Cell. Mol. Life Sci. 64 (2007) 2726 – 2732
1420-682X/07/212726-7
DOI 10.1007/s00018-007-7284-7

Cellular and Molecular Life Sciences

Visions & Reflections (Minireview)

How plants recognize pathogens and defend themselves

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Received 24 June 2007; received after revision 18 July 2007; accepted 15 August 2007
Online First 17 September 2007

Abstract. Plants have an innate immunity system to defend themselves against pathogens. With the primary immune system, plants recognize microbe-associated molecular patterns (MAMPs) of potential pathogens through pattern recognition receptors (PRRs) that mediate a basal defense response. Plant pathogens suppress this basal defense response by means of effectors that enable them to cause disease. With the secondary immune system, plants have gained the ability to recognize effector-induced perturbations of host targets through resistance proteins (RPs) that mediate a strong local defense response that stops pathogen growth. Both primary and secondary immune responses in plants depend on germ line-encoded PRRs and RPs. During induction of local immune responses, systemic immune responses also become activated, which predispose plants to become more resistant to subsequent pathogen attacks. This review gives an update on recent findings that have enhanced our understanding of plant innate immunity and the arms race between plants and their pathogens.

Keywords. MAMP, plant innate immunity, microbial effector, infection, local and systemic resistance, guard model.

Biotrophic and necrotrophic plant pathogens

Plants become infected by pathogens with different lifestyles [1]. Biotrophic pathogens are specialized to feed on living plant tissues, and some have developed an intimate relationship with their host plant, co-evolving into obligate biotrophs that cannot be cultured on synthetic media. Non-obligate biotrophs can be cultured on synthetic media, but neither obligate nor non-obligate biotrophs can grow as saprophytes. Biotrophs have a narrow host range, and strains of these pathogens have often adapted to a specific line of a given plant species. Many biotrophs live in the intercellular space between leaf mesophyl cells, and some produce haustoria as feeding structures that invaginate the plasma membrane of host cells, enabling them to create a specific micro-environment for retrieval of nutrients [2, 3].

Necrotrophic pathogens are less specialized and have a much less intimate relationship with their host plants. They often grow on plant tissues that are wounded, weakened or senescent and frequently produce toxins to kill host tissue prior to colonization. Necrotrophs can also grow outside the host as saprophytes and can easily be cultured on synthetic media [1].

Primary innate immunity in plants

Plants are sessile organisms that cannot hide or escape when attacked but are, like all other multicellular organisms, continuously threatened by potential pathogens. Unlike animals, plants do not have a recombinatorial adaptive immune system with a diverse repertoire of B and T lymphocytes [4, 5].

Plants have developed a two-layered innate immune system for defense against pathogens [6–10]. Primary innate immunity, the first line of defense of plants, is achieved through a set of defined receptors, also referred to as pattern recognition receptors (PRRs), that recognize conserved microbe-associated molecular patterns (MAMPs) [6, 7]. Upon MAMP recognition, primary defense responses are induced such as cell wall alterations, deposition of callose and the accumulation of defense-related proteins including chitinases, glucanases and proteases, which all negatively affect colonization by potential pathogens [11] (Fig. 1a). Several MAMPs have been identified for plant pathogens, including flagellin, lipopolysaccharide (LPS) and elongation factor Tu (EF-Tu) from Gram-negative bacteria as well as chitin and β-glucans from fungi and oomycetes [6, 7]. PRRs recognize a particular domain of a larger MAMP molecule that often possesses structural or enzymatic functions that are crucial for a microbe or pathogen. The genes coding for PRRs specific for flagellin (flg22) and bacterial elongation factor Tu (elf18) epitopes have been identified in plants as FLS2 and ERF, respectively [12–16]. FLS2 is a receptor kinase (RLK) with extracellular leucine-rich repeats (LRRs) and a cytoplasmic serine/threonine kinase domain [12]. Recognition of flg22 by FLS2 restricts growth of the bacterial pathogen *Pseudomonas syringae* pv. *tomato* in the plant, whereas plants lacking FLS2 are more susceptible to this bacterium, indicating that FLS2 mediates a flg22-induced primary defense response [13]. Similarly, elf18 triggers a primary defense response in *Arabidopsis thaliana* plants carrying ERF, which is structurally very much related to FLS2 [15]. Interestingly, whereas flg22 and elf18 are recognized by different RLKs, the primary defense responses induced upon their recognition are largely similar [15]. This seems to be an evolutionary advantage, as in this way recognition of different MAMPs by different PRRs converges into a limited number of signaling pathways that all activate primary defense responses. Although most MAMPs and their PRRs are believed to be fairly monomorphic, variations do occur [17].

A. thaliana and rice contain over 400 RLKs involved in both plant development and defense, suggesting that additional MAMPs might be recognized by similar RLKs [18–19]. In addition to RLKs, in some plants a LysM receptor kinase that recognizes fungal chitin [20–21] and another receptor that recognizes oomycete β-glucans have been identified [22–23]. Plants also carry many LRR-containing receptor-like proteins (RLPs) representing another class of PRRs that structurally resemble RLKs but lack the cytoplasmic kinase domain [24]. One such RLP has been reported to induce a primary immune response in tomato upon interaction with a fungal xylanase [25]. It is anticipated that in the future many more PRRs from plants recognizing additional MAMPs will be discovered. In contrast, humans have only a dozen different Toll-like receptors (TLRs) involved in recognition of common MAMPs that trigger primary defense responses in dendritic cells and subsequently activate the highly specific and effective adaptive immune system controlled by B and T cells [4–5]. As FLS2 in plants and TLR5 in humans both recognize flagellin, it is tempting to speculate that the primary innate immune system in plants and animals diverged from a common ancestral immune system [26]. However, the LRRs of FLS2 and TLR5 recognize different domains of flagellin, and their structure varies significantly. In addition, the defense signaling pathways downstream of the two receptors are also very different. FLS2 has an intracellular serine/threonine domain, whereas TLR5 contains an intracellular TIR (for Drosophila Toll and human interleukin-1 receptor) domain. This suggests that MAMP recognition in animals and plants has most likely evolved independently by convergent evolution [4, 27].

Effectors of plant pathogens suppress primary innate immune responses

True pathogens of plants and animals are able to breach or suppress basal defense activated in the primary innate immune system. Viral, bacterial, fungal and oomycete pathogens of animals have developed sophisticated mechanisms to escape or suppress recognition of MAMPs and the subsequent induction of primary defense responses [4–5]. Plant and animal pathogenic bacteria contain four secretory systems, of which the type III secretion system (TTSS) appears to be the most important for virulence. By the TTSS, plant pathogenic bacteria inject multiple effectors into the host plant; without a functional TTSS, they only induce the primary defense response and are not pathogenic [28–30]. It has now been shown that many TTSS-injected effectors of plant pathogenic bacteria suppress primary defense responses of plants (Fig. 1b), and for some bacteria 30–40 effectors have been described [31–32]. For a subset of effectors, the mechanism of suppression has been elucidated: *P. syringae* effectors AvrPto, AvrRpt2 and AvrRpm1 all compromise responses elicited by MAMPs [32–33]. Apart from suppressing hypersensitive response (HR) [34], AvrPtoB also induces the abscisic acid (ABA) pathway in plants, thus facilitating disease [35]. Some plant pathogenic bacteria produce metabolites such as coronatine, a jasmonic acid (JA) analogue that

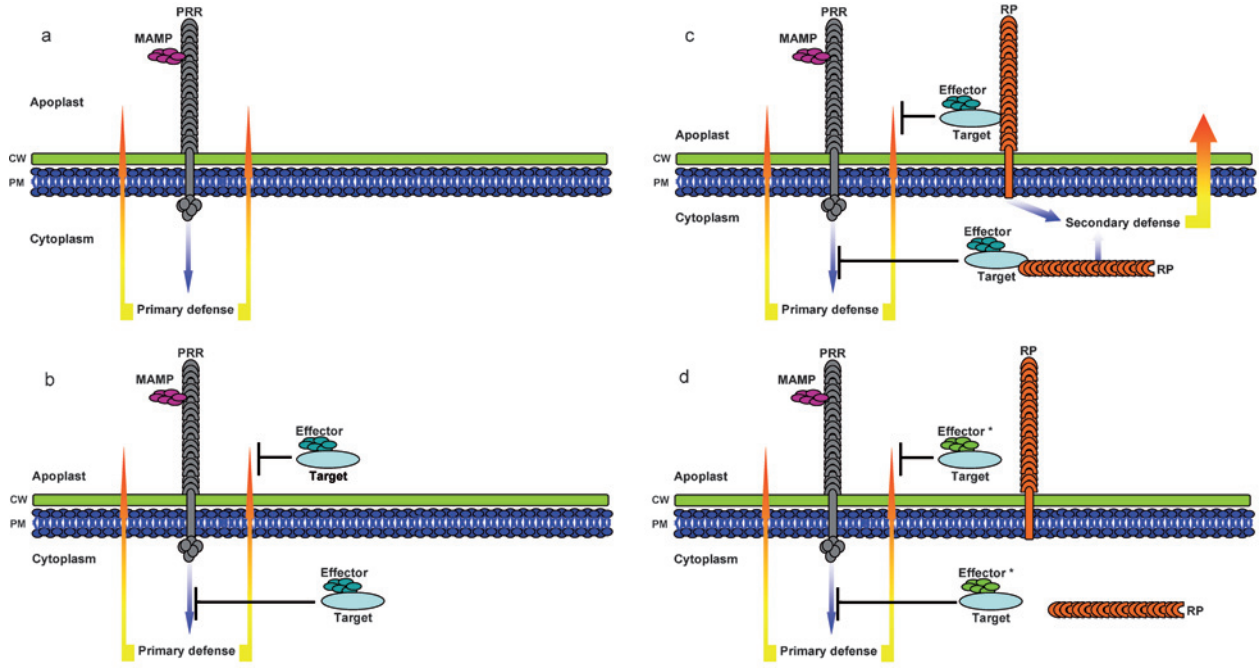

Figure 1. Induction and suppression of primary and secondary immune responses in plants by microbial pathogens. (*a*) Microbe-associated molecular pattern (MAMP) of a (pathogenic) microbe is recognized by a pattern recognition receptor (PRR), which triggers primary defense responses; this protects plants against potential pathogens. (*b*) True pathogens secrete effectors that interact with host targets and suppress primary defense responses either inside or outside the plant cell, allowing them to infect plants. (*c*) Resistant plants carry resistance proteins (RP) that recognize effector-mediated perturbations of host targets that reside outside or inside plant cells, which triggers secondary defense responses; this protects plants against true pathogens. (*d*) Pathogens produce effectors that cause perturbations that are no longer recognized by RPs, allowing the pathogens to infect plants again.

suppresses salicylic acid (SA)-induced defense responses [36–37].

The functions and mechanisms of delivery of fungal and oomycete effectors are less well understood. Of the ten effectors that are secreted by the extracellular fungus *Cladosporium fulvum* into the intercellular space of tomato, the Avr2 effector binds to and inhibits the plant cysteine protease Rcr3 [38], whereas the Avr4 effector protects the fungus against the deleterious effects of plant chitinases [39–40]. Other fungal and oomycete effectors act inside host cells as has been shown for the effectors of the flax rust fungus *Melampsora lini* [41–42], the rice blast fungus *Magnaporthe grisea* [43], the potato late blight oomycete pathogen *Phytophthora infestans* and the downy mildew oomycete pathogen of *A. thaliana, Hyaloperonospora parasitica* [44–45]. The mechanism of delivery of fungal effectors into plant cells is still unknown, although oomycete effectors all carry an RXLR motif that has been suggested to facilitate effector uptake into the plant cell. This motif has been reported to be crucial for the malaria parasite *Plasmodium falciparum*, facilitating entry of this pathogen into mammalian host cells [3, 45].

Effector-triggered secondary immune responses

Animal pathogens that manage to cross physical barriers such as the epithelium of skin and intestine are recognized by TLRs [4] present on phagocytes that trigger subsequent engulfment and destruction of the invading pathogen. Phagocytes also connect the innate immune system to the specific adaptive immune system by triggering activation of B and T lymphocytes after presentation of specific antigens to their receptors, which initiates specific cell-mediated and humoral immune responses. Plants do not have an adaptive immune system to eliminate pathogens that have entered their intercellular spaces and vascular systems. True pathogens can overcome the primary defense response by producing effectors that can suppress or breach this response. To defend themselves against true pathogens, plants have developed a secondary defense response that is triggered upon recognition of effectors or effector-mediated perturbations of host targets [9–10]. Resistance proteins (RPs) monitor these effectors or their perturbations and subsequently trigger RP-mediated secondary defense responses that often culminate in an HR (a localized programmed cell death response) associated with additional locally induced defense responses that

block further growth of the pathogen (Fig. 1c). Thus, detection of perturbed host targets by RPs is specific, whereas the induced HR is non-specific and is generally effective against multiple plant pathogens. Effectors are specific for particular strains of plant pathogens and sometimes target different domains of the same host component that is monitored by different RPs. An example of such a host target is the *A. thaliana* RIN4 protein, which is targeted by three different TTSS-dependent bacterial effectors (AvrRpm1, AvrB and AvrRpt2) and is monitored or guarded by two different RPs (RPM1 and RPS2) [46–48]. The phenomenon of indirect recognition of effector-induced perturbations of host targets that induce secondary defense responses is also known as the guard model [50–51]. Indirect recognition of effectors by RPs is observed more frequently than direct recognition [9–10, 52]. Direct recognition of effectors by RPs does occur and has been reported for the effectors of *M. grisea* [43], *M. lini* [41–42] and the bacterial pathogen *Ralstonia solanacearum* [53].

Induced systemic resistance in plants

Plants are also protected by a mechanism called systemic acquired resistance (SAR), which occurs at sites distant from primary and secondary immune responses and protects plants from subsequent pathogen attacks. Systemic resistance is induced by pathogens that usually infect leaves or stems of plants and is induced simultaneously with local primary and secondary immune responses [54]. SAR is effective against a broad range of pathogens and is dependent on different plant hormones including salicylic acid (SA), jasmonic acid (JA), ethylene (ET), abscisic acid (ABA) or combinations thereof [54–56]. Defense pathways that are dependent on these hormones are active not only against microbial pathogens but often also against insects [57]. The level and effectiveness of both local and systemic resistance responses and the dependence on hormones is determined by the type of plant pathogen. Thus, biotrophic and necrotrophic pathogens often trigger different types of induced resistance that are regulated by different hormones [55–58].

Adaptation of pathogens to secondary innate immune responses

The arms race between plants and their pathogens has led to different modes of adaptation to primary, secondary and possibly also systemic induced defense responses. Co-evolution between plants and their pathogens has led to the generation of novel effectors that no longer directly interact with RPs or perturb host targets in ways that are no longer sensed by RPs (Fig. 1d). The type of mutations in effector genes depends on the importance of a particular effector for the pathogen's virulence and/or competitive abilities outside the host when it has to cope with antagonistic microorganisms or other hostile environments [59–60]. Thus, depending on their importance and mode of action, some effector genes can be completely removed from the pathogen genome by deletion, thus preventing their recognition by RPs, whereas others are mutated and produce effectors carrying subtle amino acid changes that decrease or avoid recognition by RPs but still retain virulence functions. Loss of an effector has often been observed in cases in which indirect interactions between RP and effector-modified host target occur, complying with the guard hypothesis. In these cases it is presumed that loss of the effector does not strongly affect the pathogen's virulence, as its function is presumably covered by functionally related effectors [9–10]. Indeed, loss or partial deletion of effector genes has frequently been observed for bacterial and some fungal pathogens that are indirectly recognized by RPs [9–10], whereas subtle amino acid changes in effectors that presumably do not affect virulence function but avoid RP recognition have been observed for effectors that directly interact with RPs [42]. For some pathogenic bacteria, loss of effector genes occurs extremely quickly on resistant plants that contain the matching RP by genome rearrangements, including excision of the effector gene [59]. Also here it is assumed that the modes of adaptive evolution depend not only on the virulence function of an effector but also on the lifestyle of a pathogen (biotrophic or necrotrophic) carrying that effector [9–10, 52].

Structure, localization and activation of RPs

Pathogens can manipulate cells of the host plant with their effectors from outside or inside plant cells, and, consequently, they are recognized by RPs that are located outside (with a transmembrane anchor) or inside plant cells in order to be able to recognize perturbations of host targets outside or inside the host cells (Fig. 1c, d). RPs can be divided structurally into five different classes [9] that all contain LRRs, and those located inside the cell contain nucleotide binding (NB) domains preceded by a TIR or leucine zipper (LZ) domain. The mechanism of effector-triggered RP-mediated activation of secondary defense responses has been partially elucidated in a few cases. As mentioned above, three different bacterial effec-

tors (AvrRpm1, AvrB and AvrRpt2) interact with the plant protein RIN4 [46–49]. AvrRpm1 and AvrB phosphorylate RIN4, which is predicted to activate the cytoplasmic NB-LRR protein RPM1 that mediates the secondary defense response, whereas AvrRpt2 is a cysteine protease that is activated inside the host cell and cleaves the RIN4 protein, which subsequently activates the cytoplasmic NB-LRR protein RPS2. The extracellular effector Avr2 of the fungal tomato pathogen *C. fulvum* interacts with, and inhibits, the extracellular cysteine protease Rcr3 from tomato, which is required for activation of the extracellular RLP Cf-2 in order to trigger secondary defense responses. The mechanism of activation of the Cf-2 protein by Rcr3 is not yet understood [38].

Activation of cytoplasmic NB-LRR proteins involves intramolecular and intermolecular modifications. The LRR domain is believed to be involved in recognition of effector-perturbed host targets or in direct recognition of effectors, whereas the NB domain represents the activation domain that is triggered by the exchange of a nucleotide diphosphate by a nucleotide triphosphate [61]. Both MAMP- and effector-induced PRR- and RP-mediated defense signaling often involve MAP kinase cascades that phosphorylate transcription factors, including TGAs and WRKYs [62–65], that subsequently activate defense genes that code for proteins that are either antimicrobial themselves or catalyze the production of antimicrobial compounds such as phytoalexins or reactive oxygen species [11]. Pathogen effectors mainly inhibit PRR-mediated primary defense responses, but some also inhibit RP-mediated secondary defense responses [66].

Concluding remarks

In recent years much progress has been made in understanding the molecular basis of primary and secondary defense responses of plants against their pathogens. Plant pathogens have to overcome both the primary and secondary lines of plant defense in order to establish successful infections and obtain their nutrition. Effectors that can suppress or manipulate both layers of defense have been reported for bacteria, fungi and oomycetes. Plants have co-evolved for millions of years with facultative and obligate biotrophic pathogens. This has caused an ongoing arms race between plants and their pathogens, both in natural plant-pathogen ecosystems and in modern man-made agricultural systems that depend on monocultures of plant genotypes that contain RPs introduced by plant breeders from related wild species. These RPs are sometimes quickly overcome by pathogens due to adaptive evolution. Sequenced genomes from pathogens and plants show that pathogens can secrete up to a few hundred effectors that are exploited to manipulate the host plant and that host plants contain many RPs that monitor effector activities. Some effectors can target and modify different domain of a crucial host protein, such as RIN4 in *A. thaliana.* Other effectors directly interact with RPs. All these different types of interactions are under strong selection pressure and have led to an arms race between host plants and pathogens showing different modes of adaptation of pathogens to the plant innate immune system. The absence of a recombinatorial adaptive immune system in plants is apparently compensated for by the presence of distantly acting SAR that predisposes plants to a more efficient defense against repeated attacks by pathogens. After all, like for other organisms, the vast majority of plants found in nature are healthy and do not suffer from pathogen attack.

Acknowledgements. I thank Bart P. H. J. Thomma, Matthieu H. A. J. Joosten and Ioannis Stergiopoulos (Laboratory of Phytopathology, Wageningen University) for useful comments and Peter H. van Esse for drawings.

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