Signaling and Communication in Plants

P. Vidhyasekaran

PAMP Signals in Plant Innate Immunity

Signal Perception and Transduction

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Contents

Chapter 1
Introduction

Abstract Innate immunity is the first line of defense against invading microorganisms in plants. Pathogen-associated molecular patterns (PAMPs) are the classical activators of immune responses. These are alarm signal molecules are perceived as 'nonself' by plant pattern recognition receptors (PRRs) to switch on the plant immune responses. PAMPs are not only detected in pathogens, but also detected in nonpathogens and even in saprophytes. The PAMPs are often called as microbe-associated molecular patterns (MAMPs). MAMPs are molecular signatures typical of whole classes of microbes and their recognition by PRRs activates the plant innate immunity. Most of the PRRs are receptor-like kinases (RLKs) and RLKs are proteins with a "receptor" and a "signaling domain" in one molecule. The extracellular domains of RLKs bind directly to legands to perceive extracellular signals, whereas the cytoplasmic kinase domains transduce these signals into the cell. PRRs interact with additional transmembrane proteins which act as "signaling amplifiers". PAMPs induce autophosphorylation of the kinase domain of PRRs and the autophosphorylated PRRs are translocated to endosomes. The biogenesis of transmembrane PRRs occurs through endoplasmic reticulum (ER) with the aid of ER-resident chaperones. The PRR in ER is transported from ER to plasma membrane and *N*-glycosylation of PRRs is required for the transport of PRRs. Second messengers deliver the information generated by the PAMP/PRR signaling complex to the proteins which decode/interpret signals to initiate defense gene expression. Calcium ion is a ubiquitous intracellular second messenger involved in various defense signaling pathways. Ca^{2+} is a master regulator of gene expression in plants. Calcium signatures are recognized by calcium sensors to transduce calcium-mediated signals into downstream events. Guanosine triphosphate (GTP)-binding proteins (G-proteins) act as molecular switches in signal transduction system. Mitogen-activated protein kinase (MAPK) cascades transduce extracellular stimuli into intracellular responses in plants. Reactive oxygen species is a second messenger in transmitting the PAMP signal. Nitric oxide (NO) is a diffusible second messenger acting in cellular signal transduction through stimulus-coupled S-nitrosylation of cysteine residues. The plant hormones salicylic acid, jasmonate,

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ethylene, abscisic acid, auxin, cytokinin, gibberellins, and brassinosteroids play important role in immune response signaling. Plant hormones activate different signaling pathways inducing distinctly different defense genes. These signaling pathways can crosstalk with each other and this crosstalk helps the plant to "decide" which defensive strategy to follow, depending on the type of attacker it is encountering. Potential pathogens produce several effectors to nullify the defense responses induced by the innate immune system. Pathogens may also hijack some signaling systems to cause disease. The war between the plant and pathogen appears to be in fine-tuning the signaling systems to cause disease or to enhance host defense response. Recent advances in our understanding of the molecular basis of plant innate immunity have opened new era in developing potential tools in management of crop diseases.

Keywords Pathogen-associated molecular patterns (PAMPs) • Microbe-associated molecular patterns (MAMPs) • Plant pattern recognition receptors (PRRs) • Endocytosis of PRR proteins • PAMP-triggered immunity (PTI) • PAMP-PRR signaling complex

1.1 Classical PAMPs

Innate immunity is the first line of defense against invading microorganisms in vertebrates and the only line of defense in invertebrates and plants (Silipo et al. 2010; Zamioudis and Peterse 2012). Several elicitors of microbial origin have been identified as primary danger/alarm signal molecules to switch on the plant immune systems culminating in activation of defense genes (Aziz et al. 2003; D'Ovidio et al. 2004; Cavalcanti et al. 2006; Vidhyasekaran 2007; Thomma et al. 2011). The classical general elicitors reported in plant pathogens resemble the pathogen-associated molecular patterns (PAMPs), the classical activators of innate immune responses in mammals (Nürnberger and Brunner 2002; Nürnberger et al. 2004; Nürnberger and Lipka 2005). These historically termed general elicitors have been renamed as PAMPs (Jones and Dangl 2006; Bent and Mackey 2007). PAMPs are often vital for microbial survival and are therefore not subject to mutational variation (Gust et al. 2007; Zhang and Zhou 2010). PAMPs are defined as evolutionarily conserved building blocks of microbial surfaces that directly bind to plant pattern recognition receptors (PRRs) and induce defense responses (Nürnberger and Brunner 2002; Qutob et al. 2006; Nicaise et al. 2009; Tsuda and Katagiri 2010; Thomma et al. 2011). The molecular signatures in PAMPs are not present in the host and these are perceived as 'non-self' by plant pattern recognition receptors (Mackey and McFall 2006).

PAMPs that trigger innate immune responses in various vertebrates and non-vertebrate organisms include eubacterial flagellin, elongation factors, lipopolysaccharides (LPS) from gram-negative bacteria, viral and bacterial nucleic acids, fungal cell wall-derived chitins, glucans, mannans, or proteins and peptidoglycans from gram-positive bacteria (Zipfel and Felix 2005; Jones and Dangl 2006). Similar

PAMPs have been detected in a wide range of plant pathogens (Shinya et al. 2007; Boller and Felix 2009; Silipo et al. 2010; Tsuda and Katagiri 2010; Nürnberger and Kufner 2011). One of the common features of PAMPs is their presence in a broad range of microbial species (Brunner et al. 2002). The general structure of lipopolysaccharides (LPS) is shared by all gram-negative bacteria (Medzhitov 2001) and the protein PAMP flagellin is highly conserved among bacterial taxa (Felix et al. 1999). Chitin is the widespread, conserved, and intrinsic structure detected in fungi (Thomma et al. 2011). CBEL (for Cellulose-Binding Elicitor Lectin) is a glycoprotein PAMP and it occurs widely in the oomycete *Phytophthora* species (Khatib et al. 2004). The PAMP double-stranded RNA is a structural signature of several groups of viruses (Medzhitov 2001; Ding 2010).

PAMPs are exclusively recognized as the molecules involved in triggering innate immunity. PAMPs are actually defined as the molecules, which bind to plant PRRs and induce defense responses (Nicaise et al. 2009; Tsuda and Katagiri 2010). However, most of the PAMPs also have virulence functions besides eliciting defense responses (Thomma et al. 2011). The well characterized PAMP flagellin also has a role in virulence. Glycosylation of the flagellin molecule has been shown to be required for virulence in *Pseudomonas syringae* pv. *tabaci* (Taguchi et al. 2010). *P. syringae* pv. *tabaci* flagellin mutants affected in their elicitor activity also showed reduced virulence in plants due to reduced motility (Naito et al. 2008; Taguchi et al. 2010). The bacterial lipopolysaccharide (LPS) generally acts as PAMP inducing defenses (Tellström et al. 2007; Aslam et al. 2008; Silipo et al. 2008; Thomma et al. 2011). However, changes in composition of LPS affect bacterial virulence, suggesting a role for LPS in virulence of pathogens (Newman et al. 2007). When the PAMP chitin synthesis was disrupted in the fungal pathogen *Botrytis cinerea*, virulence of the pathogen was drastically reduced (Soulie et al. 2006). Mutation of peptidoglycan (PGN) genes reduces the virulence of *Ralstonia solanacearum* and of *Erwinia amylovora* (Cloud-Hansen et al. 2006), suggesting the role of the PAMP peptidoglycan in virulence of pathogens.

PAMPs are detected not only in pathogens, but also in several nonpathogens, and saprophytes. Since the PAMPs are detected in all microbes, the PAMPs are better called as microbe-associated molecular patterns (MAMPs) (Viterbo et al. 2007; Zhang et al. 2007; Denoux et al. 2008; Aslam et al. 2009; Jeworutzki et al. 2010; Thomma et al. 2011; de Freitas and Stadnik 2012). MAMPs are molecular signatures typical of whole classes of microbes, and their recognition plays a key role in innate immunity (Boller and Felix 2009).

1.2 Plant Pattern Recognition Receptors (PRRs)

PAMPs are perceived as alarm/danger signals by cognate plant pattern recognition receptors (PRRs) and the PAMP-PRR complex activates the plant immune system (Takakura et al. 2004; Jones and Dangl 2006; Altenbach and Robatzek 2007; He et al. 2007; Wan et al. 2008; Iriti and Faoro 2009). Several receptors for the PAMPs

have been recognized in plasma membrane of plant cells (Nicaise et al. 2009; Petutschnig et al. 2010; Shinya et al. 2010; Schulze et al. 2010; Segonzac and Zipfel 2011). The PRRs identified to date are modular proteins harbouring an extracellular domain consisting of leucine-rich repeat (LRR) or lysine motifs (LysM) (Saijo 2010; Segonzac and Zipfel 2011). Most of the PRRs are receptor-like kinases (RLKs) and the sensors for extracellular molecules consisting of an extracellular ligand-binding domain, a single transmembrane domain, and a cytosolic protein kinase domain are called RLKs (Seifert and Blaukopf 2010). RLKs are proteins with a "receptor" and a "signaling domain" in one molecule. The extracellular domains of RLKs bind directly to legands to perceive extracellular signals (PAMPs), whereas the cytoplasmic kinase domains transduce these signals into the cell (Bi et al. 2010).

PRRs interact with additional transmembrane proteins which act as signaling amplifiers to achieve their functionality (Zipfel 2009). PAMPs bind with PRRs and induce conformational alteration in PRRs leading to their activation (Ali et al. 2007). PAMPs trigger increased transcription of PRR genes and accumulation of PRR proteins (Qutob et al. 2006; Lohmann et al. 2010). Most of the PRRs are receptor kinases and the PAMPs induce autophosphorylation of the kinase domain of PRRs (Kanzaki et al. 2008; Xiang et al. 2008).

The plasma membrane resident autophosphorylated PRRs are translocated to endosomes and it helps to extend the signaling surface ensuring a robust and efficient cellular signaling system (Geldner and Robatzek 2008). PAMPs induce ubiquitin-proteasome- or clathrin-mediated endocytosis of PRR proteins (Robatzek et al. 2006; Aker and de Vries 2008). PAMP-induced PRR-induced endocytosis has been shown to be dependent on phosphorylation of the PRR (Robatzek et al. 2006). PAMP-induced internalization of PRRs from the plasma membrane is closely correlated with their immune function (Bar et al. 2009; Saijo 2010). The biogenesis of trans-membrane PRRs may occur through the endoplasmic reticulum (ER) with the aid of ER –resident chaperones (Dodds and Rathjen 2010; Popescu 2012). After biosynthesis of PRR in ER, it is transported from the ER to the plasma membrane. *N*-glycosylation of PRRs is required for transport of PRRs from ER to plasma membrane (Häweker et al. 2010). Sustained activation of plasma membrane–resident PRR signaling is important for mounting robust PAMP-triggered immunity (Saijo 2010).

1.3 Second Messengers in PAMP Signal Transduction

The plant immune system uses several second messengers to encode information generated by the PAMP/PRR signaling complex and deliver the information downstream of PRRs to proteins which decode/interpret signals and initiate defense gene expression (van Verk et al. 2008; Mersmann et al. 2010; Boudsocq et al. 2010; Hwang and Hwang 2011). It is still not known how the PAMP signals are transmitted downstream of PRR. In plant cells, the calcium ion is a ubiquitous intracellular second messenger involved in numerous signaling pathways (Luan 2009; McAinsh

and Pittman 2009: Abdul Kadar and Lindsberg 2010; DeFalco et al. 2010; Hamada et al. 2012; Stael et al. 2012).

Guanosine triphosphate (GTP)-binding proteins (G-proteins) are the regulatory GTPases, which act as molecular switches in signal transduction system (Yalowsky et al. 2010; Zhang et al. 2011, 2012). Two classes of signaling G-proteins, heterotrimeric G-proteins and small monomeric G-proteins (Ras/Ras-like small GTPases), have been reported. In the Ras superfamily of small GTPases, only the Ras and Rho families have been shown to transmit extracellular signals (Gu et al. 2004). Ras superfamily is named the Ras superfamily because the founding members are encoded by human Ras genes initially discovered as cellular homologs of the viral *ras* oncogene. Plants do not possess a true Ras GTPase such as those that are pivotal signaling in animals. Instead, they have a unique subfamily of Rho-family GTPases, called ROPs (Rho-related GTPase of plants). ROP is the sole subfamily of Rho GTPase in plants. ROPs are also referred to as RAC (for Ras [rat sarcoma oncogene product] related C3 botulinum toxin substrate) proteins (Gu et al. 2004; Kiirika et al. 2012). RAC/ROP small GTPases share a common ancestor with Rho, cdc42 and Rac and they are the only Rho-like GTPases in plants (Gu et al. 2004).

Ca^{2+} is a master regulator of gene expression in plants (Galon et al. 2010). Calcium ion acts as a signal carrier (Allen et al. 2000). Calcium signaling is modulated by specific calcium signatures. Ca^{2+} signatures are generated in the cytosol, and in noncytosolic locations including the nucleus and chloroplast through the coordinated action of Ca^{2+} influx and efflux pathways (McAinsh and Pittman 2009). Specific calcium signatures are recognized by different calcium sensors to transduce calcium-mediated signals into downstream events (Reddy et al. 2011; Wang et al. 2012; Hashimoto et al. 2012).

Mitogen-activated protein kinase (MAPK) cascades are major pathways downstream of sensors/receptors that transduce extracellular stimuli into intracellular responses in plants (Hettenhausen et al. 2012; Zhang et al. 2012). A typical MAPK signaling module consists of three interconnected protein kinases: a MAP kinase kinase kinase (MAPKKK or MEKK [for MAPK/Extracellular signal-regulated kinase Kinase Kinase]), a MAP kinase kinase (MAPKK or MKK), and a MAP kinase (MAPK or MPK) (Mészáros et al. 2006). MAP kinase cascade involves sequence of phosphorylation events (Hirt 2000). MAPKs function at the bottom of the three-kinase cascade and are activated by MAPKKs through phosphorylation on the Thr and Tyr residues in their activation motif between the kinase subdomain VII and VIII. The activity of MAPKKs is, in turn, regulated by MAPKKKs via phosphorylation of two Ser/Thr residues in the activation loop of MAPKKs. MAPKKKs receive signals from upstream receptors/sensors (Ichimura et al. 2002; Li et al. 2012).

The oxidative burst involving rapid and transient production of reactive oxygen species (ROS) is a very rapid response, occurring within seconds (Bolwell et al. 1995) or within a few minutes (Arnott and Murphy 1991) of PAMP treatment, suggesting that the oxidative burst may not require *de novo* protein synthesis but involves the activation of pre-existing enzymes. NADPH oxidase (Bae et al. 2006), peroxidases (Halliwell 1978; Lehtonen et al. 2012), and xanthine oxidase (Allan and Fluhr

1997; Ori et al. 1997) have been shown to be involved in triggering ROS production. ROS is a messenger in transmitting the PAMP signal. Nitric oxide (NO) has been identified as a gaseous second messenger (Besson-Bard et al. 2008; Bellin et al. 2013). NO is a diffusible molecular messenger that plays an important role in the plant immune response signal transduction system (Grennan 2007). PAMPs trigger NO burst within minutes in plant cells (Foissner et al. 2000; Lamotte et al. 2004; Tischner et al. 2010). NO acts substantially in cellular signal transduction through stimulus-coupled S-nitrosylation of cysteine residues (Benhar et al. 2008). It serves as a key redox-active signal for the activation of various defense responses (Klessig et al. 2000).

1.4 Plant Hormone Signals in Plant Immune Signaling System

The plant hormones salicylic acid (Mukherjee et al. 2010; Dempsey et al. 2011; Liu et al. 2011a, b), jasmonate (Wang et al. 2009; Sheard et al. 2010; Bertoni 2012), ethylene (Boutrot et al. 2010; Laluk et al. 2011; Nie et al. 2011; Nambeesan et al. 2012), abscisic acid (Yazawa et al. 2012), auxin (Fu and Wang 2011), cytokinin (Choi et al. 2011), gibberellins (Qin et al. 2013), and brassinosteroids (De Vleeschauwer et al. 2012) play important role in defense signaling against various pathogens. It has been demonstrated that specific plant hormone signaling pathways should be activated to confer resistance against specific pathogens. JA and SA signaling systems may differentially contribute for resistance against specific pathogens. JA-mediated pathway effectively confers resistance against necrotrophic fungal pathogens (Berrocal-Lobo and Molina 2004; McGrath et al. 2005; Zheng et al. 2006), while SA- mediated pathway confers resistance against biotrophic fungal pathogens and also against virus and bacterial diseases in some plants (Thomma et al. 1998, 2001; Thaler and Bostock 2004; Nie 2006; De Vos et al. 2006; Spoel et al. 2007; Zheng et al. 2006, 2007). Two forms of induced resistance, systemic acquired resistance (SAR) and induced systemic resistance (ISR), have been recognized based on the induction of specific plant hormone signaling systems (Li et al. 2008). SAR refers to a distinct signaling pathway mediated by SA (Oostendorp et al. 2001), while ISR refers to the signaling pathway mediated by JA and ET. SA signaling system activates not only local resistance, but also systemic acquired resistance (SAR) observed in distal (systemic) tissues. SAR is a SA-dependent heightened defense to a broad spectrum of pathogens that is activated throughout a plant following local infection (Liu et al. 2011a). SAR is associated with priming of defense (Kohler et al. 2002; Jung et al. 2009; Luna et al. 2011) and the priming results in a faster and stronger induction of defense mechanisms after pathogen attack (Conrath 2011). The priming can be inherited epigenetically from disease-exposed plants (Pastor et al. 2012) and descendants of primed plants exhibit next-generation systemic acquired resistance (Slaughter et al. 2012; Luna et al. 2011). The transgenerational SAR has been

recently reported (Luna et al. 2011). Thus, SA signal is transduced not only within the plant tissues, but also transferred even to the next generations.

Plant hormones activate different signaling pathways inducing distinctly different defense genes (Spoel et al. 2007; Zhang et al. 2007; Mitsuhara et al. 2008). These signaling pathways are not simple linear and isolated cascades, but can crosstalk with each other. Both antagonism and synergism between the signaling systems have been reported. Cross-talk between defense signaling pathways is thought to provide the plant with a powerful regulatory potential, which helps the plant to "decide" which defensive strategy to follow, depending on the type of attacker it is encountering (De Vos et al. 2005). It may also allow pathogens to manipulate plants to their own benefit by shutting down induced defense through influences on the signaling network.

1.5 War Between Host Plants and Pathogens and the Winner Is ------- ?

Plant innate immune systems have high potential to fight against viral, bacterial, oomycete, and fungal pathogens and protect the crop plants against wide range of diseases (Knecht et al. 2010; Lacombe et al. 2010; Hwang and Hwang 2011; Alkan et al. 2012). However, potential pathogens produce several effectors to nullify the defense responses induced by the innate immune system (Wu et al. 2011; Akimoto-Tomiyama et al. 2012; Cheng et al. 2012). To avoid or suppress or delay the expression of the defense gene-activating signaling systems, the pathogens secrete several effectors into the host cell (Göhre et al. 2008; Kim et al. 2010; Wu et al. 2011; Cheng et al. 2012). Pathogens may also hijack some signaling systems to cause disease (de Torres-Zabala et al. 2007; Thatcher et al. 2009; El Rahman et al. 2012). It has also been demonstrated that the virulent pathogen may suppress the particular defense signaling system which induce the expression of specific defense genes conferring resistance against the particular pathogen (van Verk et al. 2008; Koornneef and Pieterse 2008; Makandar et al. 2010). Activation of some signaling systems may induce susceptibility, rather than resistance (Atsumi et al. 2009; Yazawa et al. 2012). To overcome antiviral RNA silencing immunity, plant viruses express silencing-suppressor proteins which can counteract the host silencing-based antiviral process (Qu and Morris 2005; Ding and Voinnet 2007; Lewsey et al. 2010).

The war between the plant and pathogen appears to be in fine-tuning the signaling systems to cause disease or enhance host defense. Fast and strong activation of the plant immune responses aids the host plants to win the war against the pathogens (Großkinsky et al. 2011). Overexpression or suppression of some specific signaling systems in the plant immune system has been shown to help the plants to win in the arms race between plants and pathogens (Cheung et al. 2007; Zhang et al. 2008; Hwang and Hwang 2010, 2011; Wu et al. 2010).

Engineering durable nonspecific resistance to phytopathogens is one of the ultimate goals of plant breeding. However, most of the attempts to reach this goal fail as a

result of rapid changes in pathogen populations and the sheer diversity of pathogen infection mechanisms. Recently several bioengineering and molecular manipulation technologies have been developed to activate the 'sleeping' plant innate immune system, which has potential to detect and suppress the development of a wide range of plant pathogens in economically important crop plants (Lacombe et al. 2010). Enhancing disease resistance through altered regulation of plant immunity signaling systems would be durable and publicly acceptable (Yamamizo et al. 2006; Shao et al. 2008; Gust et al. 2010; Lacombe et al. 2010). Strategies for activation and improvement of plant immunity aim at enhancing host capacities for recognition of potential pathogens, at boosting the executive arsenal of plant immunity, and interfering with virulence strategies employed by microbial pathogens (Gust et al. 2010). Major advances in our understanding of the molecular basis of plant immunity and of microbial infection strategies have opened new ways for engineering durable resistance in crop plants (Gust et al. 2010; Huffaker et al. 2011). This book describes the most fascinating PAMP-PRR signaling complex and signal transduction systems. It discusses the highly complex networks of signaling pathways involved in transmission of the signals to induce distinctly different defense-related genes to mount offence against different pathogens.

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