequencing of oligonucleotides. Oligogalacturonides (OGs), fragments released from pectin present in plant cell walls, were among the first DAMPs to be characterized. Initially, they were not purified to homogeneity and were described as the wound-hormone proteinase inhibitor-inducing factor (PIIF) (180). Because of the complex structure of pectin, great effort from several groups was needed to identify the chemical nature of the elicitor. In 1981, analysis revealed that the endogenous elicitor is galacturonide rich (67), and after further purification and characterization, Nothnagel and colleagues reported that plant cell wall–derived OGs indeed elicit phytoalexin production (148).

Table 3 Examples of plant pattern recognition receptors (PRRs) with proposed ligands/agonists, plants in which they have been discovered, and methods of identification

Family[a]	PRR	Apoplastic ligand/agonist	Origin	Identification	Reference
Receptor kinases					
LRR XII	XA21[b]	RaxX	*Oryza longistaminata*	Forward genetics	202
LRR XII	FLS2	Flagellin (flg22 epitope)	*Arabidopsis thaliana*, *Nicotiana benthamiana*, *Oryza sativa*, *Solanum lycopersicum*, *Vitis vinifera*	Forward genetics	62, 69, 174, 207, 210
LRR XII	FLS3	Flagellin (flgII-28 epitope)	*Solanum pimpinellifolium*	Forward genetics	73
LRR XII	EFR	EF-Tu (elf18 epitope)	*A. thaliana*	Reverse genetics	250
LRR XII	XPS1	Xanthine/uracil permease (xup25 epitope)	*A. thaliana*	Reverse genetics	142
LRR XII	CORE	csp22	*S. lycopersicum*	Forward genetics	222
LRR XI	PEPR1	Pep1-6	*A. thaliana*, *S. lycopersicum*, *Zea mays*	Biochemical properties	122, 236, 227
LRR XI	PEPR2	Pep1-2	*A. thaliana*	Reverse genetics	236
LRR XI	RLK7	PIP1	*A. thaliana*	Reverse genetics	76
WAK	WAK1	Oligogalacturonides	*A. thaliana*	Biochemical properties	103
WAK	Snn1/TaWAK	SnTox1	*Triticum aestivum*	Forward genetics	197
LysM	AtCERK1	Chitin	*A. thaliana*	Reverse genetics	141
LysM	AtLYK5	Chitin	*A. thaliana*	Reverse genetics	21
LysM	EPR3	Extracellular polysaccharides	*Lotus japonicus*	Forward genetics	9
L-LEC	LecRK-I.9/ DORN1	eATP	*A. thaliana*	Forward genetics	31
G-Lec	SD1-29/LORE[b]	Lipopolysaccharides	*A. thaliana*	Forward genetics	170
G-Lec	I-3[b]	Avr3/Six1	*Solanum pennellii*	Forward genetics	24
Receptor-like proteins					
LRR	Cf-2[b]	Rcr3 protease (guarded to detect Avr2 and Gr-VAP1)	*Solanum pimpinellifolium*	Forward genetics	45, 178
LRR	Cf-4[b]	Avr4	*Solanum hirsutum*	Forward genetics	208
LRR	Hcr9-4E[b]	Avr4E	*S. hirsutum*	Forward genetics	208, 229
LRR	Cf-5[b]	Avr5	*S. lycopersicum* var. *cerasiforme*	Forward genetics	44
LRR	Cf-9[b]	HABS (guarded to detect Avr9)	*S. pimpinellifolium*	Forward genetics	86, 125
LRR	Ve1[b]	Ave1	*S. lycopersicum*	Forward genetics	96
LRR	LeEix2	EIX	*S. pennellii*	Forward genetics	177

(*Continued*)

Table 3 (*Continued*)

Family[a]	PRR	Apoplastic ligand/agonist	Origin	Identification	Reference
Receptor-like proteins					
LRR	LepR3/RLM2[b]	AvrLm1 and AvrLm2	*Brassica napus*	Forward genetics	109, 110
LRR	RLP1/ReMAX	eMax[c]	*A. thaliana*	Forward genetics	84
LRR	RLP23	nlp20	*A. thaliana*	Reverse genetics	2
LRR	RLP30[b]	SCFE1[c]	*A. thaliana*	Forward genetics	245
LRR	RLP42/RBPG1	EndoPG	*A. thaliana*	Forward genetics	244
LRR	RLP85/ELR[b]	Elicitins	*Solanum microdontum*	Forward genetics	48
LRR	CSPR	csp22	*N. benthamiana*	Biochemical properties	182
LRR	CuRe1[b]	Cuscuta factor[c]	*S. lycopersicum*	Forward genetics	71
LRR	I[b]	Avr1/Six4	*S. pimpinellifolium*	Forward genetics	23
LysM	OsCEBiP	Chitin	*O. sativa*	Biochemical properties	91
LysM	OsLYP4 and OsLYP6	Peptidoglycans/chitin	*O. sativa*	Biochemical properties	118
LysM	AtLYM2	Chitin	*A. thaliana*	Biochemical properties	51, 164
LysM	AtLYM1[b] and AtLYM3[b]	Peptidoglycans	*A. thaliana*	Biochemical properties	230

[a]According to Reference 200.
[b]Ligand binding not yet demonstrated.
[c]Not purified to homogeneity.

Bacterial flagellin is one of the best-studied PAMPs and is widely used to study PTI. Flagellin was initially identified as a PAMP after purification by anion exchange chromatography from liquid culture extracts and by *N*-terminal protein sequencing (53). To identify lipidic PAMPs, other analytical tools have been employed, such as infrared (IR) spectroscopy to identify fungal ergosterol from *C. fulvum* extracts (64) and ^{1}H nuclear magnetic resonance (NMR) spectroscopy and fast atom bombardment (FAB)-MS analysis to identify cerebroside from *Magnaporthe oryzae* (102). In recent years, MS has become the favored analytical tool for identifying the composition of unknown organic biomolecules. This technique has revealed the nature of recently identified PAMPs, such as the glycolipidic ascarosides from the nematode *Meloidogyne* sp. (131), the protein PeBL1 from the bacterium *Brevibacillus laterosporus* (221), and the glycoside hydrolase (XEG1) from *Phytophthora sojae* (129).

Despite the increasing sensitivity of the available analytical tools, several recent studies have highlighted the fact that PAMP identification remains challenging. For example, separations on cation-exchange chromatography columns and biochemical assays have only enabled the partial characterization of the *Sclerotinia sclerotiorum* fungal elicitor that is recognized by *Arabidopsis* RLP30 (245); attempts to purify this PAMP to homogeneity have so far been unsuccessful, and its exact nature remains elusive. Enigmatic MAMP of *Xanthomonas* (eMAX) is, as indicated by its name, another PAMP that also remains to be identified and is recognized by ReMAX/RLP1 (84).

Ligand-fishing using pattern recognition receptors as molecular bait. Affinity chromatography may prove to be a promising tool for identifying PAMPs that interact directly with PRR ectodomains. Although this approach has not yet been used for receptor-based PAMP capture, Shinohara & Matsubayashi (198) successfully immobilized the ectodomain of a plant LRR-RK on microbeads and visualized the interactions with its ligand, the phytosulfokine peptide, and were able to retrieve it from complex natural extracts. The main challenges to using affinity purification for direct capture of unknown PAMPs reside in potentially weak ligand-receptor affinity, in difficulty in ectodomain purification and immobilization, and in the vast diversity of chemistries, structures, and functions of the ligands that could be encountered.

Sequence and Genome Analysis

Advances in comparative genomics have recently enabled the identification of novel microbial PAMPs.

Genetics. Although forward genetics is a proven and powerful approach for identifying new PRRs, its potential is rather limited in the discovery of PAMPs. Indeed, genetic mapping requires strains harboring genetic variations in PAMP-encoding genes that result in differential eliciting activity. However, as several PAMPs may be required for important biological functions, mutants with a loss or modification of these PAMPs would likely be unfit in natural environments. Forward-genetic approaches can, however, be considered under laboratory conditions that are conducive to the growth of such mutants.

An example of such a mutant approach is the identification of siderophores as PAMPs through the use of a siderophore-deficient strain of the bacterium *Pseudomonas fluorescens*. This mutant is associated with a partial loss of induction of resistance against *Tobacco necrotic virus* (TNV) in tobacco (133), and Leeman and colleagues later demonstrated that a purified siderophore could indeed induce resistance against *F. oxysporum* f. sp. *raphani* in radish (113). The identification of the bacterial PAMP RaxX was also found in such a mutant screen; genetic analysis of *X. oryzae* pv. *oryzae* (*Xoo*) revealed that the operon *raxSTAB* is required for XA21-induced immunity (37), and the bacterial type I–secreted sulfated protein RaxX was identified as the inducer of XA21-mediated immunity in rice (166). The *AvrStb6* gene encodes a secreted protein from *Zymoseptoria tritici*, which was also identified by genetic mapping (247). Comparative population genomics, in combination with expression profiling, was also used to identify the apoplastic elicitor Ave1 secreted by the fungus *Verticillium dahliae* (40), whereas comparative transcriptome sequencing has been used to identify the fungal protein Avr5 produced by *Cladosporium fulvum* (138).

Sequence homology. The analyses of gene orthology and variations in primary sequences of proteinaceous PAMPs have led to the identification of variants of bacterial flagellin (53), fungal cerato-platanin (156), and oomycete elicitin (41). The necrosis- and ethylene-inducing protein 1 (Nep1)-like (NLP) family of PAMPs is potentially the largest example of such families of PAMPs determined by homology, as these proteins are found in bacteria, fungi, and oomycetes (2, 11, 152). The 24-kDa Nep1 protein was originally discovered in the fungus *F. oxysporum* (6), but NLPs were later identified by homology in the oomycetes *Pythium aphanidermatum* (215) and *P. sojae* (168) as well as in the bacteria *Bacillus halodurans* and *Streptomyces coelicolor* (168). NLPs carry a conserved pattern of 24 amino acids (nlp24), which is sufficient to trigger plant immune responses (2, 11, 152).

Functional screening of cDNA libraries. To identify proteins that can produce disease symptoms or activate plant defense responses in the apoplast, Luderer and colleagues have used a complete cDNA collection and a functional assay to identify Avr2 as the *C. fulvum* elicitor responsible for Cf-2-mediated HR (126). Recently, in silico analyses have been largely adopted to identify features of apoplastic elicitors (e.g., transcription pattern, presence of a signal peptide, and absence of transmembrane domains as well as other features of an apoplastic compound); hence, the number of cDNA candidates to evaluate for elicitor capacity has been reduced. With this approach, Qutob and colleagues focused their functional analysis on a collection of only 16 *P. sojae* cDNA (168), from which they identified the NLP PsojNIP as an active elicitor. Analyzing gene transcription profiles also led to the identification of the protein Gr-VAP1 from nematodes (123) as well as several fungal proteins able to induce a cell-death response (26, 50).

Evolutionary signatures. Because apoplastic elicitors betray the pathogen presence and induce plant defenses, they are under strong selective pressure to evolve and evade recognition by PRRs (17, 34). However, most PAMPs support crucial biological functions, thus constraining frequent mutations. However, within functional domains under strong negative selection, amino acids with relaxed selective pressure show strong positive selection to evade PRR recognition. During study of the evolution of the plant pathogen *Pseudomonas syringae* pv. *tomato*, this reasoning led to the identification of possible parallel evolution events in the flagellin-encoding gene *fliC* (20). Interestingly, these non-synonymous mutations, which are driven by a strong pressure to evade tomato immune response, are found in an epitope distinct from the well-described flg22. FlgII-28, a 28–amino acid peptide corresponding to the ancestral allele of this new epitope, is able to effectively induce PTI in tomato (20), and its corresponding PRR, FLS3, was recently identified (73). Other in-depth studies have also analyzed the selection pressure on otherwise highly conserved bacterial proteins to identify new potential PAMPs (134, 142). After comparing the genome of six phytopathogenic bacteria (three pathovars from *P. syringae* and three from *Xanthomonas campestris*), McCann and colleagues identified orthologs for 1,322 functionally constrained core genes and 56 candidate proteins with positively selected residues enriched within domains under strong negative selection (134). The well-characterized bacterial PAMP EF-Tu (107) was identified as one of the proteins showing positively selected sites. Although the elf18 immunogenic epitope exhibits this molecular signature of natural selection, a second cluster revealed multiple positively selected sites that overlap with the *Acidovorax avenae* EFa50 domain. This latter domain was identified by purification from crude extracts as a second active epitope of EF-Tu that was perceived by rice and verified by deletion analysis (59). Using a similar comparative genomic analysis of 54 *P. syringae* isolates, Mott and colleagues also successfully identified six new proteinaceous elicitors, including the xanthine/uracil permease and its epitope, xup25 (142). This bioinformatics-based methodology thus presents great potential for the identification of novel PAMPs.

METHODS TO IDENTIFY PATTERN RECOGNITION RECEPTORS

Several strategies to identify plant PRRs have been employed, the most fruitful being forward or reverse genetics (**Table 3**). Biochemical methods using ligand-based affinity also led to the identification of several PRRs, such as the rice OsCEBiP (91) and the *Arabidopsis* PEPR1 (237).

Genetics

Forward-genetic approaches using mutagenized populations or natural variation have successfully led to the identification of several plant PRRs. The recent gain of knowledge in PRR-encoding

genes is also allowing the wider use of reverse-genetic strategies to identify PRRs from collections of mutated candidate genes.

Forward-genetic approaches. Forward genetics is one of the most efficient approaches for identifying PRRs. This strategy requires the identification of two parents with different phenotypic traits, namely individuals with and without responsiveness to a given PAMP. After generating mapping populations, the genetic loci that influence these traits is determined by genetic mapping using map-based cloning or next-generation sequencing. Parents with differential phenotypes can be identified from plant breeding programs, mutagenized populations, or collections of natural ecotypes.

Using natural variations. Natural variation is a great source of potential phenotype diversity regarding PAMP perception and responsiveness. Using forward-genetic approaches, many studies have identified RKs as being involved in crop resistance to various pathogens. However, in the absence of functional characterization with regard to PAMP or crude extract responsiveness, many of these proteins can be considered only as candidate PRRs. Using map-based cloning, XA21 from *O. longistaminata* was identified as an LRR-RK conferring resistance to *Xoo* (98, 202). The RaxX protein was recently proposed to be the XA21 ligand, although no direct interaction with XA21 has yet been shown (166).

The rice B-lectin RK Pi-d2 (28), the LRR-RK OsBRR1 (163), and the WAK-RK OsWAK1 (115) confer resistance to the fungal rice blast *M. oryzae*, whereas the rice OsLecRK1, OsLecRK2, and OsLecRK3 confer strong resistance to the brown planthopper (121). The wheat LRK10L-RKs TaRLK-R1, 2, and 3 contribute to HR against the stripe rust fungus (248). The tomato LysM-RKs Bti9 and SILyk13 contribute to immunity against *P. syringae* pv. *tomato* (241), and the tomato G-type lectin I-3 confers resistance to Fusarium wilt disease (24). The corn WAK-RK ZmWAK confers quantitative resistance to head smut (251), and ZmWAK-RLK1 confers resistance to northern corn leaf blight (78). In *Arabidopsis*, the RKs RFO1 and RFO3 are required for resistance to the wilt pathogen *F. oxysporum* f. sp. *matthioli* (33, 42). Finally, the *Nicotiana benthamiana* LRR-RKs NbIRK, required for resistance to *Tobacco mosaic virus* (TMV) (22), and *Nicotiana attenuata* LecRK1 are required for resistance against the herbivore *Manduca sexta* (61) and should also be evaluated for their potential PRR function.

Natural variation has also been exploited to identify several RLPs as likely PRRs for fungal apoplastic elicitors. Tomato Cf-4 (208) is the candidate PRR for Avr4 (88), tomato Ve1 (96) is the candidate PRR for Ave1 (40), and *Brassica napus* LepR3/RLM2 (109, 110) is the candidate PRR for *Leptosphaeria maculans* AvrLm1 and AvrLm2. In addition, the rice RLP Xa21D confers partial resistance to *Xoo* (219). The pepper mannose-binding lectin CaMBL1 contributes to resistance against the bacterial pathogen *X. campestris* pv. *vesicatoria* (79). Vfa2/HcrVf2 and Vfa1/HcrVf1 from apple have also been shown to confer resistance to the fungal pathogen *Venturia inaequalis* (8, 130).

Variations in PAMP responsiveness have also been investigated in large collections of *A. thaliana* natural accessions. Coupled with other important genetic resources in this species, these collections are enabling the rapid identification of candidate PRRs by forward genetics. For example, Jehle and colleagues screened 61 ecotypes and identified the accession Shakhdara (Sha) as being unique in its lack of recognition of eMax (83). The use of well-characterized recombinant-inbred lines derived from Sha and eMax-responsive Landsberg *erecta* (La-*er*) allowed the rapid identification of AtRLP1/ReMAX as a potential PRR for eMax. In a comparable approach, 70 *A. thaliana* accessions were screened to identify AtRLP30 as the RLP required for sensitivity to the elicitor present in the SCFE1 extract from *Sclerotinia sclerotiorum* (245). Finally, 47 *A. thaliana* accessions

were tested for responsiveness to fungal polygalacturonase, leading to the identification of the RLP AtRLP42/RBPG1 (244).

For most of these examples, the absence of detailed information on ligand identity prevents firm conclusions about the true receptor function of these RLPs from being drawn, some of which might alternatively have a regulatory function. Forward-genetic strategies using natural variations have, however, led to the identification of certain RLPs as bona fide PRRs, such as the *Arabidopsis* RLP42/RBPG1 for which ligand binding could be demonstrated (244).

Using mutagenized populations. The LRR-RK FLS2, the PRR for the epitope flg22 derived from bacterial flagellin, was identified using an ethyl methanesulfonate (EMS)-mutagenized population of the *A. thaliana* ecotype La-*er* (62). Screening for loss of elicitor-induced calcium burst in an EMS-mutagenized population of *A. thaliana* expressing the calcium reporter aequorin recently enabled the identification of LecRK-I.9/DORN1 as the eATP PRR (31) and SD1–29/LORE required for perception of bacterial LPSs (170). The exopolysaccharide receptor EPR3 was also recently identified using an EMS-mutagenized population of *Lotus japonicus* (95).

Reverse-genetic approaches. Collections of *A. thaliana* T-DNA insertion mutants have been assembled for systematic functional analysis of RKs and RLPs, with a special emphasis on those whose expression is induced upon PAMP/DAMP treatment and/or infection. These collections include, for example, mutants for 22 out of 28 flg22-induced LRR-RKs (250), all 57 genes encoding LRR-RLPs (218), all 47 genes encoding RKs missing the conserved arginine (R) and aspartate (D) in the subdomain VIb of their kinases (non-RD) (39), 169 out of 216 LRR-RKs (142), 41 out of the 45-L-type lectin RKs (LecRKs) (223), and 41 out the 44 genes encoding cysteine-rich RKs (CRKs) (14). From the collection of 22 flg22-induced LRR-RKs, Zipfel and colleagues identified EFR, the *Brassicaceae*-specific PRR for bacterial EF-Tu, and its epitope elf18 (250). Recently, AtRLP23, the PRR for Nep1-like protein (NLP), was also identified from a collection of T-DNA insertion mutants in 44 genes encoding LRR-RLPs (2), and the screening of 169 of 216 LRR-RK mutants led to the identification of XPS1 as the PRR for bacterial xup25 (142).

As LysM domains are able to bind chitin-related oligosaccharides (91), T-DNA mutants for genes encoding LysM-containing RKs and RLPs have been evaluated for their ability to respond to chitin and PGN. In this way, *Arabidopsis* AtCERK1 (141), AtLYK5 (21), and AtLYM2 (51) have been found to be required for chitin perception, and AtLYM1 and AtLYM3 have been found to be required for PGN sensing (230). RNAi silencing of the rice genes *OsLYP4* and *OsLYP6* also demonstrated the involvement of these RLPs in chitin and PGN perception (118).

For a reverse-genetic approach, the expression of dominant negative forms of RKs could constitute another powerful strategy to assess their function as potential PRRs. The ectodomain of FLS2 induces the formation of inactive signaling complexes, thus creating a dominant-negative effect (204). Similarly, chimeras could be used to confirm the function of a given RK in PAMP perception, as was done to confirm that the *Arabidopsis* RK WAK1 mediates oligogalacturonides (OGs) perception (18).

Biochemistry

The PRR biochemical properties have also allowed the identification of several plant PRRs, although this approach is still technically challenging and thus in its infancy when compared to genetic approaches.

Ligand affinity. PRRs and ligands interact with high specificity and affinity, allowing the identification of PRRs using labeled or immobilized elicitors. Labeling ligands with the iodine-125 radioisotope is a useful strategy to detect binding to their corresponding PRRs. After selective photo–cross-linking of the labeled ligands to the receptors, PRRs can be separated by analytical sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and identified by mass spectroscopy or Edman sequencing. Using this approach, the photo-affinity labeling of an oomycete β-glucan resulted in the identification of the high-affinity binding protein GEBP from soybean (140). GEBP is, however, secreted into the apoplast and has glucan hydrolase enzymatic activity. Thus, the observed interaction may better represent an enzyme-substrate complex than a receptor-ligand interaction (54). Photo-affinity radiolabeling of chitin also led to the partial characterization of a rice binding protein (81), which was later identified as the chitin PRR OsCEBiP (91). By direct radiolabeling of the *Arabidopsis* peptide AtPep1, Yamaguchi and colleagues could also successfully isolate the corresponding PEPR1 receptor (237).

Insoluble or immobilized ligands can be used for affinity purification of PRRs. As discussed for the affinity purification of elicitors, this strategy is, however, possibly limited by the constraints imposed on the ligand-receptor molecular interactions and by difficulties in ligand immobilization. By immobilizing *N*-acetylchitooctaose on affinity matrixes, Kaku and colleagues were, however, successful in specifically eluting and identifying OsCEBiP, the rice PRR for chitin (91). Chitin could also be covalently attached to biotin to be recovered using a streptavidin column, which led again to the recovery of OsCEBiP after elution (199). Alternatively, chitin can be attached to magnetic beads, which can be recovered by magnetic isolation, which led to the identification of LYM2 from *Arabidopsis* cell extracts (164). Although AtCERK1 was identified by reverse genetics (141), its ability to bind insoluble colloidal chitin or chitin beads allowed the recovery of this PRR in pellets after centrifugation (80). Using biotinylated flg22, Shinya and colleagues reported that detection and identification of PRRs are, however, sometimes limited by their low natural abundance in plant cell extracts (199).

Combining photo-affinity labeling of a ligand and a heterologous expression library of *Arabidopsis* RK/RLP ectodomains could constitute a powerful strategy to identify PRRs. This gain-of-function approach was successfully employed to identify the receptor of a plant peptide secreted during nitrogen starvation (205) but has not yet been used for PRR discovery.

Co-receptors as molecular bait. In *Arabidopsis*, BAK1 and related SERK proteins are LRR receptors involved in several immune receptor complexes and function as co-receptors that form stable complexes with PRRs in a ligand-specific manner (127). They can thus be used as molecular bait to identify unknown PRRs after elicitor treatment. Schulze and colleagues have demonstrated that, in wild-type *Arabidopsis*, FLS2 can be identified after flg22 treatment and immunoprecipitation of BAK1 (190). The same strategy coupled to mass-spectrometry analysis of co-immunoprecipitated proteins has been used to identify NbCSPR, a *N. benthamiana* LRR-RLP required for responsiveness to the epitope csp22 derived from bacterial cold shock protein (182). Recently, the tomato LRR-RK CORE was identified by natural variation as also being required for csp22 perception, and direct binding of csp22 to CORE could be demonstrated (222).

TRANSFER AND ENGINEERING OF PATTERN RECOGNITION RECEPTORS TO IMPROVE CROP DISEASE RESISTANCE

Annually, ten to twenty percent of crop production worldwide is lost due to plant diseases, thus affecting food security (150). In addition to traditional chemical control strategies, genetic methods

are needed to improve crop disease resistance, including the use of PRRs that would provide broad-spectrum disease resistance (38).

Intraspecies Pattern Recognition Receptor Transfer

By including PRR-triggered resistance in integrated pest management strategies, breeding programs can benefit from a layer of basal immunity. Given that PRR-encoding genes are expanding in plant genomes with time (200), plant cell surfaces typically harbor multiple PRRs, thus multiplying the number of potential ligands that can be perceived and therefore increasing the likelihood of microbe detection. As discussed in the Forward-Genetic Approaches section above, conventional breeding programs have already widely deployed RKs and RPLs for durable and broad-spectrum disease resistance in crops (8, 24, 28, 78, 96, 121, 130, 202, 208, 251), demonstrating the importance of increasing elicitor recognition for the management of many economically important crop diseases.

Interspecies Pattern Recognition Receptor Transfer

Recently, transgenic approaches have revealed that interspecies transfer of PRRs can be used to confer responsiveness to previously unrecognized elicitors. For example, the transfer of *A. thaliana* EFR increases resistance to *Ralstonia solanacearum* in tomato (108), *Xoo* and *Acidovorax avenae* subsp. *avenae* in rice (124, 193), and *P. syringae* pv. *oryzae* in wheat (187). Similarly, expression of the *O. longistaminata* XA21 in sweet orange (137), tomato (1), and banana (211) enhances resistance to *Xanthomonas citri*, *R. solanacearum*, and *X. campestris* pv. *musacearum*, respectively. Interspecies transfer of *Solanum microdontum* LRR-RLP ELR in *Solanum tuberosum* confers broad-spectrum recognition of elicitins and enhanced resistance to *Phytophthora infestans* (48). The transfer of *Arabidopsis* RLP23 to potato is another example of PRR deployment that has conferred increased disease resistance, in this case to the oomycete *P. infestans* and to the fungus *S. sclerotiorum* (2). Canker lesions caused by *X. citri* can also be decreased by expressing *N. benthamiana* FLS2 in orange (70). Interestingly, expression of the *Arabidopsis* eATP PRR DORN1/LecRK-I.9 in potato enhanced resistance to the hemibiotroph *P. infestans* but not to the necrotroph *Botrytis cinerea* (15), reflecting that PTI efficiency may sometimes depend on pathogen lifestyles as well as their virulence.

Engineering Pattern Recognition Receptors

Different domains of plant RKs can be uncoupled, with ectodomains retaining their specific ligand recognition and intracellular domains retaining their original signaling output ability. For example, a chimera between BRI1 and WAK2 revealed that perception of the brassinosteroid hormone by the BRI1 ectodomain could induce the maintenance of cellular osmotic status controlled by the WAK2 kinase domain (104). Modular assemblies between FLS2, EFR, and WAK1 (18), FLS2, EFR, and BAK1 (3), and EFR and XA21 (74) have since demonstrated that PRRs can be successfully engineered to increase the magnitude of the defense response that they trigger or to widen their recognition spectrum. These studies also revealed that chimeric PRRs must retain their original intracellular transmembrane domains to be functional. For interspecies transfer of RLPs, Jehle and colleagues have used ReMAX and EiX2 to demonstrate that swapping the transmembrane regions between two RLPs can also improve their PRR functions (83).

Systematic analyses in different plant species have demonstrated that FLS2 orthologs have variable affinities and perception mechanisms for the same flg22 ligand (143, 216). Thus, although

a PRR can be engineered to function with an improved kinase, the ectodomain itself can be optimized to improve or expand the ligand specificity of the chimeric PRR.

Ultimately, PRRs can also be engineered to induce a stronger output (101). As rice XA21 (202) and tomato Pi-d2 (28) induce HR-like responses, their intracellular domains have been used to create chimeric PRRs with the rice OsCEPiP ectodomain (100, 105). The corresponding chimeras increased cell death upon chitin treatment as well as resistance to the fungal pathogen *M. oryzae*.

To summarize, PTI is an efficient layer of immunity that can be exploited to confer durable resistance in plant. As PRRs are able to perceive a great range of microbial elicitors, the discovery and engineering of new PRRs will enable new breeding strategies to exploit the wide diversity of elicitor perception to enhance crop disease resistance.

SUMMARY POINTS

1. Plants use RKs and RLPs as PRRs to sense apoplastic elicitors (PAMPs or DAMPs).
2. PAMPs and DAMPs have been identified by functional characterization of known molecules, by biochemistry, and by sequence and genome analyses.
3. PRRs have principally been identified using genetic and biochemical approaches.
4. PRRs can be deployed in different plant species to increase their immunity against adapted pathogens.
5. PRRs can be engineered to improve ligand recognition and intracellular immune outputs.

DISCLOSURE STATEMENT

Dr. Zipfel and Dr. Boutrot collaborate with the 2Blades Foundation to develop commercial and charitable applications of plant disease resistance mediated by pattern recognition receptors. Dr. Zipfel is an inventor on a patent filing on the *EFR* gene.

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