

REVIEW PAPER

Receptor-mediated signalling in plants: molecular patterns and programmes

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Abstract

A highly evolved surveillance system in plants is able to detect a broad range of signals originating from pathogens, damaged tissues, or altered developmental processes, initiating sophisticated molecular mechanisms that result in defence, wound healing, and development. Microbe-associated molecular pattern molecules (MAMPs), damage-associated molecular pattern molecules (DAMPs), virulence factors, secreted proteins, and processed peptides can be recognized directly or indirectly by this surveillance system. Nucleotide binding-leucine rich repeat proteins (NB-LRR) are intracellular receptors and have been targeted by breeders for decades to elicit resistance to crop pathogens in the field. Receptor-like kinases (RLKs) or receptor like proteins (RLPs) are membrane bound signalling molecules with an extracellular receptor domain. They provide an early warning system for the presence of potential pathogens and activate protective immune signalling in plants. In addition, they act as a signal amplifier in the case of tissue damage, establishing symbiotic relationships and effecting developmental processes. The identification of several important ligands for the RLK-type receptors provided an opportunity to understand how plants differentiate, how they distinguish beneficial and detrimental stimuli, and how they co-ordinate the role of various types of receptors under varying environmental conditions. The diverse roles of extra- and intracellular plant receptors are examined here and the recent findings on how they promote defence and development is reviewed.

Key words: DAMPs, defence, development, MAMPs, RLK, RLP.

It is humankind's duty to respect all life, not only animals have feelings but also trees and plants.

Michel de Montaigne (French Philosopher and Writer. 1533–1592)

Introduction

Plants are immobile organisms, capable of receiving and responding to endogenous and exogenous signals. Discriminating beneficial or detrimental stimuli and initiating an appropriate response has emerged over a long evolutionary history. Endogenous stimuli, generally derived from stressed, damaged or malfunctioning cells (damage-associated molecular pattern molecules; DAMPs) (Lotze *et al.*,

2007) promote responses in both animal and plant cells. Exogenous stimuli comprise (i) pathogen- or microbe-associated molecular pattern molecules (PAMPs or MAMPs); virulence factors such as toxins (Friesen *et al.*, 2008), enzymes (Beliën *et al.*, 2006), and effector molecules (Kamoun, 2006; Tör, 2008), and (ii) non-microbial or abiotic stress inducers such as toxic compounds, pollutants, UV-B light, injury, or ozone.

Receptors that have an affinity within the low nM range for ligands (Ogawa *et al.*, 2008) exist across the individual kingdom, play a significant role in the detection of stimuli and the activation of programmes that direct development and defence. Animals rely on a limited number of Pattern Recognition Receptors (PRRs) including membrane bound Toll-like receptors (TLRs), cytoplasmic NOD-like proteins (NLRs), and RIG-I-like receptors (RLRs) for the activation of innate immunity (Lotze *et al.*, 2007), which promotes the

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development of an adaptive immune response. Plants, however, lack an adaptive immune system and rely solely on innate immune mechanisms. In addition, each plant cell is surrounded by the cell wall matrix that acts as a barrier as well as a nutrient source for would-be pathogens. Pathogens overcoming this barrier are under molecular surveillance by the plant cell, usually by receptors that reside at the cell surface or within the cytoplasm. Membrane bound plant PRRs include receptor-like kinases (RLKs) (Shiu and Bleeker, 2003) that have an extracellular domain such as leucine rich repeats (LRRs), lectin, lysine motif (LysM) or wall associated kinases (WAK) with a single transmembrane spanning region and a cytoplasmic kinase domain; receptor-like proteins (RLPs) (Wang G *et al.*, 2008) that possess an extracellular LRR domain and a C-terminal membrane anchor but lack the cytoplasmic kinase domain, and polygalacturonase inhibiting proteins (PGIP) (Di Matteo *et al.*, 2003) that have only an extracellular LRR domain. Intracellular plant PRRs are NB-LRR proteins (nucleotide binding site-leucine-rich repeats) (Meyers *et al.*, 2003) that are encoded by the so-called disease resistance genes (Fig. 1). Functions for several PRRs have been assigned for a number of plants including rice, tomato, and *Arabidopsis thaliana*. Recent findings have increased our understanding of the role of PRRs in diverse biological settings and the focus is on these more novel findings in the studies reviewed below.

RLP-type receptors rely on others to communicate the message

The number of RLP-type receptors predicted from genomic sequences varies according to the plant species studied. *Arabidopsis* has 57 while rice has more than 90 (Fritz-Laylin *et al.*, 2005; Wang G *et al.*, 2008). Some of these receptors also contribute to development or defence. For example, *Arabidopsis* CLAVATA2 (CLV2, AtRLP10) and Too Many Mouths (TMM, AtRLP17) proteins play a significant role in meristem and stomatal development, respectively (Jeong *et al.*, 1999; Nadeau and Sack, 2002). Conversely, in the tomato, the RLP-encoding *Cf* and *Ve* genes confer race specific resistance to *Cladosporium fulvum* and *Verticillium* spp isolates, respectively (Kawchuk *et al.*, 2001; Kruijt *et al.*, 2005). Recently, in collaboration with several other laboratories, homozygous T-DNA insertion lines have been identified for all the *Arabidopsis* RLP-encoding genes. These were subjected to a wide range of stress inducers including adapted and non-adapted pathogens, MAMPs, and abiotic stimuli. It has also been investigated if the mutation in these RLP-type receptors causes altered plant growth or development (Wang G *et al.*, 2008). A number of novel developmental phenotypes were observed for the *clv2* and *tmm* insertion mutants. These were slow growth, more rosette leaves, shorter stems, and late flowering for the *Atrlp10-1* T-DNA insertion line, and chlorosis and reduced growth for the *Atrlp17-1* and *tmm-1* mutants upon abscisic acid (ABA) treatment (Wang G *et al.*, 2008). *Atrlp30* and, in addition, *Atrlp18* were found to be more susceptible to

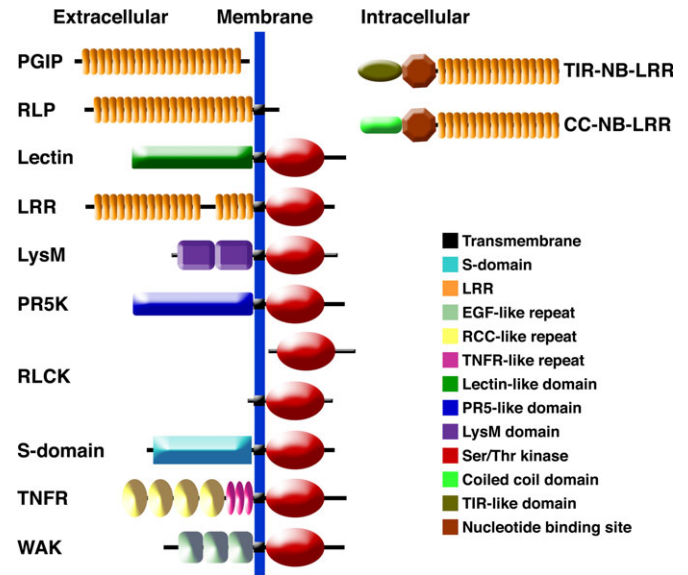


Fig. 1. Domain organization of typical extracellular and intracellular receptors in plants. Receptor proteins act as surveillance mechanisms that plants utilize to detect signals including microbe-associated molecular pattern molecules (MAMPs), damage-associated molecular pattern molecules (DAMPs), virulence factors, secreted proteins, or processed peptides. Extracellular PGIP, RLP, and RLK-type (classified according to their extracellular domains) receptors recognize these signals by direct or indirect interactions. Subsequent heterodimerization and phosphorylation events and possible conformational changes promote interactions with regulatory molecules such as RLCKs to distribute the message within the cell. Intracellular receptors, NB-LRR proteins, tend to recognize pathogen specific signals, most often effector molecules responsible for virulence, either directly or indirectly. Through conformational changes, they evoke the canonical signalling cascade and trigger resistance to the pathogen. Although NB-LRR-type receptors constitutively reside within the cytoplasm, they are also mobile and can translocate into the nucleus, chloroplast or mitochondria. RLCK-type proteins do not have extracellular domains, however, they are classified as RLKs. Abbreviations: PGIP, polygalacturonase inhibitor protein; RLP, receptor-like protein; RLK, receptor-like kinase; LRR, leucine-rich repeats; LysM, lysine motif; PR5K, pathogenesis related 5-like receptor kinase; RLCK, receptor-like cytoplasmic kinase; S-domain, self-incompatibility domain; TNFR, tumour necrosis factor receptor; WAK, wall associated kinase; NB, nucleotide binding; TIR, Toll and Interleukin 1 transmembrane receptor; CC, coiled-coil; EGF, epidermal growth factor; RCC, regulator of chromosome condensation; Ser/Thr, serine/threonine.

the non-adapted bacterial bean pathogen *Pseudomonas syringae* pv. *phaseolicola*. Similarly, it was confirmed that *AtRLP52* confers resistance to the non-adapted fungal pathogen *Erysiphe cichoracearum* (Ramonell *et al.*, 2005). Mutation in the *AtRLP41* gene leads to enhanced sensitivity to ABA, the plant hormone that integrates and fine-tunes abiotic and biotic stress-response signalling networks both in plants and animals (Asselbergh *et al.*, 2008; Nagamune *et al.*, 2008).

It is surprising that a biological role has been found for only a few of the defined *AtRLP* genes. This may be attributed to several factors; (i) the approach taken may have been biased towards the pathogens and mainly race-specific resistance may have been investigated, (ii) no insects or nematodes were included in our screen, (iii) the assay used may not have been sensitive enough to discover some of the roles that these proteins may play, (iv) these receptors may be involved in the recognition of DAMPs, which were not addressed in our study, or (v) there may be functional redundancy. In many ways, this is similar to the abundance of NLRs in the animal genome without known functions. The *Arabidopsis* genome harbours 24 loci containing a single *AtRLP* gene and 13 loci comprising multiple *AtRLP* genes (Fritz-Laylin *et al.*, 2005; Wang G *et al.*, 2008). Most homologous *AtRLP* genes reside at the same locus and the identification of a T-DNA insertion mutation in one gene may, because of the functional redundancy, not be enough to uncover the role of those genes. In addition, generation of double mutants by crossing individual T-DNA lines would be impossible. In order to overcome the problem of functional redundancy and further investigate the role of RLP-type proteins in *Arabidopsis*, Ellendorf *et al.* (2008) used an RNA interference (RNAi) approach and confirmed some of the phenotypes observed before. However, no new phenotype has been identified.

Since RLP-type receptors lack a cytoplasmic catalytic domain, one of the intriguing questions concerning RLP-mediated signalling is how the message is transmitted from the extracellular matrix to the intracellular space. Although RLP-type receptors in tomato recognize some pathogen effectors indirectly, it is not known how this message is internalized. The simplest explanation could be similar to that suggested for CLV2 and TMM where these RLPs may function in combination with RLK-type receptors CLAVATA1 and ERECTA, respectively, thus relaying the message (Waites and Simon, 2000; Shpak *et al.*, 2005). Although it has not been reported, it is tempting to speculate that AtRLP41 may also interact with an RLK such as RPK1 (Osakabe *et al.*, 2005) to regulate abscisic acid signalling in *Arabidopsis*.

RLK-type receptors are the primary communicators

RLK-type receptors comprise the largest family of receptors in plants. The *Arabidopsis thaliana* genome is predicted to contain >600 of such members while rice (*Oryza sativa*) has more than 1100 (Shiu *et al.*, 2004). The structural features of the extracellular domain of plant RLKs have been used to classify them into subfamilies including LRR, Lectin, self-incompatibility locus (S-Locus), lysine motif (LysM), wall-associated kinase (WAK), tumour necrosis factor receptor (TNFR), PR5-like receptor kinase (PR5K), and receptor-like cytoplasmic kinase (RLCK, Fig. 1). The majority of these RLKs phosphorylate serine or threonine

residues of the cytoplasmic kinase domains (Torii *et al.*, 2000; Walker, 2004; Narusaka *et al.*, 2007).

The diverse structures in the receptor domains suggest that there are likely to be several biological functions of these proteins (Table 1). The roles of some of these receptors in the perception of self or non-self molecules are described below.

Perception of MAMPs and virulence factors

Despite the large numbers of bacterial, viral, fungal, and oomycete plant pathogens, only limited numbers of MAMPs have been discovered. By contrast, hundreds of virulence factors including effectors from pathogens have been identified, and some of their functions have been uncovered. The reason for the discrepancy between the number of MAMPs and effectors could be attributed to (i) the conserved nature of MAMPs, (ii) the radical impact of effectors on agriculture where they suppress the immune system of the host plant, (iii) the amenability of effectors to rapid evolutionary change, and (iv) delivery of the effectors by the pathogen into plant cells, all of which may have contributed to identification and characterization of a wide range of effectors (Tör, 2008).

Chitin, xylanase, and ergosterol from fungi, transglutaminase (Pep-13) from oomycetes, lipopolysaccharide (LPS), flagellin (flg22), cold shock protein (CSP), and elongation factor Tu (EF-Tu) from bacteria have been studied as MAMPs in plant-pathogen interactions (Ingle *et al.*, 2006; Tör, 2008). FLS2 (Flagellin Sensing 2) and EFR (Ef-Tu receptor), LRR-RLKs, have been identified as receptors for flg22 and Ef-Tu, respectively, and their physical interactions with the receptors have been demonstrated (Zipfel *et al.*, 2004, 2006). The FLS2 and flg22 interaction has become one of the best-characterized systems in the activation of innate immunity in plants. Although flagellin has been portrayed as an invariant MAMP, data are accumulating to suggest that variation occurs within species as well as within pathovars, limiting the defence-eliciting activity of flagellin (Sun *et al.*, 2006). Therefore, further co-evolutionary studies in MAMP-receptor interactions are expected.

Race-specific pathogen-encoded virulence factors (effectors) are secreted from the bacterial pathogens into host cells via the Type III secretion system (TTSS), bind to a protein and thereby alter the activity of that protein (Mudgett and Staskawicz, 1998). This finding helped the establishment of a common link between the mechanisms of pathogenicity of the plant and animal pathogens. In addition, it has also brought a change in our thinking. Rather than killing the host cell from outside, pathogens deliver effector proteins as virulence factors into the host cell to adapt to a particular niche (Medzhitov, 2007) and manipulate it for its own purpose (Xiao *et al.*, 2007). When these effectors are recognized by the cytoplasmic receptors (described below), they are termed avirulence (AVR) proteins (Jones and Dangl, 2006). Although there are studies on apoplastic effectors from *Cladosporium fulvum* (syn. *Passalora fulva*) (Kruijt *et al.*, 2005), the majority of

Table 1. Some examples of extracellular and intracellular receptors in plant defence and development

Type	PRR	Full name	Proposed role	Ligands (if known)	References
PGIP	PGIP	Polygalacturanase inhibiting proteins	Defence	Polygalacturonases/pectin	Di Matteo <i>et al.</i> , 2003
RLP	AtRLP41		ABA sensitivity		Wang G <i>et al.</i> , 2008
	AtRLP30		Defence		Wang G <i>et al.</i> , 2008
RLK ^a	Cf-9	<i>Cladosporium fulvum</i> resistance	Defence		Kruijft <i>et al.</i> , 2005
	CLV2	CLAVATA 2	Development	CLV3 ^d	Ogawa <i>et al.</i> , 2008
	TMM	TOO MANY MOUTHS	Development		Nadeau <i>et al.</i> , 2002
	BAK1	BRI1-associated kinase 1	Defence/development		Nam and Li, 2002
	BRI1	Brassinosteroids insensitive 1	Development	Brassinosteroids	He <i>et al.</i> , 2000
	CLV1	CLAVATA 1	Development	CLV3	Ogawa <i>et al.</i> , 2008
	CR4	CRINKLY4	Development		Becraft <i>et al.</i> , 1996
	DIPM1-4	DspA/E-interacting proteins of <i>Malus×domestica</i>	Disease ^c	DspA/E	Meng <i>et al.</i> , 2006
	EFR	Ef-Tu receptor	Defence	Ef-Tu	Zipfel <i>et al.</i> , 2006
	ER	ERECTA	Development		Shpak <i>et al.</i> , 2005
	FLS2	Flagellin Sensing 2	Defence	Flagellin	Zipfel <i>et al.</i> , 2004
	LecRK1	Lectin receptor kinase 1	Unknown		Herve <i>et al.</i> , 1996
	NORK	Nodulation receptor kinase	Symbiosis		Endre <i>et al.</i> , 2002
	NFR1, NFR5	Nod-factor receptor kinase	Symbiosis		Madsen <i>et al.</i> , 2003
	PEPR1	atPep1 receptor	Defence	Atpep1	Yamaguchi <i>et al.</i> , 2006
	PBS1 ^b	<i>avrPphB</i> susceptible	Defence		Swiderski and Innes, 2001
PR5K	Pathogenesis related 5 kinase	Defence		Wang <i>et al.</i> , 1996	
PSKR	Phytosulphokine receptor	Development	Phytosulphokine	Matsubayashi <i>et al.</i> , 1996	
SRK	S-locus receptor kinase	Development		Stein <i>et al.</i> , 1991	
SYMRK	Symbiosis receptor-like kinase	Symbiosis		Stracke <i>et al.</i> , 2002	
WAK1	Wall-associated kinase	Defence/development		He <i>et al.</i> , 1996	
NB-LRR	L5, L6, L7	<i>Linum usitatissimum</i> rust resistance	Defence	AvrL567	Dodds <i>et al.</i> , 2006
	N	<i>Nicotiana glutinosa</i> virus resistance	Defence	p50	Ueda <i>et al.</i> , 2006
	Pi-Ta	<i>Oryza sativa pi-ta</i> protein	Defence	AVR-Pita	Jia <i>et al.</i> , 2000

^a For domains and classification of RLKs, see text and Fig. 1.

^b PBS1 does not have any extracellular domain and has been classified as receptor-like cytoplasmic kinase (RLCK).

^c Interaction of DspA/E and DIPM1-4 induce disease instead of defence. Interaction is with the kinase domain rather than the extracellular receptor domain.

^d CLV3; CLAVATA3.

effectors from this pathogen are recognized indirectly by RLP-type receptors (Shabab *et al.*, 2008). The rice LRR-RLK-type protein Xa21 functions similarly to cytoplasmic receptors in that they confer race-specific resistance to secreted molecules including in this instance the AvrXa21 from *Xanthomonas oryzae*, the causal agent of bacterial blight disease of rice (Lee *et al.*, 2008).

The effector protein (Dsp)A/E of *Erwinia amylovora* (causal agent of fire blight on apple, pear, and other Rosaceae plants) is absolutely required for its pathogenicity (Gaudriault *et al.*, 1997). It is delivered by TTSS inside the cell and interacts specifically and directly with the cytoplasmic kinase domain of at least four different LRR-RLK-type receptors, DIPM1 to 4, (DspA/E-interacting proteins of *Malus×domestica*) to induce disease (Meng *et al.*, 2006). This finding suggests that (i) these putative receptors may act as compatibility factors or (ii) pathogens may use their effectors to target these receptors to block the signal transmission and evade recognition. Recent findings with the AvrPto and AvrPtoB from *Pseudomonas syringae* support the anti-receptor strategy of the pathogens (Xiang *et al.*, 2008). Shan *et al.* (2008) demonstrated that when expressed in *Arabidopsis*, AvrPto and AvrPtoB interact with

BAK1 (brassinosteroid-receptor 1 associated kinase 1) (He *et al.*, 2007), which acts as an adaptor or co-receptor with FLS2 and EFR (Chinchilla *et al.*, 2007; Heese *et al.*, 2007), and interferes with the ligand promoted association of FLS2 with BAK1.

Perception of DAMPs

Mechanical injury, insect or herbivore damage releases specific signals, which have been known as wound-inducing proteins in plants. However, these molecules are also released during programmed cell death (PCD), or hypersensitive reaction (HR), or trailing necrosis, the term ‘damage-associated molecular pattern molecules (DAMPs)’ would be more precise. DAMPs are generated at the damage site and signals arising from them are delivered to other undamaged parts of the plant in a systemic manner. PRRs at the cell surface of the healthy cells can then recognize these DAMPs in a similar fashion to MAMPs and activate the defence signalling cascade.

DAMP molecules differ according to the plant species investigated. For example, systemin is only found in solanaceous species such as tomato. In damaged tomato

leaf, systemin, an 18-aa peptide, derived from a 200-aa precursor protein, can travel over long distances activating a defence response (Pearce *et al.*, 1991; Scheer and Ryan, 2002). Systemin binds the LRR-RLK, SR160/BRI1 (Systemin receptor 160kDa/ brassinosteroid insensitive 1), however, SR160/ BRI1 mutant plants are still capable of eliciting a systemin induced defence response (Holton *et al.*, 2007), suggesting that additional systemin receptor(s) are present. Indeed, other systemin binding proteins including SBP50 (systemin binding protein 50 kDa) have been identified (Schaller and Ryan, 1994). BRI1 also binds and participates in brassinosteroid (BR) signalling through BRI1, in a synergistic interaction with other LRR-RLKs including BAK1 and BKK1 (BAK1-LIKE1) (He *et al.*, 2000). It should be noted that BAK1 and BKK1 have been reported to have dual physiological roles: positively regulating a BR-dependent plant growth pathway, and negatively regulating a BR-independent cell-death pathway (Kemmerling *et al.*, 2007; He *et al.*, 2007).

Arabidopsis has six PROPEP proteins that are precursors for peptides that act as DAMPs. AtPep1, a 23-aa peptide derived from PROPEP1, can be found in the apoplast. PEPR1 is an LRR-RLK-type PRR, which directly interacts with AtPep1 and initiates defence signalling (Yamaguchi *et al.*, 2006). Interestingly, the PROPEP proteins can be induced by their own peptides, MAMPs such as flg22 and elf18, salicylic acid, jasmonic acid or ethylene. AtPep1 has been suggested to act as a signal amplification loop for the innate immune response in plants (Ryan *et al.*, 2007). In the animal systems, High mobility group box1 (HMGB1) protein is the best-characterized DAMP molecule and binds to receptors (TLR2/4, RAGE) on the cell membrane or inside the cell (TLR9) and triggers innate immunity (Lotze *et al.*, 2007). There are several orthologues of HMGB1 in *Arabidopsis* but it is not known if they activate the immune system in plants by binding to the PRRs, in a similar fashion to that observed in animals. Their role in regulating autophagy in response to stressors is also under investigation.

Perception of developmental cues

Brassinosteroids (BRs) are one of the best-characterized examples of hormones in plants that regulate growth processes such as cell expansion, cell elongation, vascular differentiation, pollen tube formation, and acceleration of senescence (Gendron *et al.*, 2007) and the receptors, BRI, BAK1, and BKK1 involved in the BR signalling (Karlova *et al.*, 2006; Albrecht *et al.*, 2008) are discussed above.

Plant cells can be dedifferentiated and proliferate *in vitro* as totipotent cells, called calli. Phytosulphokine (PSK), a five-residue peptide, is the growth factor that induces the dedifferentiation and callus growth with the help of auxin and cytokinin, two well-studied hormones in plants that regulate root and shoot formation (Matsubayashi and Sakagani, 1996). PSK triggers cell proliferation by binding directly to an LRR-RLK-type receptor, PSKR (phytosulphokine receptor) (Matsubayashi *et al.*, 2002).

Mutation in the *Arabidopsis CLAVATA1 (CLV1)* gene causes a variety of morphological phenotypes, including club-shaped gynoecia. Mutation in two other genes, *CLV2* and *CLV3* also produce similar phenotypes. *CLV1* is an LRR-RLK, *CLV2* is an LRR-RLP and *CLV3* is a secreted protein that acts as a ligand for *CLV1*. Interactions of these three proteins regulate the size of the meristem (Clark *et al.*, 1997; Fletcher *et al.*, 1999). Recently, a novel receptor kinase, *CORYNE*, has been shown to act synergistically with *CLV2* but independently of *CLV1* to transmit *CLV3* signalling (Miwa *et al.*, 2008; Muller *et al.*, 2008).

INFLORESCENCE DEFICIENT IN ABSCISSION (*IDA*) is another secreted protein that acts as a potential ligand for LRR-RLK-type receptors, *HAESA (HAE)*, and *HAESA-LIKE2 (HSL2)* in *Arabidopsis*. These receptors and the putative ligand are involved in the regulation of abscission of the floral organs (Cho *et al.*, 2008; Stenvik *et al.*, 2008).

There are other RLK-type receptors such as members of *Arabidopsis ERECTA* (Shpak *et al.*, 2005) and *STRUBBELIG* family proteins (Eyüboğlu *et al.*, 2007) that are involved in plant development. However, the ligands for these receptors are not yet known. Their roles and orthologues in other plants have been reviewed extensively by others (Morillo and Tax, 2006).

Recognition of signals that determine self-incompatibility

Many plants have the capacity to recognize pollen from close relatives, and reject these nominally to prevent inbreeding and maintain genetic diversity within a species, a system that is known as self-incompatibility (SI). In *Brassica* species, a soluble extracellular protein, the S-locus glycoprotein (SLG), and a membrane bound receptor SRK (S-locus receptor kinase), an RLK with an S-locus extracellular domain at the stigma surface have been identified (Stein *et al.*, 1991; Yamakawa *et al.*, 1994). Further studies led to the identification of SCR/SP11 (S-locus cysteine rich protein or S-locus protein 11) that is expressed predominantly in the anther and interacts directly with SRK resulting in SI (Shiba *et al.*, 2001). When pollen and pistil share the same allele, a ligand–receptor interaction induces a signalling cascade in the female papillar cell, which then signals back to the pollen and inhibits its germination. Some other S-locus RLKs are up-regulated in response to pathogen recognition, MAMPs, and wounding, indicating a similarity between perception of self and non-self molecules and activation of downstream signalling (Sanabria *et al.*, 2008).

Perception of beneficial microbes

Nitrogen is essential for plant growth and certain plant species such as legumes can utilize gaseous N₂ in the atmosphere in symbiosis with nitrogen-fixing bacteria of the Rhizobiaceae family. In the interaction between plants and nitrogen-fixing bacteria, flavonoid compounds from

plants attract rhizobial bacteria, which are triggered to produce nodulation (Nod) factors, lipochito-oligosaccharides. When the plant detects this signal, a series of events, especially in root development, occur, leading to the encapsulation of bacteria and the formation of nodules where the bacteria fix nitrogen in return for nutrients derived from the plant (Trevaskis *et al.*, 2002). Receptors that play a significant role in the regulation of nodule formation include LRR-RLK-type receptors such as the nodulation receptor kinase (NORK) in alfalfa (Endre *et al.*, 2002), symbiosis receptor-like kinase (SYMRK) in lotus and pea (Stracke *et al.*, 2002), and hypernodulation receptor (HAR1) in lotus (Nishimura *et al.*, 2002), and LysM-RLK-type receptors, such as Nod-factor receptor kinase (NFR1 and NFR5) in lotus (Madsen *et al.*, 2003; Radutoiu *et al.*, 2003).

What happens to the MAMP-activated immunity in symbiotic relations? Lipopolysaccharide (LPS), a MAMP that triggers innate immunity in animals and plants, plays a positive role in the establishment of symbiosis by suppressing the oxidative burst. Alterations in the LPS structure result in delayed nodulation, abortion of infection threads, formation of non-fixing nodules, and the induction of plant defence reactions (Tellström *et al.*, 2007), suggesting a need for bacterial LPS for the bacteria to form its symbiotic relation with the host plant. Not a dissimilar response is noted in the setting of NK (Natural killer) recognition of paternal allogantigens in implantation of the mammalian fetus (Eastabrook *et al.*, 2008).

Conveying the message: ligand binding activates RLKs

Since there are several RLKs with known ligands, the question as to how these receptors are activated and transmit the message from the extracellular space into the cell arises. From recent studies on several RLK-type PRRs described above, it has become clear that ligand binding (i) promotes heterodimerization among members of CLAVATA, ERECTA, and BRI family proteins as well as between FLS2 and BAK1; (ii) increases activating phosphorylation of these proteins; (iii) promotes conformational changes that generate docking sites for adaptor molecules such as BAK1 for BRI1; (iv) promotes phosphorylation of residues at the juxta-membrane domain, the region between kinase domain and the transmembrane, which act as docking sites for downstream signalling or regulatory molecules such as membrane bound receptors including cytoplasmic kinases (RLCK), which in turn may also promote phosphorylation (Waites and Simon, 2000; Shiu *et al.*, 2003; Russinova *et al.*, 2004; Shpak *et al.*, 2005; Wang *et al.*, 2005; Wang X *et al.*, 2008; Karlova *et al.*, 2008). Once cytoplasmic signalling molecules, such as Rho GTPase in the case of CLV1, receive the message from RLKs, it is distributed further within the cell via a canonical MAPK signalling cascade (Trotochaud *et al.*, 2004).

It should be noted that these receptors are under the strict regulation of phosphorylation inhibitors, phosphatases such as KAPP (kinase associated protein phosphatase), endocyto-

sis, ubiquitin-mediated protein degradation, and possibly of autophagy (Tör *et al.*, 2003; Robatzek *et al.*, 2006; Wang *et al.*, 2006; Park *et al.*, 2008; Trujillo *et al.*, 2008; Todde *et al.*, 2009). Once the message is conveyed, they are down-regulated by some of the same mechanisms.

Intracellular receptors

Plant NB-LRR proteins (nucleotide-binding site-leucine-rich repeats) have been studied in detail and some members are well characterized as immune receptors. They are traditionally referred to as disease resistance proteins or *R*-genes and form the bridge between molecular cell biology in plant immunity and plant breeding for agriculture. They form one of the largest gene families in plants. There are more than 140 predicted members in *Arabidopsis* and more than 400 in rice. Their gene products promote resistance to viral, bacterial, fungal, and oomycete pathogens. Their tripartite structure is very similar to the mammalian CLR, a central nucleotide binding site, carboxyl LRR domain (hence NB-LRR), and a variable TIR or coiled-coil N-terminal domain (DeYoung *et al.*, 2008).

NB-LRR proteins recognize pathogen-specific signals, most often effector molecules responsible for virulence, either directly or indirectly. Recognition of either modified host protein or a pathogen-derived protein leads to conformational changes in the amino-terminal and LRR domains of these receptor proteins. Such conformational alterations promote the exchange of ADP for ATP by the NB domain, which activates a signalling cascade in turn, promoting resistance to the pathogen (DeYoung and Innes, 2006). Although these proteins reside within the cytoplasm, they are also mobile and can translocate into the nucleus, chloroplast or mitochondria. For example, barley MLA, tobacco N, and *Arabidopsis* RPS4 translocate into the nucleus. In such cases, it has been proposed that these NB-LRR proteins de-repress basal defence by associating with WRKY transcription factors in the nucleus (Shen *et al.*, 2007).

Activation of defence responses by extracellular and intracellular PRRs have been defined as primary and secondary immune responses, respectively (Shen and Schulze-Lefert *et al.*, 2007). In both cases, a localized hypersensitive response (HR, a kind programmed cell death of the infected cell) has been reported (Naito *et al.*, 2008), and the main differences between these responses have been reviewed (Jones and Dangl, 2006; Tör, 2008). Recent studies demonstrated that individual effectors could be recognized by the same intracellular receptor, especially by those that recognize incoming effectors indirectly (de Wit, 2007). In addition, not only do some NB-LRR proteins act additively to provide a resistance response (Marathe and Dinesh-Kumar, 2003; Sinapidou *et al.*, 2004), but also some NB-LRR type receptors are required for RLP-mediated defence responses (Gabriëls *et al.*, 2007).

Nearly all NB-LRRs proteins have been reported to function as disease resistance proteins, however, exceptions

do occur. Recently, Sweat *et al.* (2008) reported that *LOVI* (*LOCUS ORCHESRATING VICTORIN EFFECTSI*), a CC-NB-LRR gene, shows natural and induced variation and confers victorin sensitivity and disease susceptibility in *Arabidopsis*, indicating that the NB-LRR genes could also have diverse roles.

NB-LRR proteins are also strictly regulated by mechanisms including repression by the chromosomal structure, feedback amplification from the receptor protein, and repression by their negative regulators at the transcriptional level (Li *et al.*, 2007) or ubiquitin-mediated degradation (Tör *et al.*, 2003).

Conclusions

Plants have many proteins that act as pattern recognition receptors (PRRs) at the cell surface or within the cytoplasm. They have a crucial role in the plant's life and its response to stress elicited by micro-organisms or damage; the means of transmitting the signal is exceedingly complex and equally fascinating. Whether primary or secondary defence responses, wound healing or developmental processes ensue, the outcome is dictated by the presence and type of exogenous and endogenous inducers including MAMPs, DAMPs, effectors, secreted proteins, and processed peptides. Despite large numbers of receptor proteins having been identified at the cell surface, only a small numbers of ligands have been identified. Recent studies on effectors that are delivered inside the cell uncovered a vast number of putative virulence molecules. Although a few examples of effectors that are delivered into the apoplast are known, more information on these types of molecules are needed to develop a clearer picture of their recognition at the cell surface.

Homo- or hetero-dimerization of RLK-type receptors to initiate an appropriate response is currently known for only a few members and additional candidates are expected to be identified. Similarly, the mobility of NB-LRR proteins within several intracellular locations brought attention to the convergence of MAMP-triggered and effector-triggered immunity.

DAMPs have been regarded as wound-inducing proteins in plants and have not received the same attention as their counterparts in animal systems. Although, plants can easily dispense with dying or dead cells, there is still a lot to learn from the process of responding to damage or injury and there may be ancient prototypical recognition systems such as the hydrophobic portions of molecules (Hyppos) that unify some aspects of plant and animal immunity (Seong and Matzinger, 2004).

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References

- Albrecht C, Russinova E, Kemmerling B, Kwaaitaal M, de Vries SC.** 2008. Arabidopsis SOMATIC EMBRYOGENESIS RECEPTOR KINASE proteins serve brassinosteroid-dependent and -independent signaling pathways. *Plant Physiology* **14**, 611–619.
- Asselbergh B, De Vleeschauwer D, Höfte M.** 2008. Global switches and fine-tuning-ABA modulates plant pathogen defence. *Molecular Plant-Microbe Interactions* **21**, 709–719.
- Becraft PW, Stinard PS, McCarty DR.** 1996. CRINKLY4: A TNFR-like receptor kinase involved in maize epidermal differentiation. *Science* **273**, 1406–1409.
- Beliën T, Van Campenhout S, Robben J, Volckaert G.** 2006. Microbial endoxylanases: effective weapons to breach the plant cell-wall barrier or, rather, triggers of plant defense systems? *Molecular Plant-Microbe Interactions* **19**, 1072–1081.
- Chinchilla D, Zipfel C, Robatzek S, Kemmerling B, Nurnberger T, Jones JD.** 2007. A flagellin-induced complex of the receptor FLS2 and BAK1 initiates plant defence. *Nature* **448**, 497–500.
- Cho SK, Larue CT, Chevalier D, Wang H, Jinn TL, Zhang S, Walker JC.** 2008. Regulation of floral organ abscission in *Arabidopsis thaliana*. *Proceedings of the National Academy of Sciences, USA* **105**, 15629–15634.
- Clark SE, Williams RW, Meyerowitz EM.** 1997. The *CLAVATA1* gene encodes a putative receptor kinase that controls shoot and floral meristem size in *Arabidopsis*. *Cell*, **89**, 575–585.
- De Wit PJGM.** 2007. How plants recognize pathogens and defend themselves. *Cell and Molecular Life Sciences* **64**, 2726–2732.
- DeYoung BJ, Innes RW.** 2006. Plant NBS-LRR proteins in pathogen sensing and host defence. *Nature Immunology* **7**, 1243–1249.
- Di Matteo A, Federici L, Mattei B, Salvi G, Johnson KA, Savino C, De Lorenzo G, Tsernoglou D, Cervone F.** 2003. The crystal structure of polygalacturonase-inhibiting protein (PGIP), a leucine-rich repeat protein involved in plant defence. *Proceedings of the National Academy of Sciences, USA* **100**, 10124–10128.
- Dodds PN, Lawrence GJ, Catanzariti AM, Teh T, Wang CI, Ayliffe MA, Kobe B, Ellis JG.** 2006. Direct protein interaction underlies gene-for-gene specificity and coevolution of the flax resistance genes and flax rust avirulence genes. *Proceedings of the National Academy of Sciences, USA* **103**, 8888–8893.
- Eastabrook G, Hu Y, von Dadelszen P.** 2008. The role of decidual natural killer cells in normal placentation and in the pathogenesis of preeclampsia. *Journal of Obstetrics and Gynaecology Canada* **30**, 467–476.

- Ellendorff U, Zhang Z, Thomma BPHJ.** 2008. Gene silencing to investigate the roles of receptor-like proteins in *Arabidopsis*. *Plant Signaling and Behaviour* **3**, 893–896.
- Endre G, Kereszt A, Kevei Z, Mihacea S, Kaló P, Kiss GB.** 2002. A receptor kinase gene regulating symbiotic nodule development. *Nature* **417**, 962–966.
- Eyüboğlu B, Pfister K, Haberer G, Chevalier D, Fuchs A, Mayer KF, Schneitz K.** 2007. Molecular characterization of the STRUBBELIG-RECEPTOR FAMILY of genes encoding putative leucine-rich repeat receptor-like kinases in *Arabidopsis thaliana*. *BMC Plant Biology* **7**, 16.
- Fletcher JC, Brand U, Running MP, Simon R, Meyerowitz EM.** 1999. Signaling of cell fate decisions by CLAVATA3 in *Arabidopsis* shoot meristems. *Science* **283**, 1911–1914.
- Friesen TL, Faris JD, Solomon PS, Oliver RP.** 2008. Host-specific toxins: effectors of necrotrophic pathogenicity. *Cell Microbiology* **10**, 1421–1428.
- Fritz-Laylin LK, Krishnamurthy N, Tör M, Sjölander KV, Jones JDG.** 2005. Phylogenomic analysis of the receptor-like proteins of rice and *Arabidopsis* reveals four major super-clades of resistance proteins and new candidate developmental genes. *Plant Physiology* **138**, 611–623.
- Gabriëls SH, Vossen JH, Ekengren SK, et al.** 2007. An NB-LRR protein required for HR signalling mediated by both extra- and intracellular resistance proteins. *The Plant Journal* **50**, 14–28.
- Gaudriault S, Malandrin L, Paulin JP, Barny MA.** 1997. DspA, an essential pathogenicity factor of *Erwinia amylovora* showing homology with AvrE of *Pseudomonas syringae*, is secreted via the Hrp secretion pathway in a DspB-dependent way. *Molecular Microbiology* **26**, 1057–1069.
- Gendron JM, Wang ZY.** 2007. Multiple mechanisms modulate brassinosteroid signaling. *Current Opinion in Plant Biology* **10**, 436–441.
- He K, Gou X, Yuan T, Lin H, Asami T, Yoshida S, Russell SD, Li J.** 2007. BAK1 and BKK1 regulate brassinosteroid-dependent growth and brassinosteroid-independent cell-death pathways. *Current Biology* **17**, 1109–1115.
- He Z, Wang ZY, Li J, Zhu Q, Lamb C, Ronald P, Chory J.** 2000. Perception of brassinosteroids by the extracellular domain of the receptor kinase BRI1. *Science* **288**, 2360–2363.
- He ZH, Fujiki M, Kohorn BD.** 1996. A cell wall-associated, receptor-like protein kinase. *Journal of Biological Chemistry* **271**, 19789–19793.
- Heese A, Hann DR, Gimenez-Ibanez S, Jones AM, He K, Li J, Schroeder JI, Peck SC, Rathjen JP.** 2007. The receptor-like kinase SERK3/BAK1 is a central regulator of innate immunity in plants. *Proceedings of the National Academy of Sciences, USA* **104**, 12217–12222.
- Hervé C, Dabos P, Galaud JP, Rougé P, Lescure B.** 1996. Characterization of an *Arabidopsis thaliana* gene that defines a new class of putative plant receptor kinases with an extracellular lectin-like domain. *Journal of Molecular Biology* **258**, 778–788.
- Holton N, Caño-Delgado A, Harrison K, Montoya T, Chory J, Bishop GJ.** 2007. Tomato BRASSINOSTEROID INSENSITIVE1 is required for systemin-induced root elongation in *Solanum pimpinellifolium* but is not essential for wound signaling. *The Plant Cell* **19**, 1709–1717.
- Ingle RA, Carstens M, Denby KJ.** 2006. PAMP recognition and the plant–pathogen arms race. *Bioessays* **28**, 880–889.
- Jia Y, McAdams SA, Bryan GT, Hershey HP, Valent B.** 2000. Direct interaction of resistance gene and avirulence gene products confers rice blast resistance. *EMBO Journal* **19**, 4004–4014.
- Jeong S, Trotochaud AE, Clark SE.** 1999. The *Arabidopsis* CLAVATA2 gene encodes a receptor-like protein required for the stability of the CLAVATA1 receptor-like kinase. *The Plant Cell* **11**, 1925–1933.
- Jones JD, Dangl JL.** 2006. The plant immune system. *Nature* **444**, 323–329.
- Kamoun S.** 2006. A catalogue of the effector secretome of plant pathogenic oomycetes. *Annual Review of Phytopathology* **44**, 41–60.
- Karlova R, Boeren S, Russinova E, Aker J, Vervoort J, de Vries S.** 2006. The *Arabidopsis* SOMATIC EMBRYOGENESIS RECEPTOR-LIKE KINASE1 protein complex includes BRASSINOSTEROID-INSENSITIVE1. *The Plant Cell* **18**, 626–638.
- Karlova R, Boeren S, van Dongen W, Kwaaitaal M, Aker J, Vervoort J, de Vries S.** 2008. Identification of *in vitro* phosphorylation sites in the *Arabidopsis thaliana* somatic embryogenesis receptor-like kinases. *Proteomics* **12**, 24.
- Kawchuk LM, Hachey J, Lynch DR, et al.** 2001. Tomato *Ve* disease resistance genes encode cell surface-like receptors. *Proceedings of the National Academy of Sciences, USA* **98**, 6511–6515.
- Kemmerling B, Schwedt A, Rodriguez P, et al.** 2007. The BRI1-associated kinase 1, BAK1, has a brassinolide-independent role in plant cell-death control. *Current Biology* **17**, 1116–1122.
- Kruijt M, Kip DJ, Joosten MH, Brandwagt BF, de Wit PJ.** 2005. The Cf-4 and Cf-9 resistance genes against *Cladosporium fulvum* are conserved in wild tomato species. *Molecular Plant–Microbe Interactions* **18**, 1011–1021.
- Lee SW, Jeong KS, Han SW, Lee SE, Phee BK, Hahn TR, Ronald P.** 2008. The *Xanthomonas oryzae* pv. *oryzae* PhoPQ two-component system is required for AvrXA21 activity, hrpG expression, and virulence. *Journal of Bacteriology* **190**, 2183–2197.
- Li Y, Yang S, Yang H, Hua J.** 2007. The TIR-NB-LRR gene *SNC1* is regulated at the transcript level by multiple factors. *Molecular Plant–Microbe Interactions* **20**, 1449–1456.
- Lotze MT, Zeh HJ, Rubartelli A, Sparvero LJ, Amoscato AA, Washburn NR, Devera ME, Liang X, Tör M, Billiar T.** 2007. The grateful dead: damage-associated molecular pattern molecules and reduction/oxidation regulate immunity. *Immunology Review* **220**, 60–81.
- Madsen EB, Madsen LH, Radutoiu S, et al.** 2003. A receptor kinase gene of the LysM type is involved in legume perception of rhizobial signals. *Nature* **425**, 637–640.
- Marathe R, Dinesh-Kumar SP.** 2003. Plant defence: one post, multiple guards? *Molecular Cell* **11**, 284–286.
- Matsubayashi Y, Sakagami Y.** 1996. Phytosulfokine, sulfated peptides that induce the proliferation of single mesophyll cells of *Asparagus officinalis* L. *Proceedings of the National Academy of Sciences, USA* **93**, 7623–7627.

- Matsubayashi Y, Ogawa M, Morita A, Sakagami Y.** 2002. An LRR receptor kinase involved in perception of a peptide plant hormone, phytosulfokine. *Science* **296**, 1470–1472.
- Medzhitov R.** 2007. Recognition of microorganisms and activation of the immune response. *Nature* **449**, 819–826.
- Meng X, Bonasera JM, Kim JF, Nissinen RM, Beer SV.** 2006. Apple proteins that interact with DspA/E, a pathogenicity effector of *Erwinia amylovora*, the fire blight pathogen. *Molecular Plant–Microbe Interactions* **19**, 53–61.
- Meyers BC, Kozik A, Griego A, Kuang H, Michelmore RW.** 2003. Genome-wide analysis of NBS-LRR-encoding genes in *Arabidopsis*. *The Plant Cell* **15**, 809–834.
- Miwa H, Betsuyaku S, Iwamoto K, Kinoshita A, Fukuda H, Sawa S.** 2008. The receptor-like kinase SOL2 mediates CLE signaling in *Arabidopsis*. *Plant and Cell Physiology* **49**, 1752–1757.
- Morillo SA, Tax FE.** 2006. Functional analysis of receptor-like kinases in monocots and dicots. *Current Opinion in Plant Biology* **9**, 460–469.
- Mudgett MB, Staskawicz BJ.** 1998. Protein signaling via type III secretion pathways in phytopathogenic bacteria. *Current Opinion in Microbiology* **1**, 109–114.
- Muller R, Bleckmann A, Simon R.** 2008. The receptor kinase CORYNE of *Arabidopsis* transmits the stem cell-limiting signal CLAVATA3 independently of CLAVATA1. *The Plant Cell* **20**, 934–46.
- Nadeau JA, Sack FD.** 2002. Control of stomatal distribution on the *Arabidopsis* leaf surface. *Science* **296**, 1697–1700.
- Nagamune K, Hicks LM, Fux B, Brossier F, Chini EN, Sibley LD.** 2008. Abscisic acid controls calcium-dependent egress and development in *Toxoplasma gondii*. *Nature* **451**, 207–210.
- Naito K, Taguchi F, Suzuki T, Inagaki Y, Toyoda K, Shiraishi T, Ichinose Y.** 2008. Amino acid sequence of bacterial microbe-associated molecular pattern flg22 is required for virulence. *Molecular Plant–Microbe Interactions* **21**, 1165–1174.
- Nam KH, Li J.** 2002. BRI1/BAK1, a receptor kinase pair mediating brassinosteroid signaling. *Cell* **110**, 203–212.
- Narusaka Y, Kawakami N, Kaku H, Shibuya N.** 2007. CERK1, a LysM receptor kinase, is essential for chitin elicitor signaling in *Arabidopsis*. *Proceedings of the National Academy of Sciences, USA* **104**, 19613–19618.
- Nishimura R, Hayashi M, Wu GJ, et al.** 2002. HAR1 mediates systemic regulation of symbiotic organ development. *Nature* **420**, 426–429.
- Ogawa M, Shinohara H, Sakagami Y, Matsubayashi Y.** 2008. *Arabidopsis* CLV3 peptide directly binds CLV1 ectodomain. *Science* **319**, 294.
- Osakabe Y, Maruyama K, Seki M, Satou M, Shinozaki K, Yamaguchi-Shinozaki K.** 2005. Leucine-rich repeat receptor-like kinase1 is a key membrane-bound regulator of abscisic acid early signaling in *Arabidopsis*. *The Plant Cell* **17**, 1105–1119.
- Park CJ, Peng Y, Chen X, Dardick C, Ruan D, Bart R, Canlas PE, Ronald PC.** 2008. Rice XB15, a protein phosphatase 2C, negatively regulates cell death and XA21-mediated innate immunity. *PLoS Biology* **6**, e231.
- Pearce G, Strydom D, Johnson S, Ryan CA.** 1991. A polypeptide from tomato leaves induces wound-inducible proteinase inhibitor proteins. *Science* **253**, 895–897.
- Radutoiu S, Madsen LH, Madsen EB, et al.** 2003. Plant recognition of symbiotic bacteria requires two LysM receptor-like kinases. *Nature* **425**, 585–592.
- Ramonell K, Berrocal-Lobo M, Koh S, Wan J, Edwards H, Stacey G, Somerville S.** 2005. Loss-of-function mutations in chitin responsive genes show increased susceptibility to the powdery mildew pathogen *Erysiphe cichoracearum*. *Plant Physiology* **138**, 1027–1036.
- Robatzek S, Chinchilla D, Boller T.** 2006. Ligand-induced endocytosis of the pattern recognition receptor FLS2 in *Arabidopsis*. *Genes and Development* **20**, 537–542.
- Rusinova E, Borst JW, Kwaaitaal M, Cano-Delgado A, Yin Y, Chory J, de Vries SC.** 2004. Heterodimerization and endocytosis of *Arabidopsis* brassinosteroid receptors BRI1 and AtSERK3 (BAK1). *The Plant Cell* **16**, 3216–3229.
- Ryan CA, Huffaker A, Yamaguchi Y.** 2007. New insights into innate immunity in *Arabidopsis*. *Cellular Microbiology* **9**, 1902–1908.
- Sanabria N, Goring D, Nürnberger T, Dubery I.** 2008. Self/nonself perception and recognition mechanisms in plants: a comparison of self-incompatibility and innate immunity. *New Phytologist* **178**, 503–514.
- Schaller A, Ryan CA.** 1994. Identification of a 50-kDa systemin-binding protein in tomato plasma membranes having Kex2p-like properties. *Proceedings of the National Academy of Sciences, USA* **91**, 11802–11806.
- Scheer JM, Ryan Jr CA.** 2002. The systemin receptor SR160 from *Lycopersicon peruvianum* is a member of the LRR receptor kinase family. *Proceedings of the National Academy of Sciences, USA* **99**, 9585–9590.
- Seong SY, Matzinger P.** 2004. Hydrophobicity: an ancient damage-associated molecular pattern that initiates innate immune responses. *Nature Reviews Immunology* **6**, 469–478.
- Shabab M, Shindo T, Gu C, Kaschani F, Pansuriya T, Chinthra R, Harzen A, Colby T, Kamoun S, van der Hoorn RA.** 2008. Fungal effector protein AVR2 targets diversifying defence-related cysteine proteases of tomato. *The Plant Cell* **20**, 1169–1183.
- Shan L, He P, Li J, Heese A, Peck SC, Nürnberger T, Martin GB, Sheen J.** 2008. Bacterial effectors target the common signaling partner BAK1 to disrupt multiple MAMP receptor-signaling complexes and impede plant immunity. *Cell, Host and Microbe* **4**, 17–27.
- Shen QH, Schulze-Lefert P.** 2007. Rumble in the nuclear jungle: compartmentalization, trafficking, and nuclear action of plant immune receptors. *EMBO Journal* **26**, 4293–4301.
- Shiba H, Takayama S, Iwano M, Shimosato H, Funato M, Nakagawa T.** 2001. A pollen coat protein, SP11/SCR, determines the pollen S-specificity in the self-incompatibility of *Brassica* species. *Plant Physiology* **125**, 2095–2103.
- Shiu SH, Bleecker AB.** 2003a. Expansion of the receptor-like kinase/Pelle gene family and receptor-like proteins in *Arabidopsis*. *Plant Physiology* **132**, 530–543.
- Shiu SH, Karlowski WM, Pan R, Tzeng YH, Mayer KF, Li WH.** 2004. Comparative analysis of the receptor-like kinase family in *Arabidopsis* and rice. *The Plant Cell* **16**, 1220–1234.

- Shpak ED, McAbee JM, Pillitteri LJ, Torii KU.** 2005. Stomatal patterning and differentiation by synergistic interactions of receptor kinases. *Science* **309**, 290–293.
- Sinapidou E, Williams K, Nott L, Bahkt S, Tör M, Crute I, Bittner-Eddy P, Beynon J.** 2004. Two TIR: NB:LRR genes are required to specify resistance to *Peronospora parasitica* isolate Cala2 in *Arabidopsis*. *The Plant Journal* **38**, 898–909.
- Stein JC, Howlett B, Boyes DC, Nasrallah ME, Nasrallah JB.** 1991. Molecular cloning of a putative receptor protein kinase gene encoded at the self-incompatibility locus of *Brassica oleracea*. *Proceedings of the National Academy of Sciences, USA* **88**, 8816–8820.
- Stenvik GE, Tandstad NM, Guo Y, Shi CL, Kristiansen W, Holmgren A, Clark SE, Aalen RB, Butenko MA.** 2008. The EPIP peptide of INFLORESCENCE DEFICIENT IN ABSCISSION is sufficient to induce abscission in *Arabidopsis* through the receptor-like kinases HAESA and HAESA-LIKE2. *The Plant Cell* **20**, 1805–1817.
- Stracke S, Kistner C, Yoshida S, et al.** 2002. A plant receptor-like kinase required for both bacterial and fungal symbiosis. *Nature* **417**, 959–962.
- Sun W, Dunning FM, Pfund C, Weingarten R, Bent AF.** 2006. Within-species flagellin polymorphism in *Xanthomonas campestris* pv. *campestris* and its impact on elicitation of *Arabidopsis* FLAGELLIN SENSING2-dependent defences. *The Plant Cell* **18**, 764–779.
- Sweat TA, Lorang JM, Bakker EG, Wolpert TJ.** 2008. Characterization of natural and induced variation in the *LOV1* gene, a CC-NB-LRR gene conferring victorin sensitivity and disease susceptibility in *Arabidopsis*. *Molecular Plant-Microbe Interactions* **21**, 7–19.
- Swiderski MR, Innes RW.** 2001. The *Arabidopsis* PBS1 resistance gene encodes a member of a novel protein kinase subfamily. *The Plant Journal* **26**, 101–112.
- Tellström V, Usadel B, Thimm O, Stitt M, Küster H, Niehaus K.** 2007. The lipopolysaccharide of *Sinorhizobium meliloti* suppresses defence-associated gene expression in cell cultures of the host plant *Medicago truncatula*. *Plant Physiology* **143**, 825–837.
- Todde V, Veenhuis M, der Klei IJ.** 2009. Autophagy: principles and significance in health and disease. *Biochimica et Biophysica Acta* **1792**, 3–13.
- Torii KU, Clark SE.** 2000. Receptor-like kinases in plant development. In: Callow JA, ed. *Advances in botanical research: incorporating advances in plant pathology* **32**, 226–268.
- Tör M.** 2008. Tapping into molecular conversation between oomycete pathogens and their host plants. *European Journal of Plant Pathology* **122**, 57–69.
- Tör M, Yemm A, Holub E.** 2003. Role of proteolysis in *R*-gene mediated defence in plants. *Molecular Plant Pathology* **4**, 287–296.
- Trevaskis B, Colebatch G, Desbrosses G, Wandrey M, Wienkoop S, Saalbach G, Udvardi M.** 2002. Differentiation of plant cells during symbiotic nitrogen fixation. *Comparative and Functional Genomics* **3**, 151–157.
- Trotochaud AE, Hao T, Wu G, Yang Z, Clark SE.** 1999. The CLAVATA1 receptor-like kinase requires CLAVATA3 for its assembly into a signaling complex that includes KAPP and a Rho-related protein. *The Plant Cell* **11**, 393–406.
- Trujillo M, Ichimura K, Casais C, Shirasu K.** 2008. Negative regulation of PAMP-triggered immunity by an E3 ubiquitin ligase triplet in *Arabidopsis*. *Current Biology* **18**, 1396–1401.
- Ueda H, Yamaguchi Y, Sano H.** 2006. Direct interaction between the tobacco mosaic virus helicase domain and the ATP-bound resistance protein, N factor during the hypersensitive response in tobacco plants. *Plant Molecular Biology* **61**, 31–45.
- Waites R, Simon R.** 2000. Signaling cell fate in plant meristems: three clubs on one touse. *Cell* **103**, 835–838.
- Walker J.** 2004. Structure and function of the receptor-like protein kinases of higher plants. *Plant and Molecular Biology* **26**, 1599–1609.
- Wang G, Ellendorff U, Kemp B, et al.** 2008. A genome-wide functional investigation into the roles of receptor-like proteins in *Arabidopsis*. *Plant Physiology* **147**, 503–517.
- Wang X, Goshe MB, Soderblom EJ, Phinney BS, Kuchar JA, Li J, Asami T, Yoshida S, Huber SC, Clouse SD.** 2005. Identification and functional analysis of *in vivo* phosphorylation sites of the *Arabidopsis* BRASSINOSTEROID-INSENSITIVE1 receptor kinase. *The Plant Cell* **17**, 1685–1703.
- Wang X, Kota U, He K, Blackburn B, Li J, Goshe MB, Huber SC, Clouse SD.** 2008. Sequential transphosphorylation of the BRI1/BAK1 receptor kinase complex impacts early events in brassinosteroid signaling. *Developmental Cell* **15**, 220–235.
- Wang X, Zafian P, Choudhary M, Lawton M.** 1996. The PR5K receptor protein kinase from *Arabidopsis thaliana* is structurally related to a family of plant defence proteins. *Proceedings of the National Academy of Sciences, USA* **93**, 2598–2602.
- Wang YS, Pi LY, Chen X, et al.** 2006. Rice XA21 binding protein 3 is a ubiquitin ligase required for full Xa21-mediated disease resistance. *The Plant Cell* **18**, 3635–3646.
- Xiang T, Zong N, Zou Y, et al.** 2008. *Pseudomonas syringae* effector AvrPto blocks innate immunity by targeting receptor kinases. *Current Biology* **18**, 74–80.
- Xiao F, Giavalisco P, Martin GB.** 2007. *Pseudomonas syringae* type III effector AvrPtoB is phosphorylated in plant cells on serine 258, promoting its virulence activity. *Journal of Biological Chemistry* **282**, 30737–30744.
- Yamaguchi Y, Pearce G, Ryan CA.** 2006. The cell surface leucine-rich repeat receptor for AtPep1, an endogenous peptide elicitor in *Arabidopsis*, is functional in transgenic tobacco cells. *Proceedings of the National Academy of Sciences, USA* **103**, 10104–10109.
- Yamakawa S, Shiba H, Watanabe M, Shiozawa H, Takayama S, Hinata K, Isogai A, Suzuki A.** 1994. The sequences of S-glycoproteins involved in self-incompatibility of *Brassica campestris* and their distribution among Brassicaceae. *Bioscience, Biotechnology and Biochemistry* **58**, 921–925.
- Zipfel C, Kunze G, Chinchilla D, Caniard A, Jones JD, Boller T, Felix G.** 2006. Perception of the bacterial PAMP EF-Tu by the receptor EFR restricts *Agrobacterium*-mediated transformation. *Cell* **125**, 749–760.
- Zipfel C, Robatzek S, Navarro L, Oakeley EJ, Jones JD, Felix G, Boller T.** 2004. Bacterial disease resistance in *Arabidopsis* through flagellin perception. *Nature* **428**, 764–767.