

# Resistance to Bacterial Pathogens in Plants

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To successfully infect a plant, pathogens must overcome three layers of defense: (1) preformed physical barriers; (2) a cell-surface-based surveillance system that detects conserved pathogen molecules and (3) an intracellular surveillance system that detects effector proteins injected into host cells. Bacterial plant pathogens overcome the first layer either by invading through natural openings and wounds, and/or by secreting hydrolytic enzymes that break down surface layers. Bacteria typically overcome the second layer by injecting effectors that interfere with defense signaling. Bacteria overcome the third layer either by modifying or eliminating existing effectors, or by evolving new effectors that suppress defense activation.

## Introduction

Plant pathogenic bacteria can multiply rapidly inside plant tissue under favourable conditions, causing many serious diseases of crops, with major economic impacts. Bacterial pathogens get access to the plant milieu through mechanical openings such as wounds and pruning cuts, or through natural openings such as hydathodes (the termini of leaf veins located on the edges of leaves) and stomata (pores in the leaf surface through which gases exchange). Disease symptoms caused by bacterial pathogens include wilts, galls, specks, spots, cankers and chlorosis (yellowing). For example, wilt-causing bacteria clog the vascular tissue, preventing movement of water and nutrients. The most studied plant pathogenic bacteria belong to the genera *Pseudomonas*, *Xanthomonas*, *Erwinia*, *Ralstonia* and *Agrobacterium*. Recently, *Xylella fastidiosa* has received intense scrutiny due to fears that it may cause major losses to the grape harvest in California.

Plants have evolved several different defence mechanisms to prevent bacterial infection. Unlike vertebrates that have an adaptive immune system, plants have to rely solely on their innate immune system to defend themselves against invading pathogens. Plant bacterial pathogens, and in general other pathogens, reveal themselves to the host immune system through molecules called pathogen-associated molecular patterns (PAMPs), such as flagellin or bacterial lipopolysaccharides (LPS). Since nonpathogenic bacteria also have these structures, PAMPs are also referred to as microbe-associated molecular patterns. As discussed in detail later, plants have evolved specialized cell-surface receptors to detect conserved features of PAMPs and activate defence responses. In this article, we will discuss how these receptors are thought to activate defences, how bacterial pathogens circumvent this basal defence system and how plants have evolved a second defence layer.

Advanced article

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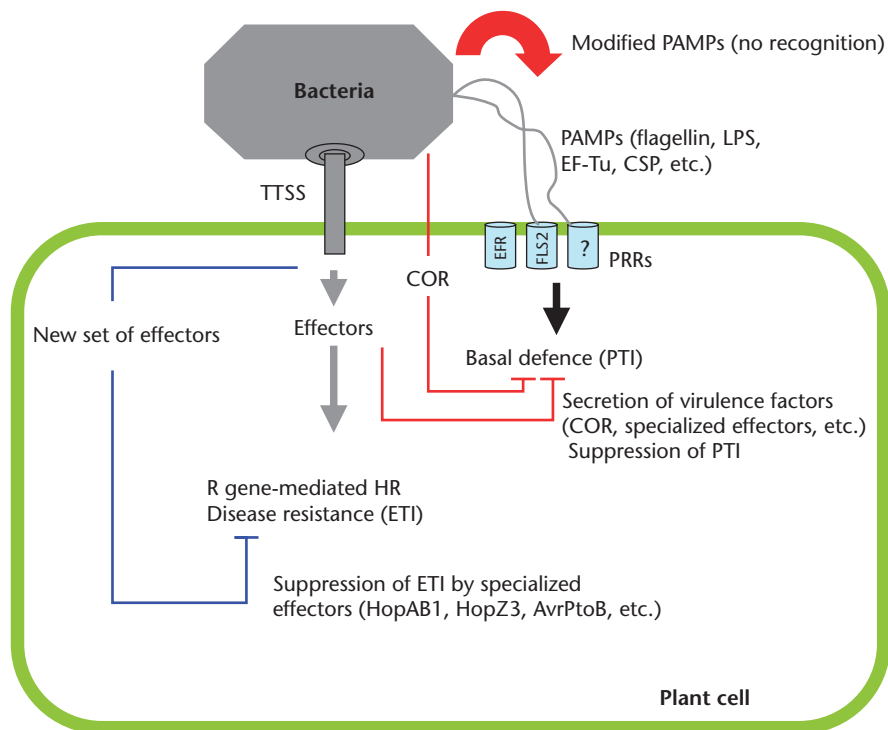
doi: 10.1002/9780470015902.a0020091

## Pre-formed Barriers to Infection by Bacterial Pathogens

The first line of protection from an initial pathogen infection is achieved through passive defence mechanisms such as physical and chemical barriers. The plant epidermis is covered by a waxy cuticle and each cell is surrounded by a complex cell wall containing highly crosslinked polysaccharides, proteins and phenolic compounds that bacterial pathogens must overcome to access cell nutrients. To breach these barriers, many plant pathogenic bacteria produce a range of extracellular virulence factors such as cutin-degrading enzymes and cell wall-degrading enzymes. These enzymes are typically secreted via a type II secretion system and include cell wall-degrading enzymes such as cellulases, pectinases and endoglucanases. Such enzymes are particularly important in causing soft-rot diseases induced by bacteria in the *Erwinia* genus.

## Basal Defence against Bacterial Pathogens

During the initial contact between a plant and a bacterial pathogen, the plant can detect bacterial PAMPs such as flagellin and LPS. The perception of PAMPs activates signal-transduction cascades that turn on basal defences. These basal defence responses include callose and silicone deposition to reinforce the cell wall, production of reactive oxygen species and ethylene, transcriptional induction of a large suite of defence genes, including pathogenesis-related genes (PR) and post-transcriptional suppression of the auxin-signalling pathway. These responses are triggered by plant extracellular receptors specialized in the recognition of PAMPs termed pattern recognition receptors (PRRs)



**Figure 1** Interaction between bacterial pathogens and plants: Plants sense the presence of bacteria via detection of pathogen-associated molecular patterns (PAMPs) such as flagellin, lipopolysaccharides (LPS), elongation factors Tu (EF-Tu) and cold shock proteins (CSP). PAMPs are detected by *trans*-membrane pattern recognition receptors (PRRs) (e.g. FLS2, EFR, etc.), which activate a basal defence system known as pathogen-triggered immunity, PTI (black arrow). Some bacteria counteract by modifying their PAMPs and/or secreting virulence factors to suppress PTI (red lines and arrows). Resistant plants express R proteins that detect the presence of pathogen effector proteins inside the plant cell, and then activate multiple defences including the hypersensitive response (HR), a form of programmed cell death (grey arrows). Most successful pathogens secrete new effectors to suppress this effectors-triggered immunity (ETI) by blocking the HR (blue line).

(Figure 1). These basal defences are generally sufficient to halt the growth of pathogenic and nonpathogenic microbes and prevent their establishment.

A well-characterized bacterial molecule that activates host basal defences is flagellin, the major protein component of bacterial flagella. A 22-amino-acid peptide derived from bacterial flagellin called flg22 can induce basal defence responses such as alkalization of the extracellular space and production of active oxygen species (Felix *et al.*, 1999). In *Arabidopsis*, the response includes closure of stomata, which restricts bacterial penetration. Flagellin and flg22 are detected in *Arabidopsis* by the PRR FLS2, which is a transmembrane receptor kinase. *Arabidopsis fls2* mutants are more susceptible to infection by *Pseudomonas syringae* pv. *tomato* DC3000 (Pst DC3000) when the bacteria are applied to the leaf surface, but not when the bacteria are infiltrated into the leaf intercellular space (Zipfel *et al.*, 2004). This observation indicates that FLS2 activates early defence responses that restrict penetration of bacterial pathogens into the plant tissue. Consistent with this conclusion, the FLS2 protein is expressed in epidermal cells and stomatal-guard cells, as well as mesophyll cells and cells in the stem, flower petals and roots.

Recently, flagellin has also been shown to downregulate the messenger ribonucleic acid (mRNA) levels of specific

auxin receptor genes (Navarro *et al.*, 2006). Interestingly, this downregulation was shown to occur via a post-transcriptional mechanism employing the micro(RNA) miR393. Flagellin induces expression of miR393, which then targets cleavage of mRNAs from the auxin-receptor genes, *TIR1*, *AFB2* and *AFB3*. This, in turn, blocks induction of auxin-responsive genes that would otherwise be induced by pathogens such as *P. syringae* that are known to produce auxin. Suppression of auxin signalling contributes to basal resistance as overexpression of auxin receptors enhances susceptibility to *P. syringae* (Navarro *et al.*, 2006)

In addition to flagellin, the elongation factor Tu (EF-Tu), which is the most abundant protein in a growing bacterial cell, acts as an inducer of basal defences in plants (Kunze *et al.*, 2004). EF-Tu is a 43 kDa protein. The *N*-terminal 18 amino acids of EF-Tu, elf18, can trigger basal defences by itself. Recognition of elf18 in *Arabidopsis* occurs through a receptor-like kinase (RLK) named EF-Tu receptor (EFR). EFR has a similar structure to FLS2, including an extracellular leucine-rich repeats (LRR) domain and an intracellular kinase domain (Zipfel *et al.*, 2006). Transformation of *Nicotiana benthamiana*, which is unable to perceive EF-Tu, with *EFR* confers the ability to respond to elf18. Likewise, *Arabidopsis* plants containing mutations in *EFR* are unable to respond to elf18. Such *efr*

mutants display enhanced susceptibility to *Agrobacterium tumefaciens* transformation, suggesting that EF-Tu is required for triggering plant defences induced by *Agrobacterium*. The cytoplasmic localization of EF-Tu in bacteria raises the question of how it can be detected by a receptor that resides on the surface of plant cells. One plausible hypothesis is that a small percentage of bacterial cells lyse in the apoplast, releasing the cell contents. Because EF-Tu is an extremely abundant protein, it would not take many lysed cells to activate a large number of EFR receptors.

Another bacterial molecule that acts as a PAMP is the cold shock protein (CSP), which induces defence responses in solanaceous plants such as tobacco and tomato. The response to this PAMP has not yet been found outside of the Solanaceae family (Felix and Boller, 2003), indicating that some PRRs have evolved relatively late in angiosperm evolution. CSPs are small highly conserved proteins (~7.4 kDa) found in eubacteria. In contrast to flagellin and EF-Tu, the receptor for CSP has not yet been identified.

Similarly, LPS, a major component of the outer membrane of Gram-negative bacteria, activates basal defence responses in plants. LPS is a glycolipid composed of three different domains: Lipid A, a conserved inner core oligosaccharide, and a variable outer polysaccharide often referred to as the O-antigen. It appears that it is the Lipid A moiety that acts as a PAMP, as this domain alone is as effective as the entire LPS in inducing defence responses in *Arabidopsis* (Zeidler *et al.*, 2004).

In summary, perception of bacteria by plant cells and activation of the basal defence response do not depend on a single bacterial factor, but can be triggered by several different factors (see Figure 1). Plants rely on the perception of multiple PAMPs for efficient recognition of bacterial pathogens. Since the activation of basal defence responses depends on the perception of PAMPs, it is also called PAMP triggered immunity (PTI) (Jones and Dangl, 2006).

## Bacterial Interference with Basal Defences

Successful pathogens must suppress or otherwise overcome basal defences. As mentioned earlier, stomata function as gates to efficiently block bacterial penetration into plant leaves through the sensing of bacterial flagellin and LPS. One strategy developed by phytopathogenic bacteria to defeat this defence is the secretion of the virulence factor coronatine (COR), a small molecule that mimics the plant hormone jasmonic acid (Melotto *et al.*, 2006). COR-mediated suppression of stomatal closure occurs via the inhibition of PAMP-induced abscisic acid (ABA) signalling in the guard cell. Coronatine minus bacterial mutants display reduced virulence compared to wild-type bacteria when inoculated on to the leaf surface. This reduction of virulence in *cor* mutants is not observed when the bacteria

are syringe infiltrated directly into the leaf apoplast, a procedure which bypasses the stomatal barrier.

To avoid detection and therefore prevent PTI, many other bacterial pathogens have found ways to mask or hide their PAMPs (Figure 1). An example is *A. tumefaciens*, which has a modified flagellin that cannot be detected efficiently by the *Arabidopsis* flagellin receptor FLS2 (Gomez-Gomez *et al.*, 1999). Similarly, variation of flagellin in *Xanthomonas campestris* pv. *campestris* strains allows this bacterial pathogen to avoid detection by FLS2 (Sun *et al.*, 2006). These variations are indicative of selection pressure for evolving unrecognizable PAMPs.

Another strategy used by bacterial pathogens to colonize host plants is the suppression of basal defences by specialized effector proteins (Figure 1). Such effectors are typically translocated directly from bacterial cells into the host cell cytoplasm using a type III secretion system (T3SS), which is found in all *Pseudomonas* pathovars, *Ralstonia solanacearum*, *Xanthomonas* and *Erwinia* and also many mammalian pathogens such as *Salmonella* and *Shigella* (Hueck, 1998). T3SS-deficient bacteria induce strong basal defences in plants and are unable to grow or cause disease symptoms.

An example of a T3SS effector protein that suppresses basal defences is AvrPto from *P. syringae* pv. *tomato*. AvrPto can block callose deposition in tomato plants induced by T3SS-deficient *P. syringae* (Hauck *et al.*, 2003). In *Arabidopsis*, the effector proteins AvrRpt2 from *P. syringae* pv. *tomato* (*Pst*) and AvrRpm1 from *P. syringae* pv. *maculicola* (*Psm*) suppress basal defences by inhibiting defence signalling induced by FLS2 and other putative PAMP receptors (Kim *et al.*, 2005). Transgenic overexpression of AvrRpm1 in *Arabidopsis* leaves enables a T3SS-deficient *P. syringae* strain to grow to near wild-type levels (Kim *et al.*, 2005).

## Effector-triggered Immunity, a Second Layer of the Plant Immune System

Although T3SS effectors can shut down basal defence signalling, plants have evolved a second layer of defence that can detect the presence of T3SS effectors inside the plant cell. This detection system employs intracellular receptors encoded by 'disease-resistance' (*R*) genes. The majority of plant *R* proteins contain a nucleotide-binding site and LRR (NBS-LRR). NBS-LRR proteins mediate resistance against a large range of plant pathogens. Activation of an *R* protein by a pathogen effector protein typically leads to activation of programmed cell death of plant cells surrounding the pathogen. This localized cell death is referred to as the hypersensitive response (HR) and such *R* protein-mediated resistance is referred to as effector-triggered immunity (ETI).

In addition to activation of programmed cell death, *R* protein-mediated resistance is associated with production of reactive oxygen species and nitric oxide, which appear to function both as signalling agents and as direct antimicrobial agents. Reactive oxygen species in concert

with nitric oxide (NO) trigger transcriptional activation of plant defence genes and the HR. It is proposed that superoxide anion ( $O_2^-$ ) and NO react with each other to form highly toxic peroxynitrite ( $ONOO^-$ ), which may be directly or indirectly involved in killing pathogens and host cells (Saito *et al.*, 2006). In self defence, pathogens have evolved a battery of enzymes, antioxidants and free-radical scavengers to combat these molecules.

A newly emerging concept is the ability of some R proteins to induce small interfering RNA (siRNA)-mediated gene silencing. In *Arabidopsis*, the RPS2 R protein was shown to induce the siRNA nat-siRNAATGB2, which leads to the silencing of the *PPRL* gene (Katiyar-Agarwal *et al.*, 2006). Overexpression of *PPRL* specifically reduces RPS2-mediated resistance to *P. syringae*, thus it appears that the RPS2 signalling pathway is negatively regulated by *PPRL* and that full induction of RPS2 signalling requires siRNA-mediated removal of *PPRL* mRNA. Whether or not bacterial pathogens can co-opt siRNA and miRNA regulatory circuits to enhance pathogenesis is still an open question.

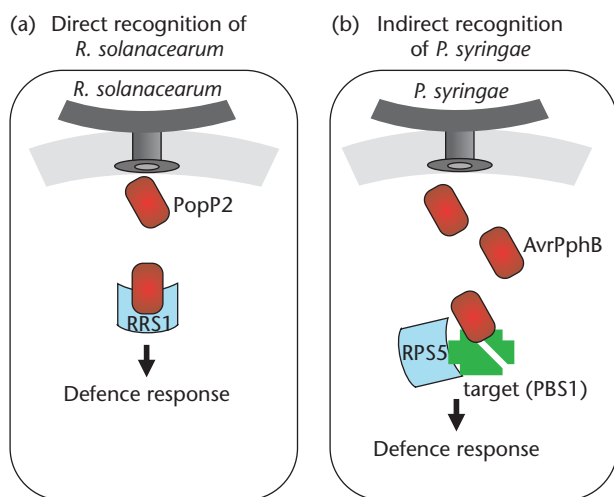
At the molecular level, recognition of pathogen effectors by plant R proteins can either be direct or indirect (Figure 2). The direct recognition model, also termed the ligand-receptor model, proposes that disease-resistant proteins function as receptors to bind pathogen-encoded effector proteins directly. To date, only one example of direct recognition has been observed for a bacterial pathogen, *Ralstonia solanacearum*, in which the R protein RRS1 binds directly to the *R. solanacearum*-effector PopP2 (Deslandes *et al.*, 2003). The indirect mode of recognition, also termed the 'Guard model', involves the detection of modifications made to host proteins by effectors. This mode of

recognition seems to be common in bacterial pathogens and has been observed for the *P. syringae* effectors AvrPphB, AvrRpm1/AvrB, AvrRpt2 and AvrPtoB (Kim *et al.*, 2002; Mackey *et al.*, 2002; Axtell and Staskawicz, 2003; Ade *et al.*, 2007).

Support for the indirect recognition model comes from work on two *Arabidopsis* R proteins, RPM1 and RPS2, which monitor the status of the *Arabidopsis* RIN4 protein. Specifically, RPM1 appears to detect phosphorylation of RIN4 induced by the *P. syringae* effectors AvrRpm1 and AvrB (Mackey *et al.*, 2002). Additional support of the indirect recognition model comes from work on the *Arabidopsis* RPS5 protein, which monitors the status of the *Arabidopsis* PBS1 protein. PBS1 is cleaved by the cysteine protease AvrPphB, a *P. syringae* effector protein. Cleavage of PBS1 is detected by RPS5, which then activates an HR (Figure 2) (Ade *et al.*, 2007). RPM1, RPS2 and RPS5 all physically associate with their 'guardees' prior to pathogen exposure. These R proteins thus function as sentinels to look out for damage caused to potential targets of pathogen effectors. **See also:** Plant Resistance to Infection by Viruses

## Suppression of Effector-triggered Immunity by Bacterial Pathogens

When new resistance traits are bred into crop varieties, such resistance is often overcome by new pathogen strains, leading to a new round of resistance breeding. This unending war between the plant and the pathogen has received much research attention. Several studies have recently provided insight into this phenomenon. Just as bacterial pathogens have developed strategies to suppress PTI, they have also developed mechanisms to suppress ETI. One of these ETI-suppressing strategies is the development of new effectors to suppress the R gene-mediated hypersensitive response associated with disease resistance. For example, the *P. syringae* pv. *syringae* effectors HopAB1 and HopZ3 are able to suppress programmed cell death initiated by other effectors of *P. syringae* pv. *syringae* in the plant *N. benthamiana* (Vinatzer *et al.*, 2006). Deletion of HopAB1 and HopZ3 from *P. syringae* pv. *syringae* restores its ability to trigger the HR. Likewise, effectors such as AvrPtoB, HopPtoE, AvrPphE<sub>Pto</sub>, AvrPpiB1<sub>Pto</sub> and HopPtoF from *Pst* DC3000 are able to suppress effector-triggered programmed cell death in tobacco. *P. syringae* pv. *phaseolicola* also contains effectors that suppress the effector-triggered PCD in bean in a cultivar-specific manner. Recently, the effector HopM1 from *P. syringae* was shown to destroy the immunity-associated protein AtMIN7 and cause infection in the model plant *Arabidopsis* (Nomura *et al.*, 2006). Taken together, these studies show that in a large range of plant species, the bacterial pathogen *P. syringae* is able to suppress the effector-triggered HR, an important component of ETI, and cause disease.



**Figure 2** Direct and indirect recognition of bacterial effectors: (a) The bacterial pathogen *R. solanacearum* injects the effector protein PopP2 into the plant cell. PopP2 is detected by the disease-resistance protein RRS1 via direct binding, which activates downstream signalling events leading to disease resistance. (b) *Pseudomonas syringae* injects the effector protein AvrPphB into the plant cell. AvrPphB functions as a protease to catalyse cleavage of the host kinase PBS1. This modification is detected by the disease resistance protein RPS5, which then activates disease resistance.

## Future Perspectives

The complete genome sequences of several plant bacterial pathogens are now available, which is greatly facilitating the discovery of genes that contribute to pathogenicity. Comparative genomic analyses will enable identification of novel virulence factors through targeted investigation of genes that are unique to specific pathogens. These analyses will be a powerful tool for identification of genes involved in host specificity and virulence.

Even though significant progress has been made towards understanding how plant pathogenic bacteria cause disease, there are still many unanswered questions. In particular, the targets of the majority of bacterial T3SS effector proteins remain unknown. Identification of these targets is critical to our understanding of how bacterial pathogens cause disease in plants. In addition, we do not know which effector targets are monitored by R proteins. Identifying effector targets will thus help us understand both bacterial pathogenesis and host resistance. How R proteins are activated by effectors to induce defence responses, including the HR, is also unclear and needs further investigation.

Finally, the biggest challenge for the future is applying our increasing knowledge of the plant immune system to development of more disease-resistant crops, and in particular, development of crops that display durable resistance across time and space. Identification of key effector targets, and the R proteins that guard them, may facilitate development of such crops.

## Acknowledgements

We would like to thank members of our laboratory for helpful discussion. Work in our laboratory is supported by the US National Institutes of Health (grant numbers R01 GM046451 and R01 GM063761 to R.W.I.) and National Science Foundation (grant number DBI-0321664).

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