

SI PLANT BIOTIC INTERACTIONS

Pattern recognition receptors and signaling in plant–microbe interactions

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SUMMARY

Plants solely rely on innate immunity of each individual cell to deal with a diversity of microbes in the environment. Extracellular recognition of microbe- and host damage-associated molecular patterns leads to the first layer of inducible defenses, termed pattern-triggered immunity (PTI). In plants, pattern recognition receptors (PRRs) described to date are all membrane-associated receptor-like kinases or receptor-like proteins, reflecting the prevalence of apoplastic colonization of plant-infecting microbes. An increasing inventory of elicitor-active patterns and PRRs indicates that a large number of them are limited to a certain range of plant groups/species, pointing to dynamic and convergent evolution of pattern recognition specificities. In addition to common molecular principles of PRR signaling, recent studies have revealed substantial diversification between PRRs in their functions and regulatory mechanisms. This serves to confer robustness and plasticity to the whole PTI system in natural infections, wherein different PRRs are simultaneously engaged and faced with microbial assaults. We review the functional significance and molecular basis of PRR-mediated pathogen recognition and disease resistance, and also an emerging role for PRRs in homeostatic association with beneficial or commensal microbes.

Keywords: pattern recognition receptors, microbe-associated molecular patterns, damage-associated molecular patterns, plant immunity, plant–microbe interactions, signaling, receptor-like protein, receptor-like kinase.

INTRODUCTION TO PLANT IMMUNITY

In plants, each individual cell expresses a repertoire of innate immune receptors that recognize invasion signals (Jones and Dangl, 2006). At the cell surfaces, pattern recognition receptors (PRRs) detect molecular structures typical of microbes, termed microbe-associated molecular patterns (MAMPs), or endogenous signals generated upon cellular disintegration, termed damage-associated molecular patterns (DAMPs), and thereby mount pattern-triggered immunity (PTI; Figure 1). PTI plays an important role in preventing non-adapted microbes, whether pathogens or not, from infecting the host, termed non-host resistance, and also in restricting infection of adapted pathogens in susceptible hosts, termed basal resistance (Couto and Zipfel, 2016; Tang *et al.*, 2017). In turn, pathogens employ a wide array of virulence effectors to overcome PTI and establish successful infection, termed effector-triggered susceptibility (ETS). However, host recognition of one or

more of pathogen effectors, mainly via intracellular nucleotide-binding (NB) leucine-rich repeat (LRR) domain receptors (NLRs), leads to robust immunity that terminates pathogen growth, termed effector-triggered immunity (ETI). Compared with PTI, ETI displays an amplified and robust form of defense programs, which is often accompanied by localized cell death called the hypersensitive response (Katagiri and Tsuda, 2010). Reiterating cycles of PTI, ETS and ETI drive host–pathogen co-evolution that has led to the diversification of effector functions and NLR recognition specificities, as illustrated in the zigzag model (Jones and Dangl, 2006). Of note, indirect recognition of pathogen effector actions is functionally analogous to PRR-mediated recognition of DAMPs. This leads to a notion that plant immunity serves as a surveillance system for danger signals in both extracellular and intracellular milieus (Cook *et al.*, 2015; Gust *et al.*, 2017). Here, we review PRR

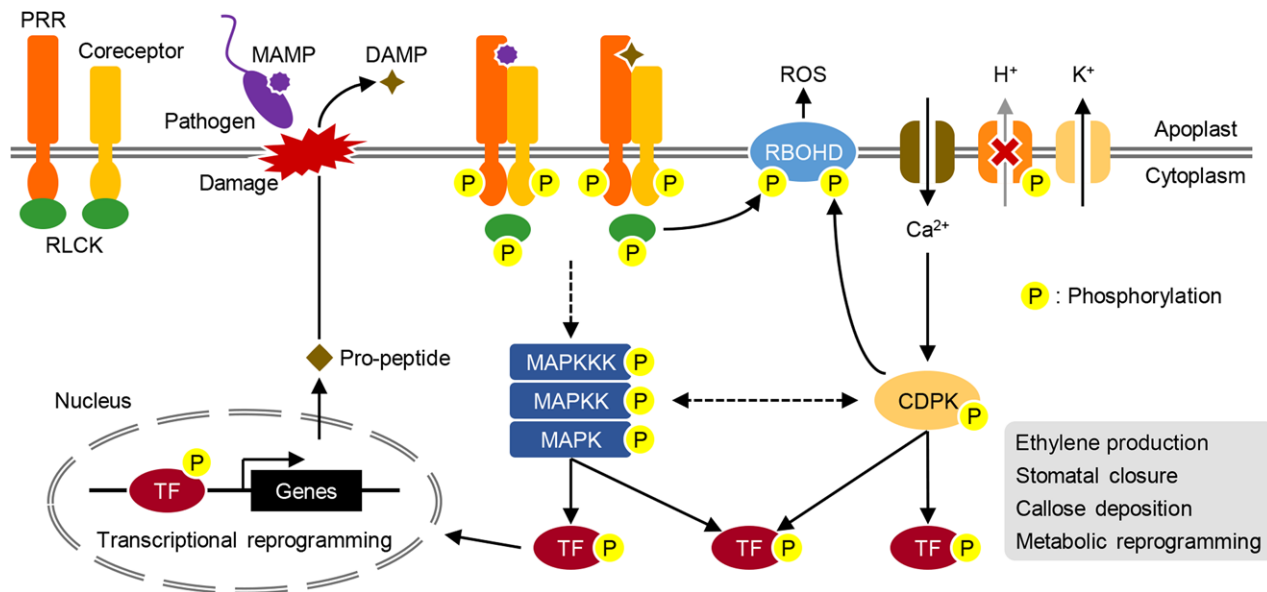


Figure 1. An overview of pattern-triggered immunity (PTI).

Perception of microbe-/damage-associated molecular patterns (MAMPs/DAMPs, respectively) by cognate pattern recognition receptors (PRRs) involves dynamic association/dissociation with co-receptors and receptor-like cytoplasmic kinases (RLCKs), and transphosphorylation within the PRR complexes to initiate the downstream signaling. PRR-derived signals are transmitted via further phosphorylation cascades including mitogen-activated protein kinases (MAPKs) and calcium-dependent protein kinases (CDPKs) to the downstream targets such as the NADPH oxidase RBOHD, the plasma membrane (PM)-resident H^+ -ATPases and transcriptional factors (TFs) during PTI.

functions and regulations that are central to the elaborate immune system of plants.

KEY PRINCIPLES OF PATTERN RECOGNITION AND RECEPTOR-TRIGGERED SIGNALING

Plant PRRs include receptor-like kinases (RLKs) and receptor-like proteins (RLPs; Couto and Zipfel, 2016; Boutrot and Zipfel, 2017). RLKs are composed of an extracellular domain, transmembrane domain and an intracellular kinase domain, whereas RLPs lack the intracellular kinase domain. LRRs, lysin motifs (LysMs), lectin-like motifs and epidermal growth factor (EGF)-like domains are among ligand-binding ectodomains described to date. Ectodomain classes largely correspond to the nature of the ligands recognized.

In *Arabidopsis thaliana*, the LRR-RLK FLS2 recognizes an N-terminal 22-amino-acid epitope (flg22) of bacterial flagellin. flg22 recognition specificities are widespread in higher plants (Gomez-Gomez and Boller, 2000; Hann and Rathjen, 2007; Robatzek *et al.*, 2007; Takai *et al.*, 2008; Boller and Felix, 2009; Trda *et al.*, 2014; Zhang *et al.*, 2017). FLS2 is required for bacterial resistance in particular following leaf surface inoculation, providing evidence that links PRR to pathogen resistance (Zipfel *et al.*, 2004). The LRR-RLK EFR recognizes an N-acetylated 18–26-amino-acid epitope (elf18–elf26) of elongation factor (EF)-Tu, one of the most abundant proteins of bacterial cells, during bacterial resistance (Kunze *et al.*, 2004; Zipfel *et al.*, 2006). elf18 perception seems restricted to the Brassicaceae family

(Boller and Felix, 2009), but the introduction of EFR alone is sufficient to confer elf18 responsiveness and bacterial resistance in other plant families (Zipfel *et al.*, 2006; Lacombe *et al.*, 2010). This suggests that PRRs function as a replaceable module in PTI, and that pathogens are specifically adapted to the existing PRR repertoire of the host. The successful interfamily transfer of EFR demonstrates the effectiveness of increasing the existing PRR repertoire in breeding disease resistance (Lacombe *et al.*, 2010; Schoonbeek *et al.*, 2015; Schwessinger *et al.*, 2015). FLS2 and EFR both belong to the LRR-RK class XII (Shiu *et al.*, 2004), and offer excellent PRR models.

Following ligand perception, FLS2 and EFR both involve the LRR-RLK BAK1 (and related SERKs) in the receptor complexes (Chinchilla *et al.*, 2007; Heese *et al.*, 2007; Roux *et al.*, 2011; Ma *et al.*, 2016), as shown for the LRR-RLK brassinosteroid (BR) receptor BRI1 (Li *et al.*, 2002; Nam and Li, 2002; Santiago *et al.*, 2013). Crystal structure of flg22-bound FLS2-BAK1 ectodomains indicates that BAK1 acts as a co-receptor (Sun *et al.*, 2013). Structure has been solved or simulated for ligand-bound ectodomains of different BAK1 (or SERK)-associated LRR-RLKs (Song *et al.*, 2017). Likewise, many LRR-RLPs constitutively associate with the adapter LRR-RLK SOBIR1, and then involve BAK1 in response to ligands (Gust and Felix, 2014; Liebrand *et al.*, 2014; Yasuda *et al.*, 2017). These heteromeric PRR complexes further involve receptor-like cytoplasmic kinases (RLCKs) such as BIK1 in intercellular signaling (Couto and Zipfel, 2016). Ligand-induced FLS2-BAK1

association leads to BAK1 activation and phosphorylation of BIK1, and then BIK1 dissociation to mediate downstream signaling (Lu *et al.*, 2010; Zhang *et al.*, 2010; Schwessinger *et al.*, 2011; Lin *et al.*, 2014). As such, PRR signaling occurs through dynamic association/dissociation and trans-phosphorylation of signaling components within and downstream of PRR kinase complexes.

Ligand-induced formation of heteromeric receptor complexes is subject to multi-layered regulation. In resting cells, BAK1 is retained in different complexes involving the LRR-RLK pseudokinase BIR2 or BIR3, thereby restricting precocious PRR-BAK1 association (Halter *et al.*, 2014; Imkamp *et al.*, 2017). In response to flg22, a pool of BAK1 is dissociated from BIR2 or BIR3, and then allowed to form an active FLS2-BAK1 complex. BIR3 also associates with FLS2 and BRI1 to restrict PTI and BR signaling, respectively. Likewise, the LRR-RLK pseudokinase BIR1 also sequesters BAK1 from BAK1-SOBIR1 association and PTI signaling, until BAK1 is recruited to ligand-bound PRRs (Gao *et al.*, 2009; Li *et al.*, 2016a).

Pattern recognition receptor abundance is also tightly controlled. Together with BAK1, the U-box E3 ligases PUB12 and PUB13 are recruited to the FLS2 complex in response to flg22 (Lu *et al.*, 2011). BAK1 phosphorylation of PUB12/PUB13 leads to FLS2 ubiquitination by the E3 ligases for receptor degradation. Consistent with this, FLS2 signaling outputs and bacterial resistance are enhanced in *pub12 pub13* plants. Following ligand-induced association with BAK1, FLS2 also undergoes endocytosis via clathrin and subsequent degradation (Robatzek *et al.*, 2006; Chinchilla *et al.*, 2007; Mbengue *et al.*, 2016). This leads to transient desensitization of FLS2 signaling, but is followed by replenishment with *de novo* synthesized receptor (Smith *et al.*, 2014). This regulation also occurs on different BAK1-associated PRRs (Mbengue *et al.*, 2016; Ortiz-Moreno *et al.*, 2016; Postma *et al.*, 2016; Yamada *et al.*, 2016c), and is closely associated with effective defense activation (Mbengue *et al.*, 2016), pointing to a positive role for specific turnover of ligand-bound receptor pools in PTI signaling. Their replenishment may occur through the exocyst Exo70B2 complex, a process suppressed by the E3 ligases PUB22/PUB23/PUB24 (Trujillo *et al.*, 2008; Stegmann *et al.*, 2012). Along with such cellular dynamics of PRRs, pattern-induced re-distribution between different membrane fractions was described for PTI signaling components (Keinath *et al.*, 2010). Advanced live-imaging with variable-angle epifluorescence microscopy and single-particle tracking revealed ligand-induced relocation of FLS2 and BRI1 to defined microdomains (Bucherl *et al.*, 2017). This indicates that ligand-induced receptor compartmentalization within membrane microdomains enables spatiotemporal separation and specific control of receptor signaling.

The phosphorylation states of key protein kinases and their substrates involved in PRR signaling are also subject

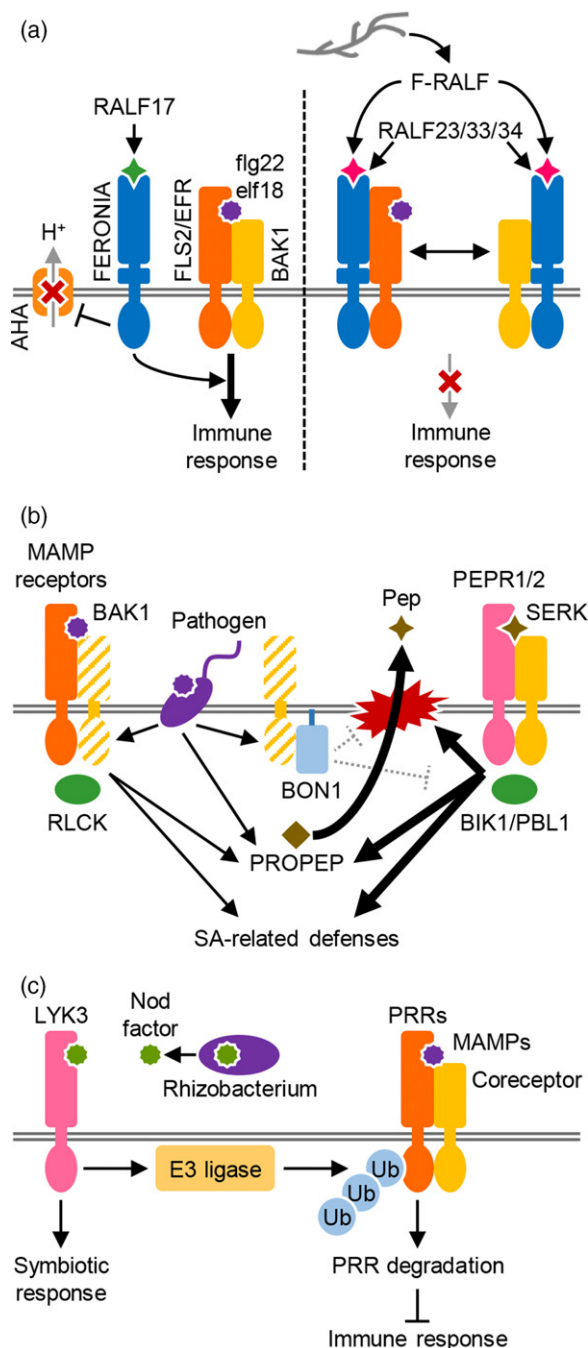


Figure 2. Signal integration between different pattern recognition receptor (PRR) pathways.

(a) Immune-inducible and immune-repressible RALF peptides act through the FERONIA scaffold to positively or negatively influence pattern-triggered immunity (PTI) signaling (left and right), respectively. F-RALF, functional homologs of RALF peptides secreted by fungal pathogens.

(b) Layered structure of functional interactions between microbe-associated molecular pattern (MAMP) receptor and PEPR signaling. Pathogen-induced BAK1 depletion results in dysfunction of BAK1/BON-mediated cell death control, increased release of PROPEP-derived damage-associated molecular patterns (DAMPs) and sensitization of salicylic acid (SA)-related defenses.

(c) Rhizobacterial NOD factors not only induce symbiotic responses but also suppress PTI signaling through PRR ubiquitination (Ub) and proteasomal degradation.

to tight regulation (Couto and Zipfel, 2016). Ser/Thr phosphatases type 2A (PP2A) negatively regulate phosphorylation levels of BAK1 and thus EFR-mediated defenses (Segonzac *et al.*, 2014). PP2Cs also negatively regulate EFR and Xa21, a receptor mediating resistance to *Xanthomonas oryzae* pv *oryzae* (Xoo) in rice (Park *et al.*, 2008; Holton *et al.*, 2015). Moreover, phosphorylation of EFR Tyr836, conserved within related LRR-RLK PRRs, is crucial for PTI signaling and is targeted for dephosphorylation by the *Pseudomonas syringae* pv *tomato* (Pst) virulence effector HopAO1 (Macho *et al.*, 2014). In resting complexes with EFR/FLS2, BIK1 is also kept inactive by PP2C38 (Couto *et al.*, 2016).

RECOGNITION OF BACTERIAL MAMPS

An inventory of elicitor-active patterns and PRRs has been extended in plants (Boutrot and Zipfel, 2017; Table 1). Flagellin has different elicitor-active epitopes than flg22 (Taguchi *et al.*, 2003; Takeuchi *et al.*, 2003; Katsuragi *et al.*, 2015). One such epitope undergoing strong selection against elicitor activity, termed flgII-28, was revealed by population genomics study on field Pst isolates in tomato (Cai *et al.*, 2011). Importantly, allelic variations of plant-infecting bacteria in both flg22 and flgII-28 epitopes significantly affect the strength of plant immune responses (Felix *et al.*, 1999; Sun *et al.*, 2006; Clarke *et al.*, 2013), without discernible effects on bacterial motility (Clarke *et al.*, 2013). Structural differences of flagellin also influence bacterial virulence in rice (Che *et al.*, 2000). Loss of flagellin from non-adapted bacteria allows their proliferation in non-host plants (Li *et al.*, 2005). These findings suggest that flagellin recognition defines a critical determinant of plant–bacterium interactions, and that MAMP diversification facilitates PTI evasion. Indeed, similar to flagellin, substantial polymorphisms exist in elicitor-active regions of otherwise highly conserved pathogen proteins (Vinatzer *et al.*, 2014). A search for such signatures in orthologous genes of six bacterial pathogens (but not in seven non-pathogens) identified novel MAMPs that are recognized in *A. thaliana* (McCann *et al.*, 2012). A middle region of EF-Tu, in addition to elf18, also undergoes positive selection. This region overlaps with an elicitor-active fragment of EF-Tu purified from the bacterium *Acidovorax avenae* extracts, which is predominantly recognized in rice (Furukawa *et al.*, 2014).

Microbe-associated molecular pattern recognition specificities often display plant lineage-specific or intra-species variations, possibly reflecting plant adaptation to MAMP diversification in microbial populations. In tomato, natural variation studies revealed the class XII LRR-RLK FLS3 as the flgII-28 receptor, demonstrating that plants employ different PRRs to recognize separate patterns from the same microbial protein (Hind *et al.*, 2016). Interestingly, flgII-28 alleles influence bacterial virulence in *A. thaliana* in a manner dependent on FLS2 (Clarke *et al.*, 2013). Given their

lack of direct binding to FLS2, it is interesting to determine how flgII-28 alterations influence flg22 recognition and/or FLS2-triggered immunity.

Peptidoglycans (PGNs) constitute cell walls of most bacteria, and their fragments, muropeptides, are released as a consequence of cell wall remodeling during bacterial growth. PGNs thus serve as signals, indicative of bacterial growth state, within bacterial populations and for eukaryotic hosts (Dworkin, 2014), and their perception induces immune responses in plants, insects and mammals (Felix and Boller, 2003; Guan and Mariuzza, 2007; Gust *et al.*, 2007). N-deacetylation of PGNs dampens immune response and helps *Listeria* evade from host immunity, possibly through reduced receptor binding (Boneca *et al.*, 2007). It is possible that the host discriminates structurally distinct PGN fragments from growing and resting bacteria. PGN perception occurs through LysM domain-containing proteins, which are widespread in almost all kingdoms of life (Zhang *et al.*, 2009). In *A. thaliana*, the LysM-RLPs AtLYM1 and AtLYM3 recognize PGNs, and presumably act in a complex with the LysM-RLK CERK1 during bacterial resistance (Willmann *et al.*, 2011). Notably, LYM1/LYM3 can bind both complex and soluble PGNs from Gram-negative or Gram-positive bacteria, while CERK1 does not. By contrast, CERK1, but not LYM1/LYM3, binds chitin, a cell wall component of fungi (Iizasa *et al.*, 2010; Petutschnig *et al.*, 2010; Liu *et al.*, 2012b), implying that CERK1 is co-opted as an adapter for LYM1/LYM3 receptors. In rice, the LysM-RLPs OsLYP4 (orthologous to LYM3) and OsLYP6 directly bind PGNs as well as chitin, thereby mediating both bacterial and fungal resistance (Liu *et al.*, 2012a). It is interesting to determine the molecular basis for the ligand promiscuity of these receptors. OsLYP4/OsLYP6 associates with and requires OsCERK1 in PGN and chitin signaling, although OsCERK1 fails to bind these ligands (Liu *et al.*, 2012a; Kouzai *et al.*, 2014).

Lipopolysaccharide (LPS) consists of three moieties, lipid A, a core oligosaccharide and a variable O-polysaccharide region. As the major outer-membrane component of Gram-negative bacteria, LPS provides a shield for bacteria but also MAMPs for their mammal and plant hosts (Ranf, 2016; Kagan, 2017). However, the use of LPS preparations from bacterial cultures in tracing plant immune responses raises concerns about possible contaminations of different MAMPs (Leulier *et al.*, 2003). Convincing evidence for plant LPS perception was obtained with the discovery of the *A. thaliana* lectin S-domain RLK LORE (previously known as SD1-29) specifically required for LPS recognition from *Pseudomonas* and *Xanthomonas* species (Ranf *et al.*, 2015). LORE-mediated LPS recognition is restricted to the Brassicaceae family, but LORE introduction is sufficient to transfer LPS recognition specificity to *Nicotiana benthamiana* (Solanaceae). This points to a critical role for LORE in LPS perception, although direct LPS–LORE binding

Table 1 Plant pattern recognition receptors and the cognate ligands

Receptor	Type	Ligand (pattern)	Plant	Reference
Recognition of bacterial pathogens				
FLS2	LRR-RLK	Flagellin (flg22)	Higher plants	Gomez-Gomez and Boller (2000), Hann and Rathjen (2007), Robatzek <i>et al.</i> (2007), Takai <i>et al.</i> (2008), Boller and Felix (2009), Trda <i>et al.</i> (2014) and Zhang <i>et al.</i> (2017)
FLS3	LRR-RLK	Flagellin (flgII-28)	<i>S. pimpinellifolium</i>	Cai <i>et al.</i> (2011)
EFR	LRR-RLK	EF-Tu (elf18)	<i>A. thaliana</i>	Kunze <i>et al.</i> (2004) and Zipfel <i>et al.</i> (2006)
CORE	LRR-RLK	Cold shock protein (csp22)	<i>S. lycopersicum</i>	Wang <i>et al.</i> (2016a)
XA21	LRR-RLK	raxX (RaxX21)	<i>O. sativa</i>	Pruitt <i>et al.</i> (2015)
XPS1	LRR-RLK	Permease (xup25)	<i>A. thaliana</i>	Mott <i>et al.</i> (2016)
LORE	LEC-RLK	Lipopolysaccharide	<i>A. thaliana</i>	Ranf <i>et al.</i> (2015)
EPR3	LysM-RLK	Extracellular polysaccharides	<i>L. japonicus</i>	Kawaharada <i>et al.</i> (2015)
ReMAX/RLP1	LRR-RLP	eMAX	<i>A. thaliana</i>	Jehle <i>et al.</i> (2013)
RLP23	LRR-RLP	Nep1-like protein (nlp20)	<i>A. thaliana</i>	Albert <i>et al.</i> (2015)
CSPR	LRR-RLP	Cold shock protein (csp22)	<i>N. benthamiana</i>	Saur <i>et al.</i> (2016)
LYM1/LYM3	LysM-RLP	Peptidoglycan	<i>A. thaliana</i>	Willmann <i>et al.</i> (2011)
Recognition of fungal pathogens				
CERK1	LysM-RLK	Chitin	<i>A. thaliana</i>	Miya <i>et al.</i> (2007), Wan <i>et al.</i> (2008), Iizasa <i>et al.</i> (2010) and Petutschnig <i>et al.</i> (2010)
LYK5	LysM-RLK	Chitin	<i>A. thaliana</i>	Cao <i>et al.</i> (2014)
I-3	LEC-RLK	Avr3/Six1	<i>S. pennellii</i>	Catanzariti <i>et al.</i> (2015)
RLP30	LRR-RLP	SCFE1	<i>A. thaliana</i>	Zhang <i>et al.</i> (2013)
Eix1/Eix2	LRR-RLP	Ethylene-inducing xylanase	<i>S. pennellii</i>	Ron and Avni (2004)
RLP42/RBPG1	LRR-RLP	Endopolygalacturonases	<i>A. thaliana</i>	Zhang <i>et al.</i> (2014)
Cf-2	LRR-RLP	Avr2, Gr-VAP1	<i>S. pimpinellifolium</i>	Dixon <i>et al.</i> (1996) and Rooney <i>et al.</i> (2005)
Cf-4	LRR-RLP	Avr4	<i>S. hirsutum</i>	Thomas <i>et al.</i> (1997)
Cf-5	LRR-RLP	Avr5	<i>S. lycopersicum</i>	Dixon <i>et al.</i> (1998)
Cf-9	LRR-RLP	Avr9	<i>S. pimpinellifolium</i>	Jones <i>et al.</i> (1994) and Luderer <i>et al.</i> (2001)
Hcr9-4E	LRR-RLP	Avr4E	<i>S. hirsutum</i>	Thomas <i>et al.</i> (1997) and Weinberger <i>et al.</i> (1999)
LepR3/RLM	LRR-RLP	AvrLm1, AvrLm2	<i>B. napus</i>	Larkan <i>et al.</i> (2013, 2015)
I	LRR-RLP	Avr1/Six4	<i>S. pimpinellifolium</i>	Catanzariti <i>et al.</i> (2017)
CEBiP	LysM-RLP	Chitin	<i>O. sativa</i>	Kaku <i>et al.</i> (2006), Shimizu <i>et al.</i> (2010) and Hayafune <i>et al.</i> (2014)
LYP4, LYP6	LysM-RLP	Chitin, Peptidoglycan	<i>O. sativa</i>	Liu <i>et al.</i> (2012a)
LYM1, LYM3	LysM-RLP	Peptidoglycan	<i>A. thaliana</i>	Willmann <i>et al.</i> (2011)
LYM2	LysM-RLP	Chitin	<i>A. thaliana</i>	Faulkner <i>et al.</i> (2013)
Recognition of oomycete pathogens				
RLP23	LRR-RLP	nlp20	<i>A. thaliana</i>	Albert <i>et al.</i> (2015)
RLP85/ELR	LRR-RLP	Elicitin	<i>S. microdontum</i>	Du <i>et al.</i> (2015)
Recognition of host cell alterations (damage-associated patterns)				
PEPR1	LRR-RLK	Pep1-Pep6	<i>A. thaliana</i>	Yamaguchi <i>et al.</i> (2006, 2010)
PEPR2	LRR-RLK	Pep1, Pep2	<i>A. thaliana</i>	Yamaguchi <i>et al.</i> (2010)
RLK7	LRR-RLK	PIP1	<i>A. thaliana</i>	Hou <i>et al.</i> (2014)
SR160	LRR-RLK	Systemin	<i>S. peruvianum</i>	Scheer and Ryan (2002)
DORN1	LEC-RLK	Extracellular ATP	<i>A. thaliana</i>	Choi <i>et al.</i> (2014)
WAK1	EGF-like-RLK	Oligogalacturonides	<i>A. thaliana</i>	Brutus <i>et al.</i> (2010)
FER	Malectin-RLK	RALF peptides	<i>A. thaliana</i>	Haruta <i>et al.</i> (2014) and Stegmann <i>et al.</i> (2017)

RLK, receptor-like kinase; RP, receptor-like protein; LRR, leucine-rich repeat; LysM, lysin motif; LEC, lectin; EGF, epidermal growth factor; *A. thaliana*, *Arabidopsis thaliana*; *B. napus*, *Brassica napus*; *L. japonicus*, *Lotus japonicus*; *N. benthamiana*, *Nicotiana benthamiana*; *O. sativa*, *Oryza sativa*; *S. hirsutum*, *Solanum hirsutum*; *S. lycopersicum*, *Solanum lycopersicum*; *S. microdontum*, *Solanum microdontum*; *S. peruvianum*, *Solanum peruvianum*; *S. pimpinellifolium*, *Solanum pimpinellifolium*.

remains to be shown. Remarkably, LORE is not required for LPS recognition from *Escherichia coli* (Ranf *et al.*, 2015), suggesting the existence of different LPS receptors in plants, as shown in mammals.

A genome-sequence-based screen on *P. syringae* isolates for bacterial conserved proteins carrying a region

under strong positive selection revealed six new MAMPs, including xanthine/uracil permease (xup25 epitope). The class XII LRR-RLK XPS1 directly recognizes xup25, thereby conferring bacterial resistance (Mott *et al.*, 2016). Comparative genomics approaches will be useful in further discoveries of MAMP–PRR pairs.

Highly abundant cold shock proteins (csp15/csp22 epitope) are immunogenic in tobacco (Felix and Boller, 2003). Natural variation studies in tomato led to the identification of the class XII LRR-RK CORE (closely related to EFR and Xa21) as a high-affinity receptor for csp22 (Wang *et al.*, 2016a). CORE is conserved in the Solanaceae family, but its introduction confers full csp22 sensitivity and, notably, enhanced *Pst* resistance in *A. thaliana*. Given the inherent adaptation of *Pst* to tomato PTI involving CORE, CORE may differentially mediate bacterial resistance in the two host plants.

RECOGNITION OF FUNGAL MAMPS

Chitin, a linear polymer (degree of polymerization ≥ 6) of β -(1,4)-linked N-acetylglucosamine (GlcNAc), and its deacetylated derivative chitosan are major components of fungal cell wall, and recognized as MAMPs in a wide range of plants (Boller and Felix, 2009). Chitin recognition requires the LysM-RLK CERK1 (Shinya *et al.*, 2015). In rice, OsCERK1 does not directly bind chitin, but functions with the chitin-binding LysM-RLP OsCEBiP in a receptor complex (Kaku *et al.*, 2006; Shimizu *et al.*, 2010; Hayafune *et al.*, 2014). In addition, the chitin-binding LysM-RLPs OsLYP4 and OsLYP6 also seem to function with OsCERK1 (Liu *et al.*, 2012a; Kouzai *et al.*, 2014). In *A. thaliana*, CERK1 directly binds chitin, thereby mediating chitin-triggered immunity (Miya *et al.*, 2007; Wan *et al.*, 2008; Iizasa *et al.*, 2010; Petutschnig *et al.*, 2010). In accordance with this, all three CEBiP homologs, LYM1, LYM2 and LYM3, are dispensable for CERK1-dependent chitin recognition (Wang *et al.*, 2012; Faulkner *et al.*, 2013), although LYM1 and LYM3, together with CERK1, are required for PGN recognition (Willmann *et al.*, 2011). LYM2 is, however, required for chitin-induced closure of plasmodesmata and fungal resistance that are independent of CERK1 (Faulkner *et al.*, 2013; Narusaka *et al.*, 2013). Consistent with this, of the three LYMs, LYM2 can specifically bind chitin (Shinya *et al.*, 2012). Recent studies revealed that the chitin-binding LysM-RLK pseudokinase LYK5 physically associates with CERK1 to mediate CERK1 homodimerization and phosphorylation in response to chitin (Cao *et al.*, 2014). Loss of LYK5 together with closely related LYK4, as well as that of CERK1, renders plants insensitive to chitin. Two separate perception systems, involving LYK5/LYK4-CERK1 or LYM2, are employed for different chitin responses in *A. thaliana*.

Ethylene-inducing xylanase (EIX) is recognized in tomato via the LRR-RLPs Eix2 and Eix1 (Ron and Avni, 2004). In response to EIX, Eix2 induces defense responses including upregulation of Eix1, whose EIX binding in turn attenuates Eix2 signaling by functioning with BAK1 (Bar *et al.*, 2010). Fungal endopolygalacturonases (PGs) hydrolyze polygalacturonic acid, the main component of plant cell wall pectin, and also display elicitor activity that is independent of enzymatic activity (Poinssot *et al.*, 2003). Natural variation

studies revealed the *A. thaliana* LRR-RLP42 (RBGP1), which recognizes several PGs from *Botrytis cinerea* and mediates PG-induced resistance to *Hyaloperonospora arabidopsidis* (*Hpa*) in a manner dependent on SOBIR1 (Zhang *et al.*, 2014).

RECOGNITION OF OOMYCETE MAMPS

Despite intensive studies on devastating oomycete pathogens such as the potato late blight pathogen *Phytophthora infestans*, knowledge is still limited for oomycete MAMP receptors in plants (Raaymakers and Van den Ackerveken, 2016). Oomycete MAMPs include cell wall components, β -1,3- and β -1,6-glucans, glucan-chitosaccharides and cellulose-binding elicitor lectin (CBEL; Fliegmann *et al.*, 2004; Khatib *et al.*, 2004; Nars *et al.*, 2013). Natural variations and BAK1 requirement were described for CBEL responsiveness in *A. thaliana* (Larroque *et al.*, 2013). The transglutaminase GP42 (Nurnberger *et al.*, 1994, 1995; Hahlbrock *et al.*, 1995) and eicosapolyenoic acids from *Phytophthora mycelia* also provide MAMPs (Bostock *et al.*, 1981). The *Phytophthora* xyloglucan-specific endoglucanase XEG1 provides a virulence factor that degrades β -glucan and xyloglucan, but also a MAMP that is recognized by BAK1-dependent mechanisms (Ma *et al.*, 2015). For these MAMPs, cognate PRRs have yet to be identified.

Necrosis and ethylene-inducing peptide 1 (Nep1)-like proteins (NLPs) are widespread from oomycetes to fungi and bacteria. While most NLPs act as toxins inducing necrosis and ethylene production in dicot plants, non-cytotoxic NLPs of *Hpa* helped identify 20–24 amino acid elicitor-active epitopes (nlp20/nlp24) conserved in NLPs across microbial kingdoms (Bohm *et al.*, 2014; Oome *et al.*, 2014). nlp20 induces defense activation without necrosis in Brassicaceae species, but not in Solanaceous species (Bohm *et al.*, 2014). The *A. thaliana* LRR-RLP RLP23 identifies an nlp20 receptor, which acts together with SOBIR1 and BAK1 in bacterial and fungal resistance (Albert *et al.*, 2015). The interfamily transfer of RLP23 also confers *P. infestans* resistance in potato.

Recognition of elicitors (~10 kDa), secreted proteins conserved in oomycete pathogens, induces necrosis and pathogen resistance in tobacco (Ricci *et al.*, 1989). The LRR-RLP85 (ELR) from wild potato is required for recognition of a range of elicitors from different oomycete species, including INF1 from *P. infestans*, although direct ELR-elicitor binding remains to be shown (Du *et al.*, 2015). ELR undergoes ligand-induced association with BAK1/SERK3. ELR introduction is sufficient to confer *P. infestans* resistance in cultivated potato. In *N. benthamiana*, BAK1/SERK3 and SOBIR1 are both required for elicitor-triggered cell death, implying the possible involvement of an ELR-BAK1-SOBIR1 complex in elicitor perception and signaling (Peng *et al.*, 2015).

ORPHAN PRRS WITH THE COGNATE PATTERNS UNIDENTIFIED

Natural variations of MAMP responsiveness have been exploited to reveal MAMP recognition mechanisms, without precise identification of the MAMP itself. This approach revealed the *A. thaliana* LRR-RLP ReMAX (RLP1) that mediates immune responses to a protein fraction from *X. axonopodis* pv *citri* (*Xac*) extracts, called eMAX (Jehle *et al.*, 2013). The LRR-RLK RLP30, together with SOBIR1 and BAK1, is required for recognition of the elicitor-active protein fraction from the fungus *Sclerotinia sclerotiorum*, called SCFE1 (Zhang *et al.*, 2013). In tomato, perception of an as-yet-unidentified pattern from parasite plants, designated the *Cuscuta* factor, requires the LRR-RLP CuRe1, which constitutively associates with SOBIR1 and mediates *Cuscuta reflexa* resistance (Hegenauer *et al.*, 2016).

Perception mechanisms analogous to PRRs are employed in cell surface recognition of pathogen effectors that act in the apoplast. Recognition of such apoplastic effectors from *Cladosporium fulvum*, *Fusarium oxysporum* and *Verticillium dahlia* involves direct and indirect modes of recognition (Table 1). In the latter cases, host cell perturbations or changes associated with the effector actions are recognized by these receptors, in a manner conceptually analogous to DAMP recognition (see below).

RECOGNITION OF HOST CELL ALTERATIONS (DAMPs)

Because MAMPs are shared by pathogens and non-pathogens, simultaneous detection of DAMPs is considered to represent signature of pathogenesis (Fontana and Vance, 2011; Blander and Sander, 2012). This hypothesis can now be tested with a growing list of plant DAMPs (Gust *et al.*, 2017).

High-mobility group box protein (HMGB) is associated with chromatin in the nucleus and also present in the cytosol of non-stressed cells, but its extracellular pool is immunogenic in both plants and mammals (Lotze and Tracey, 2005; Choi and Klessig, 2016). In *A. thaliana*, HMGB3 is released upon tissue damage during *B. cinerea* infection, thereby inducing PTI-like responses and fungal resistance (Choi *et al.*, 2016).

Extracellular ATP (eATP) triggers immune responses in plants and humans (Ralevic and Burnstock, 1998; Tanaka *et al.*, 2014). In *A. thaliana*, the lectin-like RLK DORN1/LecRK-I.9 recognizes eATP released in response to wounding, herbivory or pathogen attack to induce PTI-like defenses (Choi *et al.*, 2014; Li *et al.*, 2016b). DORN1 is unrelated in structure to the previously described nucleotide receptors in mammals, again pointing to convergent evolution of eATP recognition capacity. Whether ATP is actively exported as described in humans remains to be determined in plants.

Oligogalacturonides (OGs), fragments of plant cell wall pectin, are produced through hydrolysis by fungal or host

PGs during fungal infection or herbivory (Bergey *et al.*, 1999; De Lorenzo *et al.*, 2001; Ferrari *et al.*, 2013). OG recognition, likely through the EGF-like RLK WAK1, induces PTI-like defenses (Denoux *et al.*, 2008; Brutus *et al.*, 2010). Cutin monomers and cellulose-derived oligomers are also immunogenic (Fauth *et al.*, 1998; Souza *et al.*, 2017). Recognition of these cell-wall-derived DAMPs resembles TLR2/TLR4/TLR6-mediated recognition of degradation products from extracellular matrix in mammals (Choi and Klessig, 2016). Indeed, the malectin-like domain *Catharanthus roseus* RLK1-like (MLD-CrRLK1L) receptor THE1 and the class XII LRR-RLK MIK2 (LRR-KISS) link cell wall disintegration to defense activation (Hematy *et al.*, 2007; Van der Does *et al.*, 2017). Notably, MIK2 also acts as part of the receptor complex in the pollen tube for the DEFENSIN-LIKE peptide AtLURE1, a female guidance signal from the synergid cells (Wang *et al.*, 2016b). Whether AtLURE1-like peptides or the aforementioned carbohydrate DAMPs provide ligands for these cell wall integrity sensors requires future investigation.

Several endogenous peptides act as DAMPs, after processing from larger precursors and/or extracellular release during herbivore or pathogen resistance (Yamaguchi and Huffaker, 2011; Bartels and Boller, 2015). In tomato, the 18-amino-acid peptide systemin triggers jasmonic acid-dependent systemic signaling leading to herbivore resistance (Pearce *et al.*, 1991; McGurl *et al.*, 1992; Orozco-Cardenas *et al.*, 1993; Beloshistov *et al.*, 2017). The lack of an N-terminal leader sequence in the precursor prosystemin implies passive systemin release upon tissue injury. Hydroxyproline-rich systemins (HypSys), 18-amino-acid glycosylated peptides, also mediate herbivore defenses in Solanaceous species (Pearce *et al.*, 2009). In *A. thaliana*, PIP1 and PIP2 amplify MAMP-induced defenses via the class XI LRR-RLK RLK7 in a manner dependent on BAK1 (Hou *et al.*, 2014).

Plant elicitor peptides (Peps), including AtPep1-AtPep8 in *A. thaliana* and ZmPep1 in maize, are among the best-characterized DAMPs in plants (Yamaguchi and Huffaker, 2011; Bartels and Boller, 2015). Elicitor-active Pep epitopes are embedded in the C-terminus of PROPEP precursors, and recognized by the class XI LRR-RLKs PEPR1/PEPR2 in *A. thaliana*. The Pep-PEPR system contributes to broad-spectrum resistance against bacteria, fungi, oomycetes, nematodes and insects, and systemic immunity (Huffaker *et al.*, 2006, 2013; Liu *et al.*, 2013; Tintor *et al.*, 2013; Ross *et al.*, 2014; Lee *et al.*, 2017). The lack of an N-terminal leader sequence implies membrane damage-dependent release of PROPEPs (or derived DAMPs). Indeed, AtPROPEP3 release and apparent processing is enhanced in the presence of virulence effectors and/or host cell death during *Pst* challenge (Yamada *et al.*, 2016c). Notably, however, AtPROPEP3 is also released following sterile AtPep1 application, albeit without apparent processing. Given PEPR requirements for MAMP responses (Ma *et al.*, 2012; Tintor

et al., 2013), leaderless PROPEPs may undergo unconventional secretion, as described for interleukin 1L-1 β in humans (Malhotra, 2013). Although conserved in angiosperms, Peps from a particular plant species are only recognized in plants of the same family, pointing to the family-level diversification of recognition specificities (Huffaker *et al.*, 2011, 2013; Lori *et al.*, 2015).

RECOGNITION OF COMMON PATTERNS ACROSS KINGDOMS

In mammals, flagellin is recognized by the extracellular and intracellular PRRs TLR5 and NLRC4, respectively (Hayashi *et al.*, 2001; Kofoed and Vance, 2011; Zhao *et al.*, 2011). The flagellin site recognized by TLR5 is apart from flg22, although it partially overlaps with flgII-28 (Yoon *et al.*, 2012). The diversification of flagellin patterns and receptors points to convergent evolution of flagellin perception between plants and mammals (Ausubel, 2005). Intriguingly, muramyl dipeptides, breakdown products of PGNs, trigger immune response in metazoans, but not in *A. thaliana* (Gust *et al.*, 2007). Several classes of PRRs mediate PGN recognition in metazoans, including TLRs and nucleotide-binding oligomerization domain-containing (NOD) receptors (Guan and Mariuzza, 2007). All these receptors are again unrelated in structure to plant PGN receptors described above. LPS perception systems are also diverged between plants and mammals. The extracellular (TLR4 and CD14) and intracellular (caspase-11) receptors in mammals and LORE all recognize the lipid A moiety of LPS. However, their LPS recognition is differentially influenced by LPS acylation patterns: hexa-acylated LPS from *E. coli* fails to activate LORE but strongly activates TLR4, while in contrast penta-acylated LPS from the human pathogen *Pseudomonas aeruginosa* activates LORE signaling, but not TLR4 or caspase-11 (Tan and Kagan, 2014; Ranf *et al.*, 2015). Furthermore, unlike in plants, no genuine chitin receptor has been identified in mammals, although TLR2, Dectin-1 and the mannose receptor have been implicated in chitin-induced immune responses (Bueter *et al.*, 2013). These findings strengthen the view that lineage-specific PRRs, arisen through convergent evolution, often recognize distinct patterns from common microbial components in plants and animals.

Like mammals, plants seem to recognize RNA and DNA patterns from both microbe- and host-origins (Huang *et al.*, 2016). BAK1 and SERK1 mediate antiviral immunity and PTI-like responses to double-strand RNA (dsRNA), respectively (Korner *et al.*, 2013; Niehl *et al.*, 2016). The LRR-RLK NIK1 (related to BAK1) also contributes to antiviral immunity and identifies a virulence target for begomovirus (Santos *et al.*, 2010; Zoratto *et al.*, 2015), pointing to cell surface perception of viral patterns. Whether and if so how this is linked to RNA silencing following dicer-like (DCL)-mediated dsRNA

detection represents an interesting question in antiviral immunity.

Mammals recognize DNA-derived patterns through the endosomal TLR9 and the cytoplasmic cyclic GMP-AMP synthase-STING systems (Gallucci and Maffei, 2017). Plants may also employ PRR(s) to perceive extracellular DNA (eDNA), as eDNA induces PTI-like defenses and pathogen resistance (Wen *et al.*, 2009; Duran-Flores and Heil, 2014, 2015; Mazzoleni *et al.*, 2015; Gallucci and Maffei, 2017). Of note, substantial amounts of DNA are secreted from plant roots, and influence both plants and microbes in the soil (Ceccherini *et al.*, 2009; Driouich *et al.*, 2013). eDNA serves as a nutrient source (Paungfoo-Lonhienne *et al.*, 2010), but also causes plant growth inhibition in a conspecific manner (Mazzoleni *et al.*, 2015). Plant eDNA may act as DAMPs, to indicate life-threatening conditions to the same (or closely related) plant species (Veresoglou *et al.*, 2015).

CELLULAR AND PHYSIOLOGICAL OUTPUTS AND SIGNALING EVENTS DURING PTI

Perception of distinct patterns via cognate PRRs leads to a stereotypic set of intracellular signaling events and defense responses, which collectively contribute to the establishment of PTI. Hence, these PTI-hallmark outputs provide useful proxies to assess the strength and effectiveness of PRR signaling. They include changes in ion-fluxes across the plasma membranes (PMs), increases in cytosolic Ca²⁺ and apoplastic reactive oxygen species (ROS) levels, and mitogen-activated protein kinase (MAPK) activation, which are followed by production of phytohormones such as ethylene and salicylic acids (SA), stomatal closure, callose deposition, transcriptional and metabolic reprogramming (Boller and Felix, 2009; Yu *et al.*, 2017; Figure 1). A large number of genes are commonly up- or downregulated in response to different MAMPs/DAMPs (Zipfel *et al.*, 2006; Gust *et al.*, 2007; Denoux *et al.*, 2008; Wan *et al.*, 2008; Ross *et al.*, 2014). These findings may imply that PRRs merely represent separate entry points to PTI. However, PRR pathways display notable diversification in the defense outputs and/or regulatory modes (see below).

Immediately after pattern recognition, induced is a rapid increase of cytosolic Ca²⁺ concentrations ([Ca²⁺]_{cyt}) (Lecourieux *et al.*, 2002; Seybold *et al.*, 2014; Yuan *et al.*, 2017), which is required for a vast majority of PTI-characteristic outputs (Jeworutzki *et al.*, 2010; Kwaaitaal *et al.*, 2011; Ranf *et al.*, 2011). Ca²⁺ pumps/channels mediating Ca²⁺ influx from the apoplast and release from the internal stores need to be defined (Klusener *et al.*, 2002; Seybold *et al.*, 2014; Thor and Peiter, 2014; Yuan *et al.*, 2017). Cyclic nucleotide gated channel2 (CNGC2) and ionotropic glutamate receptor-like channels (iGluR) are required for LPS/Pep1- and flg22/elf18/chitin-induced [Ca²⁺]_{cyt} bursts, respectively (Ali *et al.*, 2007; Qi *et al.*, 2010; Kwaaitaal

et al., 2011). However, their contributions are marginal to flg22-induced $[Ca^{2+}]_{cyt}$ oscillation of guard cells (Thor and Peiter, 2014), suggesting the context-specific employment of different Ca^{2+} channels/pumps. Ca^{2+} -ATPase8 (ACA8) and ACA10 associate with FLS2 and are required for flg22-induced defenses, but not that of chitin (Frei dit Frey *et al.*, 2012). Physical and functional association of ACA8/ACA10 with BRI1 and the CLE peptide receptor CLV1 implies their broad assignment to LRR-RLKs.

Extracellular alkalinization and PM depolarization are detectable shortly after pattern recognition. PM-resident H^+ -ATPases (AHAs) mediate H^+ efflux from cytosol to establish the PM potential in resting cells, but pattern-induced AHA inactivation allows H^+ influx down the electrochemical gradient. Together with increases in Cl^- and K^+ effluxes, this results in extracellular alkalinization (Jeworutzki *et al.*, 2010; Elmore and Coaker, 2011). In *A. thaliana*, dephosphorylation at two residues and phosphorylation at Ser 899 of AHA, promoting and inhibiting AHA activity respectively, occur during PTI (Benschop *et al.*, 2007; Nuhse *et al.*, 2007). Pattern recognition also involves the endogenous RALF peptides and their receptor, the MLD-CrRLK1L FERONIA (FER) (Pearce *et al.*, 2001; Haruta *et al.*, 2008, 2014). FER phosphorylation of AHA2 at Ser 899 results in AHA2 inactivation and thus extracellular alkalinization (Figure 2a; Haruta *et al.*, 2014). By contrast, constitutive AHA activation blocks extracellular alkalinization and stomatal closure in response to flg22, an important PTI defense against microbial invasion (Liu *et al.*, 2009; Lee *et al.*, 2015). AHA activation is also among the mechanisms by which RIN4, a guard cell of the NLRs RPM1 and RPS2, attenuates PTI (Liu *et al.*, 2009; Lee *et al.*, 2015). Given the extensive reliance on PM-associated proteins, the impact of changes in the PM potential on PTI can be enormous, an interesting hypothesis remaining to be tested.

Reactive oxygen species, such as superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2), serve not only as antimicrobial and cell-wall cross-linking agents, but also as signaling molecules (Wrzaczek *et al.*, 2013; Qi *et al.*, 2017). Pattern-induced apoplastic ROS production requires the NADPH oxidase RBOHD (sufficient for the first ROS burst within 1–2 min) and the peroxidases PRX33/34 (Nuhse *et al.*, 2007; Zhang *et al.*, 2007; Daudi *et al.*, 2012; Kadota *et al.*, 2014). RBOHD is subject to Ca^{2+} -dependent and -independent regulations during PTI (Kadota *et al.*, 2015). Although the significance of direct Ca^{2+} binding is unclear, RBOHD phosphorylation by Ca^{2+} -dependent protein kinases (CDPKs), namely CPK5, CPK6, CPK11 and CPK4, leads to RBOHD activation (Ogasawara *et al.*, 2008; Boudsocq *et al.*, 2010; Dubiella *et al.*, 2013). ROS also increase $[Ca^{2+}]_{cyt}$ and CPK5 activity (Dubiella *et al.*, 2013). In addition, BIK1 phosphorylation of RBOHD further promotes RBOHD activation (Kadota *et al.*, 2014; Li *et al.*, 2014b). Notably, CPK5 and BIK1 phosphorylate RBOHD at distinct sites, and additively

promote RBOHD activation. BIK1/PBL1 also promote a $[Ca^{2+}]_{cyt}$ burst (Li *et al.*, 2014b; Ranf *et al.*, 2014) and RBOHD association with the heterotrimeric G-proteins composed of XLG2, AGB1 and AGG1/AGG2 (Liang *et al.*, 2016), thereby ensuring RBOHD activation. The G-proteins in turn mediate stable accumulation of BIK1. These findings illuminate positive feedback amplification between Ca^{2+} , ROS and BIK1/PBLs, which can strengthen PTI signaling. By contrast, CPK28 attenuates PTI signaling by phosphorylating BIK1, which leads to proteasomal BIK1 degradation (Monaghan *et al.*, 2014). The RLCK PBL13 association with RBOHD also negatively influences ROS production (Lin *et al.*, 2015). As such, fine-tuning individual RLCK activity and balancing opposing functions of different RLCK members underlie tight control of ROS production.

Separate RLCK members are assigned between LRR- and LysM-domain PRR classes, largely reflecting RLCK phosphorylation preference between BAK1 (for BIK1) and CERK1 (for PBL27). BIK1 and closely related PBL1 play a critical role in FLS2, EFR and PEPR signaling (Lu *et al.*, 2010; Zhang *et al.*, 2010; Liu *et al.*, 2013). The RLCKs PBS1, PBL2, BSK1 and PCRK1/PCRK2 also function with FLS2 (Zhang *et al.*, 2010; Shi *et al.*, 2013; Sreekanta *et al.*, 2015; Kong *et al.*, 2016), which explains the retention of some FLS2 signaling outputs in *bik1 pbl1* plants (Zhang *et al.*, 2010; Feng *et al.*, 2012; Shi *et al.*, 2013; Ranf *et al.*, 2014). In rice, OsRLCK176 and OsRLCK185 function with OsCERK1 in response to chitin and PGN (Yamaguchi *et al.*, 2013). In *A. thaliana*, chitin induces CERK1 phosphorylation of PBL27, orthologous to OsRLCK185, and in turn PBL27 phosphorylation of MAPKKK5 (Shinya *et al.*, 2014; Yamada *et al.*, 2016b). Thus, PBL27 defines a direct link between the LYK5/LYK4-CERK1 chitin receptor complex and a MAPK cascade consisting of MAPKKK5-MKK4/MKK5-MPK3/MPK6 (Yamada *et al.*, 2016b). On the other hand, BIK1/PBLs are likely to connect BAK1-associated PRRs to MAPK cascades. Although BIK1/PBL1 are dispensable for FLS2/EFR-mediated MAPK activation (Zhang *et al.*, 2010), this can be attributable to redundancy between RLCK members. Indeed, the *Xanthomonas campestris* effector AvrAC inhibits BIK1 and related PBLs, thereby suppressing MAPK activation in response to flg22 (Feng *et al.*, 2012).

In *A. thaliana*, PRR signaling involves two major MAPK cascades: one with an unknown MAPKK-kinase, MKK4/MKK5 (MAPK kinase) and MPK3/MPK6 (MAPK); and the other with MAPKKK8 (MEKK1), MKK1/MKK2 and MPK4/MPK11 (Meng and Zhang, 2013). A growing number of MAPK substrates have been described in PTI. MPK3/MPK6 phosphorylation of 1-aminocyclopropane-1-carboxylic acid synthase2 (ACS2) and ACS6 enhances ethylene production in response to flg22 (Liu and Zhang, 2004). MPK3 and/or MPK6 also phosphorylate several transcription factors (TFs) during PTI, including BES1, ERF104, WRKY33 and

VIP1 (Djamei *et al.*, 2007; Bethke *et al.*, 2009; Ishihama *et al.*, 2011; Mao *et al.*, 2011; Kang *et al.*, 2015). MPK3/MPK6 phosphorylation targets a subclass of VQ-motif-containing proteins (VQPs), including VQ4, for degradation (Pecher *et al.*, 2014). As a consequence, WRKY TFs are de-repressed from VQ4-mediated sequestration. Likewise, VQ21 (MKS1) brings together WRKY33 and MPK4, thereby having WRKY33 release dependent on MPK4 phosphorylation of VQ21 (Qiu *et al.*, 2008). Moreover, MPK3/MPK6 phosphorylation of cyclin-dependent kinase Cs (CDKs), and subsequent CDKC phosphorylation of RNA polymerase II C-terminal domain directly mediate transcriptional activation of defense-related genes (Li *et al.*, 2014a). MPK3/MPK6 and MPK4 also influence mRNA quality control in the cytoplasmic processing bodies, by phosphorylating the mRNA-binding proteins TZF9 and PAT1, respectively (Maldonado-Bonilla *et al.*, 2014; Roux *et al.*, 2015). Conversely, MPK3 phosphorylation of PUB22 inhibits its auto-ubiquitination and degradation, thereby stabilizing this negative regulator for PTI attenuation (Furlan *et al.*, 2017). flg22-induced MPK4 phosphorylation of the transcriptional repressor ASR leads to suppression of defense-related genes (Li *et al.*, 2015a). Furthermore, expression profiling in *mpk* mutants revealed previously unsuspected complex roles for MPK3 and MPK4 in flg22-induced transcriptional reprogramming (Frei dit Frey *et al.*, 2014). Together, MAPK cascades both positively and negatively regulate transcriptional reprogramming during PTI.

Mitogen-activated protein kinase cascades undergo cross-regulations between themselves and with other defense pathways. MAPKKK5 inversely influences chitin- and flg22-responses: loss of MAPKKK5, which mediates MPK3/MPK6 activation in the CERK1-PBL27 phospho-relay, enhances flg22-induced MPK3/MPK6 activation (Yamada *et al.*, 2016b). MAPKKK7 physically associates with FLS2 and attenuates flg22-induced defenses, via a process that remains elusive (Mott *et al.*, 2016). Moreover, the secreted proteases PrpL and ArgC from the bacterial pathogens *P. aeruginosa* and *X. campestris*, respectively, induce MAPK activation in a distinct mode (Cheng *et al.*, 2015). This requires heteromeric G-proteins composed of AGB1, GPA1 and AGG1/AGG2, and the conserved scaffold protein RACK1, which associates with MEKK1, MKK5, MPK3 and MPK6, but not MPK4. However, the G-proteins and RACK1 are dispensable for MPK3/MPK6 activation in response to flg22. The requirement for PrpL/ArgC catalytic activity implies the possible involvement of DAMPs in this regulation.

Ca²⁺-dependent protein kinases and MAPKs act in parallel or concert to mediate transcriptional reprogramming during PTI (Boudsocq *et al.*, 2010). PTI-inducible genes are classified into MAPK-specific, MAPK-dominant, synergistically regulated and CDPK-specific genes (Boudsocq *et al.*, 2010). CDPK- and MAPK-mediated transcriptional regulations

can be also antagonistic or complementary to each other. When [Ca²⁺]_{cyt} bursts are impaired with *aca8 aca10* mutation or iGluR inhibition, flg22 induction of CDPK-specific target genes is lowered but that of MAPK-specific target genes is enhanced (Kwaaitaal *et al.*, 2011; Frei dit Frey *et al.*, 2012). Identification of CDPK substrates will help elucidate the underlying mechanisms.

In rice, the small GTPase OsRac1 also provides a link between OsCERK1 and downstream signaling. The Rac GDP/GTP exchange factor 1 (OsRacGEF1) identifies another important substrate of OsCERK1 during chitin-triggered signaling (Akamatsu *et al.*, 2013). Phosphorylated OsRacGEF1 activates and involves OsRac1 to trigger ROS production through direct association with OsRBOHB, thereby mediating fungal resistance (Ono *et al.*, 2001; Wong *et al.*, 2007; Oda *et al.*, 2010; Akamatsu *et al.*, 2013). Experimental data suggest that two separate pathways, OsRLCK185-OsMAPKKK18/24-OsMKK4-OsMPK3/6 (corresponding to PBL27-MAPKKK5-MKK4/5-MPK3/6) and OsRacGEF1-OsRac1, mediate chitin signaling downstream of OsCERK1 (Kawasaki *et al.*, 2017; Wang *et al.*, 2017; Yamada *et al.*, 2017).

FUNCTIONAL DIVERGENCE AND SIGNAL INTEGRATION BETWEEN PRR PATHWAYS

Pattern recognition receptor pathways display substantial divergence in their sensitivity to biotic or abiotic perturbations. For instance, compared with EFR and XA21, FLS2 and PEPR1/PEPR2 better tolerate dysfunction of N-glycosylation-dependent ER quality control (QC; Tintor and Saijo, 2014). The ERQC pathway is also required for SOBIR1 function and autoimmunity in *bir1* and *bak1 serk4* plants, but not or less for BAK1 function or plant development (Sun *et al.*, 2014; Tintor and Saijo, 2014; Zhang *et al.*, 2015a; de Oliveira *et al.*, 2016). These findings suggest that an ERQC pathway is specifically employed for a large subset of cell surface defense regulators in plants. Moreover, BAK1-associated PRRs are also diverged in BAK1 or BIK1 requirements. FLS2 strictly requires BAK1, in contrast to EFR or PEPR1/PEPR2 that can promiscuously function with different SERK members (Roux *et al.*, 2011; Yamada *et al.*, 2016c). On the other hand, PEPR1/PEPR2 strictly require BIK1/PBL1 (Feng *et al.*, 2012; Yamada *et al.*, 2016c), while FLS2 is less vulnerable to the loss of them. Even within single PRR pathways, separate defense outputs often differentially require SERK or RLCK family members (Tang *et al.*, 2017). Hence, simultaneous activation of these PRR pathways that are diverged in rate-limiting steps is likely to increase the robustness of overall PTI signaling against pathogen assaults. This is relevant in natural infections, wherein plants are exposed to mixtures of MAMPs/DAMPs (Aslam *et al.*, 2009). Interestingly, substantial variations in flg22 or elf18 responsiveness are present across *A. thaliana* accessions, which are mostly uncorrelated with each other

and attributable to different genetic loci (Vetter *et al.*, 2016). It is conceivable that different PRRs have independently diversified their functions and/or regulations within or among natural plant populations, thereby facilitating plant adaptation to different habitats and microbiota thereof.

Pattern-triggered immunity is mounted in coordination between different PRR pathways and with other physiological processes. Additive or synergistic effects are often seen following simultaneous and/or sequential application of different patterns (Gust *et al.*, 2017). This is often the case for DAMPs: cutin, cellobiose, PIPs, Peps and RALF17 enhance MAMP-triggered defenses (Fauth *et al.*, 1998; Bartels *et al.*, 2013; Hou *et al.*, 2014; Souza *et al.*, 2017; Stegmann *et al.*, 2017). Conversely, flg22/elf18 pretreatment enhances Pep1-induced ROS production (Flury *et al.*, 2013). These data are compatible with the view that coincidental detection of DAMPs in addition to MAMPs is indicative of pathogenesis and strongly triggers host defense activation (Escamilla-Tilch *et al.*, 2013; Stuart *et al.*, 2013).

Importantly, functional interactions between different PRRs also occur in a layered manner. Pattern recognition often leads to further induction of DAMPs or their precursors (Gust *et al.*, 2017). More importantly, perturbations of MAMP signaling at different key steps are linked to the activation or sensitization of another defense layer at both the local and systemic levels. This resembles the indirect recognition mode of ETI activation, but differs from ETI in that specific effector recognition is not required (Couto and Zipfel, 2016; Yasuda *et al.*, 2017). For instance, BAK1 dysfunction is linked to de-repression of cell death and autoimmunity (He *et al.*, 2007; Kemmerling *et al.*, 2007; Wang *et al.*, 2011; de Oliveira *et al.*, 2016), via membrane-resident PRR-like regulators and NLRs (Yasuda *et al.*, 2017). Depletion (not catalytic inactivation) of BAK1 leads to sensitization of PEPR signaling toward SA-based defenses (Figure 2b; Yamada *et al.*, 2016c). This is critical for basal resistance against *Colletotrichum higginsianum*, which selectively depletes BAK1 during initial infection. However, *Pst* selectively targets a MAMP-induced active pool of BAK1 with the effector HopB1, without discernible counter-activation of the back-up defenses (Li *et al.*, 2016a). Likewise, dysfunction of key PTI components, including BIK1, RBOHD, the MPK4 cascade and the callose synthase PMR4, is linked to enhanced resistance against virulent pathogens (Nishimura *et al.*, 2003; Kim *et al.*, 2005; Zhang *et al.*, 2010, 2012; Laluk *et al.*, 2011; Kong *et al.*, 2012; Kadota *et al.*, 2014; Roux *et al.*, 2015).

Antagonistic effects are also seen in certain pattern combinations, for instance, between OG and flg22/elf18 in ROS and $[Ca^{2+}]_{cyt}$ bursts (Aslam *et al.*, 2009), between chitin and flg22 in MPK3/MPK6 activation (Yamada *et al.*, 2016b), and between RALF23/33/34 and flg22/elf18/chitin/RALF17 (Stegmann *et al.*, 2017). They may reflect competition for

signaling components or cellular resources. The biological significance and the underlying mechanisms require further investigation.

FER has pleiotropic roles in plant growth and development (Tavormina *et al.*, 2015), as the receptor for RALF peptides including immuno-stimulatory and immuno-repressible members (Figure 2a). Immuno-repressible RALFs act through FER to restrict ligand-induced FLS2/EFR-BAK1 association (Stegmann *et al.*, 2017). Reflecting this complexity, loss of FER enhances powdery mildew fungal resistance (Kessler *et al.*, 2010), but lowers MAMP-induced ROS production and *Pst* resistance (Stegmann *et al.*, 2017). Fine control of immune responses through RALF peptides of opposing functions resembles that of pro- and anti-inflammatory cytokines in mammals (Banchereau *et al.*, 2012). The MLD-CrRLK1L IOS1 constitutively associates with FLS2, EFR, BAK1 and CERK1, and promotes FLS2-BAK1 association, suggesting that IOS1 provides a scaffold for PRR complexes of different ectodomain classes (Yeh *et al.*, 2016). PRR homo-oligomerization or larger complex formation involving two or more PRRs may occur at such cell-surface scaffolds (Sun *et al.*, 2012). The glycosylphosphatidylinositol-anchored protein LLG1, a co-receptor for FER (Li *et al.*, 2015b), constitutively associates with FLS2/EFR to ensure FLS2 accumulation and signaling, but is dispensable for FLS2-BAK1 association (Shen *et al.*, 2017). Notably, in *llg1-3* allele, FLS2 signaling control is uncoupled from that of receptor accumulation. EFR signaling control is also uncoupled from EFR abundance control in weakly dysfunctional alleles of ERQC components (Lu *et al.*, 2009; Saijo *et al.*, 2009). Together with advances in PRR signaling mechanisms, it is interesting to address the causal relationship between receptor folding, localization and signaling functions on the cell surface scaffolds.

A well-documented tradeoff between immunity and growth also influences PTI signaling (Belkadir *et al.*, 2014). For instance, FLS2-mediated PTI signaling and BRI1-mediated BR signaling antagonize each other (Lozano-Duran and Zipfel, 2015). Among the shared signaling components between the two pathways, at least BAK1 and BSK1 are not the limiting factor for such tradeoff (Lozano-Duran *et al.*, 2013; Shi *et al.*, 2013). However, while BIK1 positively regulates FLS2 signaling, BIK1 negatively regulates BR signaling through phosphorylation of BRI1 (Lin *et al.*, 2013). Conversely, the BR-responsive TFs BZR1 and HBI1 attenuate PTI signaling (Lozano-Duran *et al.*, 2013; Fan *et al.*, 2014; Malinovsky *et al.*, 2014). Another example involves FLS2/EFR and the LRR-RLKs PSKs and PSY1R, which recognize growth-promoting Tyr-sulfated peptides PSKs and PSY1, respectively (Matsubayashi and Sakagami, 2006; Amano *et al.*, 2007). MAMP responses and bacterial and fungal resistance are negatively correlated with the dose of PSKs, PSY1R and/or Tyr protein sulfotransferase that activates PSKs (Igarashi *et al.*, 2012; Mosher *et al.*,

2013). Enforced PRR activation typically results in seedling growth inhibition (Boller and Felix, 2009). The secreted peptide CLE14 is perceived not only by the LRR-RLP CLV2 but also by PEPR2 under low-phosphate conditions, thereby inducing full differentiation of the root meristem and growth arrest of the primary root (Gutierrez-Alanis *et al.*, 2017). It is interesting to test possible influences of CLE14 on PEPR2-mediated defense signaling.

Signal attenuation mechanisms of PRRs are exploited by pathogens to subvert PTI. Fungal pathogens secrete functional homologs of RALF peptides to manipulate host physiology and immunity (Masachis *et al.*, 2016; Thynne *et al.*, 2017; Figure 2a). Their recognition by FER leads to extracellular alkalinization, which facilitates invasive hyphal growth and fungal virulence (Di Pietro *et al.*, 2001; Prusky and Yakoby, 2003), and also leads to the suppression of PTI (Masachis *et al.*, 2016).

PRR-MEDIATED CONTROL OF BENEFICIAL AND COMMENSAL MICROBES

Symbiotic microbes also exploit cross-regulations between host PRR pathways. There is a high degree of overlap between symbiotic and immune signaling (Antolin-Llovera *et al.*, 2014; Zipfel and Oldroyd, 2017). Similar constraints are imposed by the host immunity on mutualistic and pathogenic microbes, which include PTI, i.e. elicitor-inactive flg22 alleles in nitrogen-fixing rhizobacteria (Gomez-Gomez *et al.*, 1999) and flg22-induced suppression of their colonization (Lopez-Gomez *et al.*, 2012), and ETS/ETI, i.e. NLR-dependent rhizobacterial resistance (Yang *et al.*, 2010) and bacterial effector-mediated promotion or restriction of symbiosis (Marchetti *et al.*, 2010; Okazaki *et al.*, 2013; Tsukui *et al.*, 2013; Gourion *et al.*, 2015; Yasuda *et al.*, 2016). Given the shared host requirements between arbuscular mycorrhizal (AM) and root nodule symbioses (Bonfante and Genre, 2010; Oldroyd, 2013), the similar principles may broadly apply to mutualistic fungi (Plett and Martin, 2015).

Nodule symbiosis relies on host-specific recognition of microbial lipo-chitooligosaccharides (LCOs), designated NOD factors (Cullimore *et al.*, 2001; Bek *et al.*, 2010), via the LysM-RLK pairs LjNFR1-LjNFR5 and MtLYK3-MtNFP in *Lotus japonicus* and *Medicago truncatula*, respectively (Broghammer *et al.*, 2012). NOD factor perception induces symbiotic responses, and involves the LysM-RLK EPR3 that recognizes bacterial exopolysaccharides (EPS) to sustain rhizobial colonization (Kawaharada *et al.*, 2015). In addition, NOD factors or chitin oligomers (C4/C5) reduce flg22-induced defenses in soybean (Liang *et al.*, 2013). Notably, this PTI suppression also occurs in *A. thaliana* that lacks nodule and AM symbioses, through the LysM-RLK AtLYK3 (Figure 2c). In addition to the successful evasion from FLS2 recognition (Gomez-Gomez *et al.*, 1999), rhizobacteria induce FLS2/EFR degradation with NOD factors.

Lipo-chitooligosaccharides and chitin oligosaccharides from AM fungi trigger mycorrhization-associated responses (Maillet *et al.*, 2011; Genre *et al.*, 2013), through LjNFR1/MtLYK3, LjNFR5/MtNFP and related LysM-RLKs, although LjNFR5/MtNFP is dispensable for AM symbiosis (Zhang *et al.*, 2015b; Zipfel and Oldroyd, 2017). Notably, LjNFR1/MtLYK3 are orthologous to OsCERK1, which has a dual role in promoting AM symbiosis and chitin-induced immunity in rice. These CERK1 orthologs may act as a common co-receptor for mycorrhizal signals as well as chitin or PGNs. Consistent with this notion, evidence suggests a positive role for LjNFR1 and MtNFP in plant immunity (Nakagawa *et al.*, 2011; Rey *et al.*, 2013). The MLD-CrRLK1L SYMRK, a common requirement for nodule- and AM-symbioses (Stracke *et al.*, 2002), may provide a signaling scaffold. Remarkably, ligand-specific activation of defense or symbiosis via the shared (co)receptor also occurs in mammals: TLR2 mediates immune activation and suppression in response to pathogen-derived ligands and gut bacterial ligands, respectively (Round *et al.*, 2011). In the case of CERK1, in addition to the ligand specificities of the paired receptors (Bozsoki *et al.*, 2017), the Tyr-Ala-Gln/Arg motif in the CERK1 kinase domain provides a critical determinant for the competence of symbiotic signaling (Nakagawa *et al.*, 2011; Miyata *et al.*, 2014; Wang *et al.*, 2014). Further insight into this signal sorting will shed light on the decisive mechanisms that selectively activate symbiotic or immune signaling.

Phylogenetic studies propose that perception of mycorrhizal LCOs is an ancestral function for that of chitin or NOD factors (De Mita *et al.*, 2014). The loss of the micorrhization-associated CERK1 motifs in non-micorrhizal plant lineages may reflect the antagonistic relationship between symbiotic and defense signaling. Indeed, in *A. thaliana*, the CERK1-interacting (class VIII) LRR-RLK LIK1 negatively influences chitin/flg22-triggered defenses (Le *et al.*, 2014). Some filamentous pathogens exploit host symbiotic responses to promote root infection (Wang *et al.*, 2012; Rey *et al.*, 2015). These findings indicate that symbiotic microbes also contribute to the evolution of the host PTI systems.

In nature, healthy plants accommodate endophytic microbes without discernible defense activation or disease symptoms. Recent studies point to a role for host PTI in the selection and management of plant-associated microbial communities (Hacquard *et al.*, 2017). In *A. thaliana*, transcriptional reprogramming in response to an endophytic bacterium displays a large overlap with that of *Pst* challenge (Vogel *et al.*, 2016), highlighting the similarity in the host response between commensals and pathogens. The majority of the *A. thaliana* root-associated bacteria seem to lack elicitor-active flg22/elf18 alleles, suggesting that PTI evasion facilitates their colonization (Hacquard *et al.*, 2017). Indeed, PTI serves to prevent the overgrowth of endophytic leaf bacteria under high humidity (Xin *et al.*,

2016). Moreover, virulence effector expression and/or delivery are substantially reduced in the non-pathogenic mode of bacterial and fungal colonization (Mohr *et al.*, 2008; Cesbron *et al.*, 2015; Hacquard *et al.*, 2016). These findings are consistent with the idea that PTI plays a central role in the establishment and maintenance of plant-associated microbiomes.

INTERPLAY BETWEEN PTI AND ENVIRONMENTAL FACTORS

Environmental abiotic factors such as humidity, temperatures and nutrients drastically influence disease incidence and plant colonization by pathogenic and mutualistic microbes (Scholthof, 2007; Cheng *et al.*, 2013; Hacquard *et al.*, 2016; Wagner *et al.*, 2016; Xin *et al.*, 2016; Melotto *et al.*, 2017). Elucidation of functional links between plant immunity, microbial infection modes and environmental conditions offers new avenues in PTI studies. In light of the homeostatic nature of plant-associated microbial communities, it is conceivable that their alterations are sensed by PRRs as a signature of dis-homeostasis. This hypothesis is related to the question of how MAMP ligands integrated inside the microbial cells are presented to PRRs. In *A. thaliana*, PGN perception requires the host-derived hydrolase LYS1 that releases soluble elicitor-active ligands (Liu *et al.*, 2014). EF-Tu and CSPs are both secreted from the bacterial cytoplasm via an unknown process (Song *et al.*, 2009). It is important to determine how MAMP presentation is regulated, possibly depending on microbial growth status or environmental conditions. Of particular note, PRR-mediated defenses involve active control of the apoplastic environment, by releasing ROS (and scavengers), hydrolytic enzymes, enzyme inhibitors, anti-microbial proteins and compounds, which may lead to further generation of MAMPs and DAMPs.

The availability for crucial and often limiting soil nutrients such as phosphate or nitrogen also markedly influences plant interactions with pathogenic, beneficial and commensal microbes (Parniske, 2008; Vega *et al.*, 2015; Hacquard *et al.*, 2016; Castrillo *et al.*, 2017). It is possible that nutrient limitation represents signature of pathogenesis in plants (Mathioni *et al.*, 2011), as changes in metabolic states serve as DAMPs in metazoans (Gallo and Gallucci, 2013; Gust *et al.*, 2017). Nutrient status-dependent modulation of PTI and the molecular link between nutrient and microbial sensing will merit vigorous investigation.

Sugars produced by photosynthesis provide key nutrient sources for numerous plant-infecting microbes, and their apoplastic fluxes are tightly regulated via the coordination of cell-wall-bound invertases (cwlNs) and sucrose transporter proteins (STPs). PTI activation increases the uptake of hexoses (produced from sucrose via cwlNs) from the apoplast, in part through the elevated expression and BAK1-mediated phosphorylation of STP13 in the PRR

complexes (Yamada *et al.*, 2016a). This serves to deprive bacteria of metabolizable sugars, and also to suppress the type III secretion of virulence effectors. It is interesting to determine the extent to which apoplastic sugar control contributes to PTI-induced restriction of bacterial effector delivery (Crabill *et al.*, 2010) and also to the microbiome homeostasis described above.

CONCLUDING REMARKS AND PERSPECTIVES

Substantial advances have been made toward a deeper understanding of the mechanisms underlying PRR functions, from extracellular recognition of MAMPs/DAMPs to the regulation of immune signaling that culminates in pathogen resistance. It is also clear that an array of PRRs of distinct properties, not only in ligand recognition specificities but also in immune subfunctions and/or rate-limiting regulatory steps, becomes engaged and collectively contributes to robust PTI activation. However, it remains poorly understood how plants accommodate beneficial or commensal microbes while maintaining plant immunity to pathogenic microbes. Evidence indicates a critical role for the proper control of endophytic or mutualistic microbes in the establishment of beneficial associations with them (Lahrmann *et al.*, 2015; Hiruma *et al.*, 2016). Of note, the same microorganisms can be beneficial or pathogenic to the host, depending on biological contexts. In line with this, it is becoming apparent that plants employ a common set of defense components to control both pathogenic and non-pathogenic microbes. One important and challenging question involves how plants integrate MAMP/DAMP sensing with that of environmental cues to distinguish pathogens from non-pathogens in a context-dependent manner. Moreover, homeostatic control of plant-associated microbiome is likely to represent an important function of PRRs, which not only serve to sense but also to structure the proximal environment to the plant. Further excitement certainly awaits us in plant PRR studies.

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AUTHOR CONTRIBUTIONS

YS, EPL and SY wrote the paper.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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