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VERSITA

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Pathogenic and mutualistic plant-bacteria interactions: ever increasing similarities

Mini-Review

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Abstract: Plant-interacting bacteria can establish either mutualistic or pathogenic interactions that cause beneficial or detrimental effects respectively, to their hosts. In spite of the completely different outcomes, accumulating evidence indicates that similar molecular bases underlie the establishment of these two contrasting plant-bacteria associations. Recent findings observed in the mutualistic nitrogen-fixing *Rhizobium*-legume symbiosis add new elements to the increasing list of similarities. Amongst these, in this review we describe the role of plant resistance proteins in determining host specificity in the *Rhizobium*-legume symbiosis that resemble the gene-for-gene resistance of plant-pathogen interactions, and the production of antimicrobial peptides by certain legumes to control rhizobial proliferation within nodules. Amongst common bacterial strategies, cyclic diguanylate (c-di-GMP) appears to be a second messenger used by both pathogenic and mutualistic bacteria to regulate key features for interaction with their plant hosts.

Keywords: *Rhizobium* • *Plant pathogenic bacteria* • *Effectors* • *Resistance proteins* • *Antimicrobial peptides* • *C-di-GMP*

1. Introduction

All plants can be abundantly colonized by microbes that cause beneficial, neutral or detrimental effects on the host during their attempts to obtain nutrients and environmental protection. Physical associations between plants and microbes vary from extracellular to intracellular, but in all cases the competence to colonize plant habitats is important for the success of the interaction. Pathogenic bacteria establishing compatible interactions with plants can cause variable damages that often affect plant growth and reproduction. These bacteria enter plant tissues either by wounds or natural openings and occupy the apoplast of plant tissues or the xylem where they multiply and spread, in a process that often involves the participation of hydrolytic enzymes and toxins. In contrast to plant pathogenesis, the outcome of plant infections caused by microorganisms such as soil bacteria collectively known as rhizobia, is an overall benefit to both partners based on nutrient exchange. Rhizobia are able to invade legume roots in nitrogen-limiting environments, leading to the formation of a new organ, the root nodule. Differentiated forms of the bacteria within the root nodule reduce atmospheric nitrogen into ammonia that can then be used by the plant. In return, bacteria receive carbon sources from the plant in a protected niche. Compared to the establishment of plant-pathogenic bacteria interactions, the formation of nitrogen-fixing nodules is a more complex process in which rhizobial infection needs to be co-ordinated with a root developmental program [1].

Plants rely on innate immunity to restrict and repel microbial infections [2,3]. The first line of plant defence is triggered upon the recognition of general elicitors, known as microbe-associated (or pathogen-associated) molecular patterns (MAMPs/PAMPs), by host cell surface-localized pattern-recognition receptors (PRRs). Plants have evolved perception systems for different bacterial MAMPs such as flagellin, lipopolysaccharide, elongation factor Tu, cold shock protein or peptidoglycan, which trigger numerous responses leading to a basal defence response known as PAMP-triggered immunity

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or PTI [4]. Successful pathogens are able to suppress the basal defence or PTI and promote disease by synthesizing effector proteins that are injected into the host cytoplasm through specialized secretion systems (like type III and type IV secretion systems, T3SS and T4SS, respectively). In turn, resistant plants can recognize the presence or the action of these effectors through additional receptors known as resistance (R) proteins, mounting a second line of defence known as effector-triggered immunity or ETI (historically known as gene-for-gene resistance) that would block further attack. Although ETI shares significant overlap with PTI, the former is quantitatively stronger and usually results in a hypersensitive cell death response (HR) at the infection site.

How plants can discriminate between beneficial or harmful microbes has been a long raised question. It is now widely accepted that plant pathogenic and beneficial bacteria are all perceived as intruders by their hosts, that thus mount defence responses to repel the attack and prevent microbial progression. The success of the interaction will therefore depend on the strategies and weapons used by the bacteria to successfully infect plant tissues, but also on their ability to evade, block or overcome the plant defences [5,6]. The outcome of the plant-bacteria interactions depends on the abilities of the host and microbe to reconcile their respective responses to a continuous and mutual give-and-take process involving chemical signalling. Over the last ten years, evidence has accumulated on the commonalities amongst beneficial and parasitic bacteria-plant interactions. This review highlights some of the most recent findings that contribute to the increasing list of similarities found in the establishment of such contrasting interactions.

2. *Rhizobium*-legume symbiosis, a paradigm in plant-bacteria interactions

Rhizobia are able to establish mutualistic nitrogen-fixing symbioses with legume plants. These bacteria use nitrogenase, an exclusive prokaryotic enzyme to reduce molecular nitrogen into ammonia, to fulfil the host's nitrogen nutritional needs. In exchange, bacteria are provided with an exclusive ecological niche (the nodules) where they can multiply at the expense of plant carbohydrates. The formation of nitrogen-fixing nodules requires the mutual secretion and correct recognition of several signal molecules by both the plant and the bacteria [7,8] however, the process is still not fully understood. The best known strategy used by rhizobia to establish symbiosis with legume plants involves the production of lipochitooligosaccharidic Nod factors (NFs) in response to specific flavonoids excreted by the plant. Nod factors induce several responses in the plant which are essential for rhizobial infection and nodule organogenesis such as curling of the root hairs and the formation of nodule primordia after the activation of cortical cell division. Bacteria attached to root hairs penetrate the root through a tubular structure called the infection thread, which grows towards the root cortex where the nodule primordium develops. When the infection thread reaches the primordium, the bacteria are released into the plant cell cytoplasm where they differentiate into endosymbiotic forms, known as bacteroids. Particularly intriguing is how the plant is set to alter its physiology and root anatomy to gain access to nitrogen fixation, a process that will be donated by an intruder only after nodule development and bacterial infection are correctly achieved. As outlined below, some of the signals and the associated responses resemble, either structurally and/or functionally, many of those involved in pathogenic interactions.

Rhizobial infection in legumes triggers several plant responses that resemble those observed in plants challenged with pathogenic bacteria [6]. Cytological and biochemical features of HR have been observed in the legume-rhizobia interaction associated to aborted infection threads, that is interpreted as part of a mechanism called autoregulation of nodulation that allows the plant to control nodule number [9]. Accumulation of salicylic acid (SA), a phenolic compound that plays a key role in plant defence, has been observed in legume plants after inoculation with incompatible rhizobia [10]. The production of the specific NFs prevents accumulation of SA that otherwise would inhibit nodule formation. Production of reactive oxygen species (ROS) upon plant perception of avirulent pathogens have several roles directed towards confinement of the infective microbes including the killing of microbes, reinforcement of cell walls and induction of defence gene expression. ROS also accumulate during the *Rhizobium*-legume interaction but depending on the intensity and localization of the oxidative burst the ROS could have dual roles. The first role is as part of a typical defence reaction to limit bacterial entry and secondly, as compounds needed for infection thread progression or even as signals for the expression of plant and/or bacterial symbiotic genes (reviewed in [11]).

It seems clear that legumes and non-legumes have similar perception systems and protective responses against the infection by microbes. It is critical then that the establishment of any kind of compatible plant–bacteria association requires the microorganisms to evade

detection or avoid host defenses. It is also exciting that both mutualistic and pathogenic bacteria seem to use similar strategies and weapons to elude or modulate the plant's battery of resources directed to arrest bacterial invasion [5,12]. Cell-cell communication through quorum sensing (QS) is essential to coordinate within a bacterial population the expression of genes important for the colonization and infection of the host. Deficiencies in QS lead to the reduction of virulence in phytopathogens and to altered nodulation and nitrogen fixation by rhizobia [13,14]. Quorum sensing is involved in the transition from a free-living to a plant-interacting lifestyle, by turning off behaviours like motility and activating others such as the production of surface polysaccharides (SPSs), biofilm formation or secretion of proteins needed for the successful invasion of the host, both by mutualistic and pathogenic bacteria. Some of those components, like type III and type IV protein secretion systems are needed for the injection of secreted proteins that interfere with plant physiology and metabolism to modulate host defences. Surface polysaccharides can have multiple roles such as protecting the bacterial cell from antimicrobial compounds such as ROS that are released by the host or by participating in the suppression of host defence reactions. The importance of antioxidant systems, involving catalases and superoxide dismutases as virulence factors of some phytothogenic bacteria correlates with the important role of these detoxifying bacterial enzymes for the establishment of the *Rhizobium*-legume symbiosis [12]. Therefore, the *Rhizobium*-legume symbiosis can be considered a model system that can provide new insights about molecular mechanisms that could also be important for different plant-bacteria interactions.

3. Bacterial effectors and plant resistance proteins determine host specificity in the *Rhizobium*-legume symbiosis.

The *Rhizobium*-legume symbiosis is highly specific: each rhizobial species can establish root nodule symbiosis only with a limited number of plant legumes. For example the model bacterium *Sinorhizobium meliloti* can establish effective symbiosis only with *Medicago*, *Melilotus* and *Trigonella* spp. This specificity is determined by both bacterial and plant factors. The production of bacterial Nod factors in response to specific flavonoids secreted by the plant, and the subsequent perception of the bacterial signal by the cognate plant receptor is one of the earliest and key factors in determining the outcome of the *Rhizobium*-legume interaction [1]. Several additional rhizobial genes have been involved in species-specific or genotype-specific nodulation. On the contrary, very little is known about plant factors determining host specificity in the *Rhizobium*-legume symbiosis. Amongst rhizobial genes that participate in host range determination are those coding for T3SS and T4SS and the proteins secreted by these systems, present in some but not all rhizobia. T3SS have been found in *Bradyrhizobium japonicum*, *Rhizobium etli*, *Mesorhizobium loti* MAFF303099, *Sinorhizobium* sp. NGR234 and *S. fredii*, whereas a T4SS with a role in symbiosis has been identified only in *M. loti* R7A. Protein secretion by these systems is tightly regulated and as in pathogenic bacteria, it is activated through a regulatory cascade responding to the presence of the plant host. In rhizobia, protein secretion by these systems occurs during the development of the infection thread and leads to positive, negative or neutral effects on the symbiosis depending on the legume host [15-17]. One of the major roles of effectors secreted by phytopathogens is to suppress plant innate immunity triggered by MAMPs by using different strategies such as altering host protein turnover, RNA metabolism or inhibiting plant kinases involved in plant defence signalling [18]. The exact role of rhizobial effectors during the establishment of symbiosis with legumes is not yet clear. Some effectors like nodulation outer proteins NopL and NopP seem to be specific to a few rhizobia. Interestingly, NopL and NopP are phosphorylated by plant kinases and NopL probably interferes with plant defence responses [19,20]. The majority of the rhizobial effectors studied so far are homologous to proteins secreted by bacterial pathogens, suggesting that they might have similar functions (for a review see [15]). From different studies it seems clear that detrimental effects on the symbiosis caused by protein secretion through these specialized systems are often due to a single rhizobial effector, whereas positive effects are normally caused by the action of several effectors [15]. In the first case, it is very likely that the rhizobial effectors are recognized by putative legume resistance proteins triggering defence reactions that block the infection progress, a situation resembling that of avirulent pathogens and resistant plants. A recent finding supports this hypothesis [21]. Ineffective nodulation of soybean by specific rhizobial strains was known for decades to rely on dominant genes, resembling the gene-for-gene resistance of plant-pathogen interactions. The soybean *Rj2* gene was identified as responsible for the ineffective nodulation phenotype shown by *B. japonicum* strains such as USDA122, whereas the *Rfg1* was involved in preventing nodulation of American soybean cultivars

by certain *S. fredii* strains such as USDA257. In these interactions root hair curling and nodule primordium formation take place but infection thread formation is blocked. Recently, it has been shown that *Rj2* and *Rfg1* are allelic genes encoding a member of the Toll-interleukin receptor/nucleotide-binding site/leucine-rich repeat (TIR-NBS-LRR) class of plant resistance (R) proteins [21]. Interestingly, a T3SS mutant of *S. fredii* USDA257 gains the ability to nodulate soybean plants harbouring the *Rfg1* gene. The putative effector recognized by this resistance protein is not known yet. In any case, it is tempting to speculate that like in plant-pathogen interactions, rhizobial effectors can be recognized by legume resistance proteins blocking the infection process, most probably by triggering plant defence reactions.

4. Plant antimicrobial peptides in pathogenic and mutualistic interactions

Part of the plant immune system relies on the production of antimicrobial peptides (AMPs) like defensins, thionins and lipid transfer proteins [22]. AMPs are ribosomally synthesized antibiotics produced by nearly all organisms, from bacteria to plants and animals. AMPs include all peptides that can kill microbes but not those that exhibit a hydrolytic activity, such as lysozymes, chitinases and glucanases. Certain AMPs exhibit a narrow spectrum, while others are active against a broad-spectrum of microbes like Gram-negative and Gram-positive bacteria and fungi. The peptides can be membrane-disruptive resulting in cell lysis, or may also be actively taken up by transporters to reach their intracellular targets [23,24]. They bind DNA, RNA and proteins and inhibit cell wall, DNA, RNA or protein synthesis [25-27]. Most plant AMPs are characterized by typical arrangements of cysteine residues and belong to a large group of small Cysteine-Rich Peptides (CRPs) [28]. This abundance of AMP-like genes suggests that plants have a broad repertoire of AMPs to fight pathogens, but also the capacity to evolve towards new AMPs with novel specificities.

Very recently, legume AMPs have been revealed to be essential for *Rhizobium*-legume symbiosis. Inside the symbiotic nodule cells, the rhizobia become capable of reducing atmospheric nitrogen to ammonium only after differentiation into bacteroids. These are differentiated bacteria with altered physiology and metabolism. In legumes forming indeterminate nodules, like the model plant *Medicago truncatula*, bacteroids are characterized by their elongated or branched morphologies and show amplified genome content and increased membrane permeability. These bacteroids are incapable of cell division and thus are irreversibly differentiated, non-cultivable bacteria [29]. This terminal differentiation of bacteroids is not observed in all legumes and therefore is not essential *per se* for symbiotic nitrogen fixation, but it could improve the symbiotic efficiency of the bacteroids [30]. It has been recently shown that *M. truncatula* controls rhizobial bacteroid differentiation through the production of nodule-specific AMPs of the Nodule-specific Cysteine-Rich peptides (NCR) family [31-33]. These NCR peptides are targeted to the bacteria and enter the bacterial membrane and the cytosol. A rhizobial protein BacA, also present in an endosymbiotic pathogen *Brucella*, might be required for uptake of these peptides [23]. Thus, it seems that legumes such as *M. truncatula* have been able to evolve AMPs effectors of the innate immune system to manipulate their endosymbionts in order to maximize their own profits. This represents an extraordinary and clear example of how a typical plant defence response, production of antimicrobial peptides, has been adapted to control the proliferation of the invading microbe but also to obtain a benefit from the intruder.

5. c-di-GMP in bacteria interacting with plants

Different bacterial signal transduction systems link the sensing of specific environmental cues to appropriate changes in bacterial physiology and gene expression. These systems play relevant roles during the infection of the plant host as the bacteria will encounter a continuously changing environment to which they have to adapt quickly. In one or more of these signal transduction mechanisms, perception of a primary signal alters the level of a second intracellular signal also known as a second messenger. The cyclic di-GMP (also called cyclic diguanylate, 3',5'-cyclic diguanylic acid or c-di-GMP) was discovered by Benziman and colleagues as an allosteric modulator that activated the membrane-bound cellulose synthase in *Gluconacetobacter xylinus* [34]. Twenty years after its discovery, c-di-GMP is considered a ubiquitous second messenger that controls key processes in most bacteria.

c-di-GMP is synthesized from two molecules of GTP by the action of diguanylate cyclases (DGC) and is hydrolyzed to 5'-phosphoguanylyl-(3'-5')-guanosine (pGpG) and/or GMP by specific phosphodiesterases (PDE). The pGpG is subsequently hydrolyzed into two molecules of GMP. DGC activity is associated with the GGDEF domains and specific activity of c-di-GMP-PDE is associated with EAL or HD-GYP domains [35].

Cyclic diguanylate has been reported to stimulate the biosynthesis of adhesins and components of the biofilm exopolysaccharide matrix and to inhibit various forms of motility [36]. In addition, c-di-GMP controls the long-term survival and responses to environmental stresses [37], the production of antibiotics [38], regulates the proteolysis and cell cycle progression [39], the virulence of animal and plant pathogens [40] and other cellular functions. It is now universally accepted that c-di-GMP contributes to the decision to transit between the motile planktonic and the sessile biofilm lifestyles. To benefit from the advantages that the plant niche provides, phytopathogenic and symbiotic bacteria should modify their lifestyles from a free-living to another in close interaction with their hosts. This transition requires rapid and finely-tuned adaptive responses in which c-di-GMP likely plays a crucial role. Accordingly, whole-genome sequencing has revealed an abundance of c-di-GMP interacting domains containing proteins across the majority of plant symbiotic and pathogenic bacterial species. However, little is yet known about the role of c-di-GMP in plant-interacting bacteria. So far only four proteins (RpfG, XcCLP, EcpB, EcpC) were experimentally demonstrated to be c-di-GMP signalling components in phytopathogens. RpfG and XcCLP of *Xanthomonas campestris*, a HD-GYP domain containing protein and a c-di-GMP receptor respectively, link cell-cell signalling to virulence gene expression [41]. In *Dickeya dadantii*, two c-di-GMP phosphodiesterases, EcpB and EcpC, were shown to regulate multiple cellular behaviours and virulence by controlling the expression of the T3SS [42]. Recent experiments in *Pectobacterium atrosepticum* SCRI1043 have shown a crucial role for c-di-GMP in the regulation of biofilm formation and the secretion of an important adhesion factor for binding to different plants (Pérez-Mendoza *et al*., unpublished data). Similar proteinaceous adhesion factors regulated by c-di-GMP have also been described as crucial biofilm determinants in rhizospheric bacteria belonging to the Pseudomonadaceae family [43]. In rhizobia, functions of c-di-GMP are almost unknown although genomes of these bacteria encode dozens of putative c-di-GMP metabolizing enzymes [44,45]. So far, cellulose synthesis in *R. leguminosarum* is the only example of a function controlled by a c-di-GMP associated protein [46]. Also, a recent report showed that predicted GGDEF and EAL proteins in *S. meliloti* are involved in the control of motility, growth and exopolysaccharide accumulation [47]. However, the implication of c-di-GMP turnover has to be experimentally demonstrated in this latter case. In our laboratory, preliminary results have shown that intracellular c-di-GMP levels control cellular behaviours related with motility and biofilm formation in different symbiotic (e.g. *S. meliloti*) and phytopathogenic bacteria (e.g. *Pseudomonas syringae*) (D. Pérez-Mendoza, H. Prada *et al*., unpublished data). Beyond the clear need for a more complete understanding of the molecular signalling by this second messenger, the c-di-GMP field is growing at an amazing rate. The few systems reported up to now in beneficial and phytopathogenic bacteria are probably just the tip of the c-di-GMP iceberg in plant-interacting bacteria.

6. Concluding Remarks

The knowledge of strategies used by plants to recognize and respond to bacterial intruders, regardless of being beneficial or pathogenic, keeps growing. The primary goal of these plant strategies is to repel the attack and prevent microbial progression even if the invading bacteria have the potential to provide nutrients to the plant. The recent discovery of the existence in legumes of typical plant resistance proteins which are responsible for preventing nodulation by some rhizobia is an additional proof of that hypothesis. Therefore, like pathogens, rhizobia need to evade the plant innate immunity to be able to establish nitrogen fixing symbiosis. Interestingly, some components and responses of plant innate immunity have been adapted in the *Rhizobium*-legume symbiosis for the plant host benefit. The production of specific antimicrobial peptides by some legumes induces the terminal differentiation of endosymbiotic rhizobia which seems to perform better with the corresponding benefit to plant growth. Likewise, the number of common components used by phytopathogenic bacteria and rhizobia is increasing: c-di-GMP is appearing as a second messenger used by plant-interacting bacteria to control behaviours and factors required for the colonization of the host. All these new discoveries within the field of plant-bacteria interactions open the possibility of finding new strategies to fight against plant pathogenic bacteria while improving the nitrogen-fixation efficiency of specific *Rhizobium*-legume symbiosis.

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