Induced Systemic Resistance by Beneficial Microbes

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Abstract

Beneficial microbes in the microbiome of plant roots improve plant health. Induced systemic resistance (ISR) emerged as an important mechanism by which selected plant growth–promoting bacteria and fungi in the rhizosphere prime the whole plant body for enhanced defense against a broad range of pathogens and insect herbivores. A wide variety of root-associated mutualists, including *Pseudomonas*, *Bacillus*, *Trichoderma*, and mycorrhiza species sensitize the plant immune system for enhanced defense without directly activating costly defenses. This review focuses on molecular processes at the interface between plant roots and ISR-eliciting mutualists, and on the progress in our understanding of ISR signaling and systemic defense priming. The central role of the root-specific transcription factor MYB72 in the onset of ISR and the role of phytohormones and defense regulatory proteins in the expression of ISR in aboveground plant parts are highlighted. Finally, the ecological function of ISR-inducing microbes in the root microbiome is discussed.

INTRODUCTION

Rhizosphere: narrow zone immediately surrounding the root system that is influenced by root secretions and associated microbes

PGPR: plant growth–promoting rhizobacteria

PGPF: plant growth–promoting fungi

Induced systemic resistance (ISR): enhanced defensive capacity of the entire plant against a broad spectrum of pathogens; acquired upon local induction by beneficial microbes

Plants fix the solar energy that drives nearly all living processes on Earth. Consequently, plants are central players in a complex food web in which numerous members profusely take advantage of the plant's resources. Besides microbial pathogens and insect herbivores, plants also nurture a vast community of commensal and mutualistic microbes that provide the plant with essential services, such as enhanced mineral uptake, nitrogen fixation, growth promotion, and protection from pathogens (77, 136). These plant microbiota are predominantly hosted by the root system, which deposits up to 40% of the plant's photosynthetically fixed carbon into the rhizosphere, rendering this small zone around the roots one of the most energy-rich habitats on Earth (7). Several genera of the rhizosphere microbiota, which are referred to as plant growth–promoting rhizobacteria (PGPR) and fungi (PGPF), can enhance plant growth and improve health (77, 136).

In 1991, three research groups independently provided evidence that selected PGPR strains can promote plant health through stimulation of the plant immune system (5, 162, 179). Van Peer et al. (162) showed that after colonization of the root system of carnation by PGPR strain *Pseudomonas fluorescens* WCS417r, aboveground parts of the plant acquired an enhanced level of resistance against infection by the fungal pathogen *Fusarium oxysporum*. Additionally, *P. fluorescens* WCS417r–treated plants produced significantly more antimicrobial phytoalexins at the site of infection by the challenging pathogen. Hence, the authors concluded that signals provided by *P. fluorescens* WCS417r to the root system sensitize distal plant parts for enhanced pathogen defense. Using a similar approach in cucumber, Wei et al. (179) demonstrated that colonization of roots by different beneficial *Pseudomonas* and *Serratia* PGPR strains resulted in a significant reduction in disease symptoms after challenge inoculation of leaves with the anthracnose pathogen *Colletotrichum orbiculare*. In both seminal studies, PGPR and pathogen were demonstrated to have remained spatially separated during the experiments, which allowed the authors to conclude that the enhanced level of disease resistance was caused by a plant-mediated immune response called rhizobacteria-induced systemic resistance (ISR). Although Alström (5) did not provide evidence for spatial separation between PGPR and the challenging pathogen *Pseudomonas syringae* pv. *phaseolicola*, this study strongly suggested that colonization of common bean roots by PGPR strain *P. fluorescens* S97 triggered ISR in foliar tissues.

Since these first publications on rhizobacteria-mediated ISR, hundreds of studies in dicots and monocots have reported on the ability of PGPR to promote plant health via ISR. These studies mainly involved *Pseudomonas*, *Serratia*, and *Bacillus* PGPR strains and nonpathogenic *F. oxysporum*, *Trichoderma*, and *Piriformospora indica* PGPF strains, but symbiotic arbuscular mycorrhizal fungi were shown to also trigger ISR. Describing the extensive list of ISR-inducing beneficial microbes is beyond the scope of this review, so readers are referred to several excellent review articles for additional information on this topic (2, 20, 37, 46, 62, 64, 118, 136, 154, 158, 159, 175).

Since the first review on rhizobacteria-mediated ISR in this series (159), significant progress has been achieved in understanding the molecular basis of triggering, signaling, and expression of ISR, especially in the model plant species *Arabidopsis thaliana* (hereafter called *Arabidopsis*). Here, we provide an overview of the mechanisms and molecular players involved in the onset and expression of ISR as triggered by beneficial microbes, highlighting recent advances and identifying key gaps in our understanding of this process.

INDUCED RESISTANCE

The term induced resistance is a generic term for the induced state of resistance in plants triggered by biological or chemical inducers, which protects nonexposed plant parts against

future attack by pathogenic microbes and herbivorous insects (68). Plants can develop induced resistance as a result of infection by a pathogen, in response to insect herbivory, upon colonization of the roots by specific beneficial microbes or after treatment with specific chemicals (**Figure 1**). The induced state of resistance is characterized by the activation of latent defense mechanisms that are expressed upon a subsequent challenge from a pathogen or insect herbivore. Induced resistance is expressed not only locally at the site of induction but also systemically in plant parts that are spatially separated from the inducer, hence the term ISR. Generally, induced resistance confers an enhanced level of protection against a broad spectrum of attackers (175). Induced resistance is regulated by a network of interconnected signaling pathways in which plant hormones play a major regulatory role (111). The signaling pathways that regulate induced resistance elicited by beneficial microbes, pathogens, and insects share signaling components. Therefore, we first highlight the important principles of pathogen- and insect-induced resistance before reviewing the current status of ISR mediated by beneficial soilborne microbes.

MAMPs: microbe-associated molecular patterns

PTI: PAMP-triggered immunity

ETI: effector-triggered immunity

Systemic acquired resistance (SAR): enhanced defensive capacity of the entire plant against a broad spectrum of pathogens; acquired upon local induction by a pathogen

Salicylic acid (SA): plant hormone essential for the immune response against biotrophic pathogens

The Plant Immune System and Induced Resistance

In the past decade, groundbreaking conceptual advances in the understanding of the evolutionary development of the plant immune system (61) placed our knowledge on induced resistance in a clear perspective. In the current concept of the plant immune system, pattern-recognition receptors (PRRs) have evolved to recognize common microbial compounds, such as bacterial flagellin or fungal chitin, called pathogen- or microbe-associated molecular patterns (PAMPs or MAMPs) (16, 190). Plants also respond to endogenous plant-derived signals that arise from damage caused by enemy invasion, called damage-associated molecular patterns (DAMPs) (16). Pattern recognition is translated into a first line of defense called PAMP-triggered immunity (PTI), which keeps most potential invaders in check (42). Successful pathogens have evolved to minimize host immune stimulation and utilize virulence effector molecules to bypass this first line of defense, by either suppressing PTI signaling or preventing detection by the host (11, 31, 42, 109). In turn, plants acquired a second line of defense in which resistance (R) NB-LRR (nucleotide-binding–leucine-rich repeat) receptor proteins mediate recognition of attacker-specific effector molecules, resulting in effector-triggered immunity (ETI) (42). ETI is a manifestation of gene-for-gene resistance (45), which is often accompanied by a programmed cell death at the site of infection that prevents further ingress of biotrophic pathogens that thrive on living host tissue. The onset of PTI and ETI often triggers an induced resistance in tissues distal from the site of infection and involves one or more long-distance signals that propagate an enhanced defensive capacity in still undamaged plant parts (35, 134). This well-characterized form of pathogen-induced resistance is commonly known as systemic acquired resistance (SAR) (139, 171) and confers enhanced resistance against a broad spectrum of pathogens (**Figure 1**). As with the pathogen recognition system, plants also recognize herbivorous insects, most likely through a similar signaling concept (57).

Pathogen-Induced Systemic Acquired Resistance Signaling

In the 1960s, Ross coined the term SAR for the phenomenon in which uninfected systemic plant parts become more resistant in response to a localized infection elsewhere in the plant (126). Over the years, SAR has been extensively reviewed (139, 171), so here we only discuss the important principles and recent findings. In the current concept of the plant immune system, the onset of pathogen-induced SAR is triggered upon local activation of a PTI or ETI response (93) (**Figure 2**). In systemic tissues, SAR is characterized by increased levels of the hormone salicylic acid (SA) (171). Early genetic studies in tobacco demonstrated that SA accumulation and

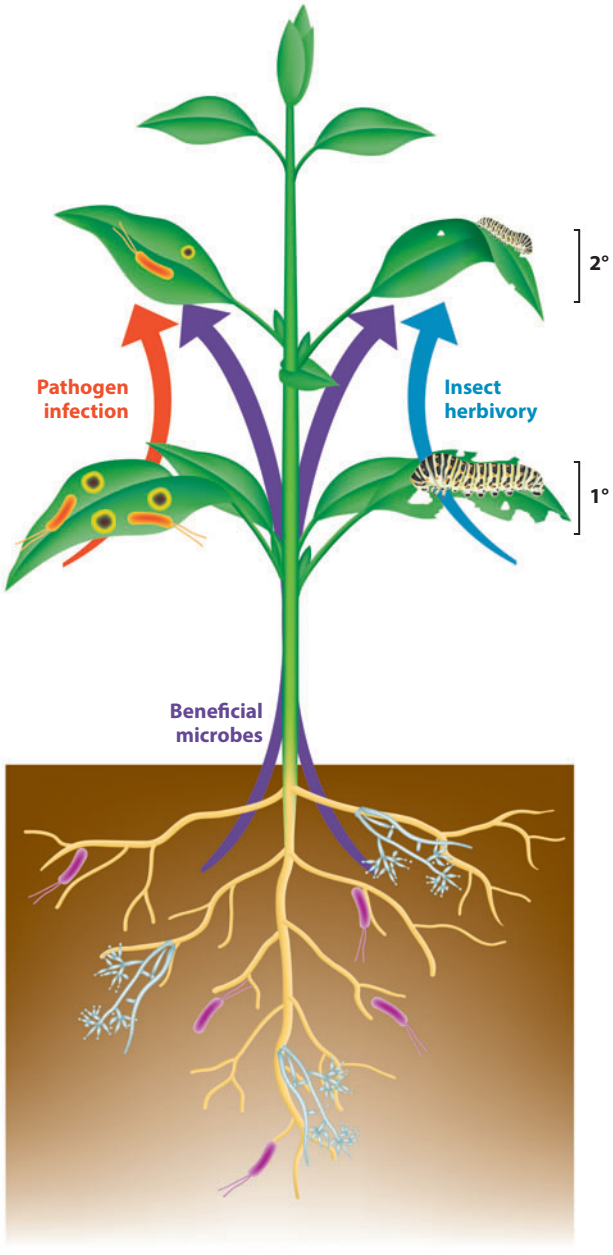

Figure 1

Schematic representation of biologically induced resistance triggered by pathogen infection (*red arrow*), insect herbivory (*blue arrow*), and colonization of the roots by beneficial microbes (*purple arrows*). Induced resistance involves long-distance signals that are transported through the vasculature or as airborne signals, and systemically propagate an enhanced defensive capacity against a broad spectrum of attackers in still healthy plant parts. Consequently, secondary (2°) pathogen infections or herbivore infestations of induced plant tissues cause significantly less damage than those in primary (1°) infected or infested tissues.

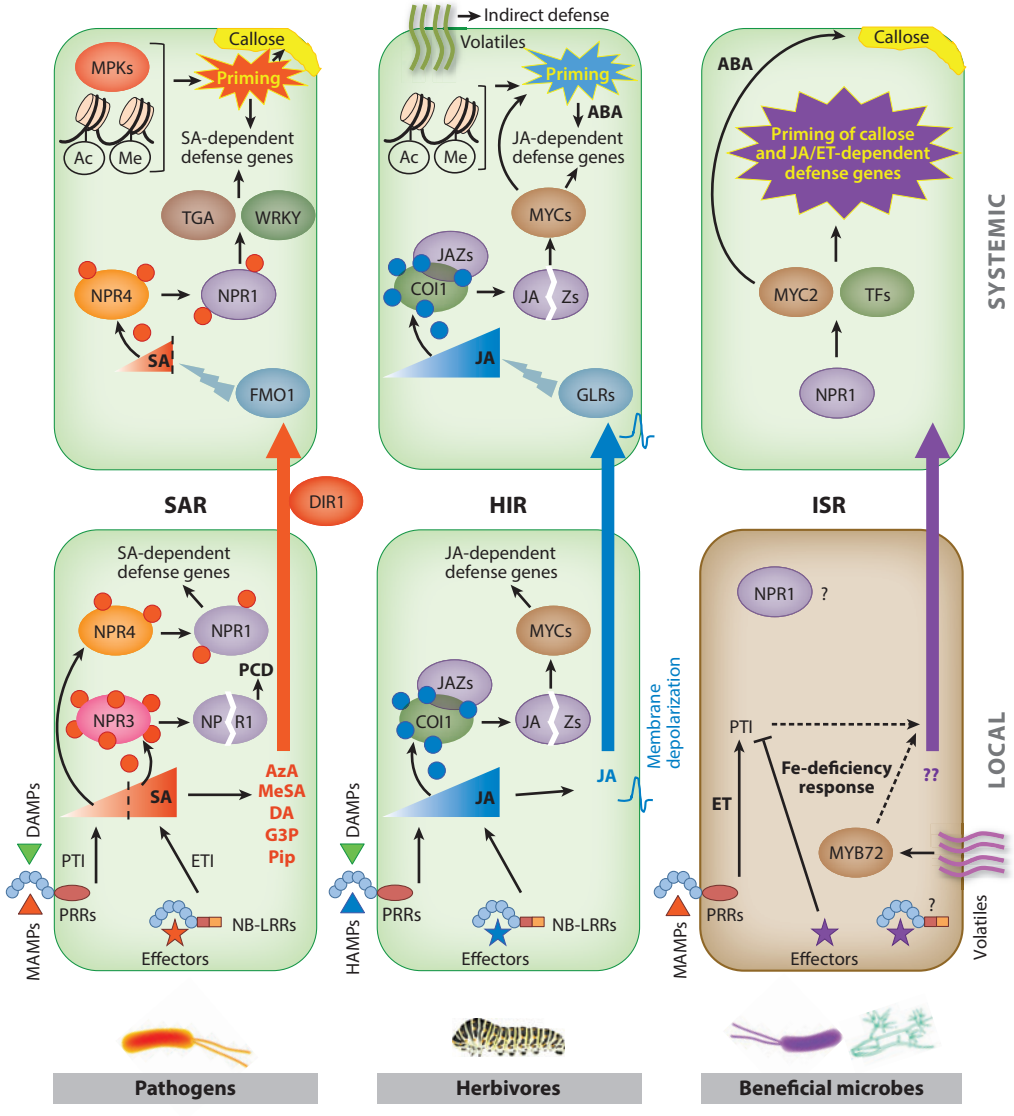

Figure 2

Schematic representation of molecular components and mechanisms involved in pathogen-induced systemic acquired resistance (SAR), herbivore-induced resistance (HIR), and induced systemic resistance (ISR) triggered by beneficial soilborne microbes. Solid black lines indicate established interactions; dashed black lines indicate hypothetical interactions. Colored arrows indicate systemic translocation of long-distance molecular or electric signals (*indicated in the same color at the base of the arrows*). Abbreviations: ABA, abscisic acid; Ac, acetylation; DAMP, damage-associated molecular pattern; ET, ethylene; ETI, effector-triggered immunity; Fe, iron; HAMP; herbivore-associated molecular pattern; JA, jasmonic acid; MAMP, microbe-associated molecular pattern; Me, methylation; NB-LRR, nucleotide-binding–leucine-rich repeat; PCD, programmed cell death; PRR, pattern-recognition receptor; PTI, PAMP-triggered immunity; SA, salicylic acid; TF, transcription factor.

signaling are essential for the establishment of SAR (170). In addition, SAR is accompanied by the coordinate activation of *PATHOGENESIS-RELATED* (*PR*) genes, many of which encode PR proteins with antimicrobial activity (160). Among the best-characterized *PR* genes is *PR-1*, which is often used as a marker for SAR (129, 160).

NPR1: redox-sensitive transcriptional regulator of SA-dependent responses, mediator of SA-JA cross talk, and regulator of SAR and ISR

Herbivore-induced resistance: enhanced defensive capacity of the entire plant against insect feeding; acquired upon local induction by an insect herbivore

For initiation of SAR in distal organs, a long-distance signaling cascade in the vascular tissues, in which the lipid-transfer protein DEFECTIVE IN INDUCED RESISTANCE1 (DIR1) is likely to act as a chaperone for the mobile SAR signal(s), appears to be crucial (24, 80). Despite the fact that SA accumulates in the phloem sap of SAR-expressing plants, grafting experiments with tobacco showed that SA itself is not the translocated SAR signal (170). After this seminal finding, the identity of the mobile SAR signal(s) has been a subject of controversy for many years, but from recent findings a more comprehensive view starts to emerge (reviewed in 35, 63, 134). Genetic and biochemical studies uncovered several metabolites putatively involved in long-distance SAR signaling, including the methyl ester of SA (MeSA), the diterpenoid dehydroabietinal (DA), a glycerol-3-phosphate (G3P)-dependent factor, azelaic acid (AzA), and pipecolic acid (Pip) (**Figure 2**). In systemic tissues, the onset of SAR requires the function of FLAVIN-DEPENDENT MONOOXYGENASE 1 (FMO1) (92), possibly to transduce or amplify long-distance signals originating from primary leaves.

SAR signaling downstream of SA is controlled by the redox-regulated protein NONEXPRESSOR OF *PR* GENES1 (NPR1), which upon activation by SA acts as a transcriptional coactivator of a large set of *PR* genes (reviewed in 43, 102, 111, 139, 171). In noninduced cells, NPR1 is sequestered in the cytoplasm as an oligomer through intermolecular disulfide bonds. SA-induced changes in the cellular redox state facilitate monomerization of NPR1, after which it translocates into the nucleus. In SA-activated cells, NPR1 interacts with members of the TGA family of transcription factors that, together with WRKY transcription factors, bind to the promoters of SA-responsive defense genes, resulting in their activation. Proper functioning of NPR1 requires that the protein is broken down by the proteasome, possibly to allow new NPR1 proteins to reinitiate the transcription cycle (141). Recently, the NPR1 paralogs NPR3 and NPR4 were identified as SA receptors that bind to SA with different affinity (48). NPR3 and NPR4 were shown to function as adaptors of the CULLIN 3 (CUL3) ubiquitin E3 ligase to mediate NPR1 degradation, thereby regulating NPR1 stability and activity. It was proposed that the differential affinity for SA causes NPR3 to mediate degradation of NPR1 at high SA levels, resulting in local programmed cell death during ETI. At lower levels of SA, such as during PTI or in distal SAR-expressing tissues, NPR4 stabilizes NPR1, resulting in the activation of *PR* gene expression. Simultaneously, Wu and coworkers (184) provided evidence that NPR1 itself acts as a SA receptor, resulting in a conformational change of the protein that unveils the NPR1 transcriptional activation domain that is required for *PR* gene activation. Both findings highlight NPR1-like proteins as receptors for the last major plant hormone for which a receptor had not been definitely identified (102) (**Figure 2**).

Herbivore-Induced Resistance Signaling

In the 1970s, Green & Ryan (49) demonstrated that herbivory and wounding of tomato leaves result in the systemic accumulation of proteinase inhibitors that inhibit digestive enzymes in the insect gut. It was proposed that long-distance signals produced at the site of tissue injury mediate a systemic resistance against herbivorous insects (**Figure 1**). Along with the production of anti-insecticidal toxins and feeding deterrents (direct defense), herbivory also triggers the production of volatiles that attract natural predators of the attacking herbivore (indirect defense). Several excellent reviews have been published on this topic (18, 38, 57, 183), so we only discuss the main points here.

Herbivore-induced resistance signaling is initiated upon the release of plant-derived signals (e.g., DAMPs) and elicitors from insect oral secretions at the site of tissue injury, called herbivore-associated molecular patterns (HAMPs) (53, 55, 94, 183) (**Figure 2**). Furthermore, insect-derived effector molecules have been reported that suppress host defenses (55). Hence, plants may have evolved *R* genes against herbivore effectors, as they did for pathogen effectors. An example of this is the *Mi* gene that confers resistance against aphid feeding (127). Perception of herbivory-related elicitors results in rapid release of oxylipins from membrane lipids. The jasmonate (JA) family of oxylipins emerged as key signals, as JA biosynthesis and signaling mutants are impaired in herbivore-induced resistance (57, 178). In the past few years, major progress has been made in unraveling the molecular mechanisms of JA signaling (reviewed in 18, 26, 57, 105, 144, 178). Jasmonoyl-isoleucine (JA-Ile) was identified as the biologically active signal, which is perceived by a coreceptor complex consisting of the F-box protein CORONATINE INSENSITIVE1 (COI1) and JASMONATE ZIM-domain (JAZ) proteins. Perception of JA-Ile by the COI1-JAZ coreceptor results in proteasome-mediated degradation of the JAZ proteins that in uninduced cells suppress positive regulators of JA-mediated defense responses, such as the transcription factors MYC2, 3, and 4. In JA-stimulated cells, the JA signaling pathway becomes derepressed, resulting in the activation of a large number of JA-responsive genes (88) (**Figure 2**).

Jasmonic acid/jasmonate (JA): plant hormone essential for the immune response against necrotrophic pathogens and herbivorous insects

The long-distance signal(s) for systemic expression of herbivore-induced resistance was obscure for a long time. Early work in tomato pointed to the hormonal peptide systemin as a likely systemic signal (106). However, grafting experiments with tomato plants provided evidence that JA itself is the long-distance signal that is systemically transmitted upon herbivory (144). In *Arabidopsis*, it was recently shown that wound-induced membrane depolarization by ion fluxes rapidly mediates JA biosynthesis and JA-responsive gene expression in distal leaves. GLUTAMATE RECEPTOR-LIKE proteins (GLRs) were shown to mediate these wound-induced surface potential changes, indicating that electric signaling is also important in wound-induced systemic signaling (96) (**Figure 2**).

HORMONAL REGULATION OF INDUCED SYSTEMIC RESISTANCE BY BENEFICIAL MICROBES

Since the discovery in 1991 that nonpathogenic microbes in the rhizosphere can trigger ISR (5, 162, 179), a wealth of studies has investigated the molecular mechanism behind this phenomenon. Because of its broad-spectrum effectiveness, rhizobacteria-mediated ISR was initially thought to be mechanistically similar to pathogen-induced SAR. However, Hoffland et al. (54) provided evidence that in radish *P. fluorescens* WCS417r-ISR against *F. oxysporum* developed without accumulation of the PR proteins that are characteristic for SAR. Similarly, *P. fluorescens* WCS417r-ISR in *Arabidopsis* was shown to develop without *PR* gene activation in systemic leaf tissue (113). Testing of transgenic *Arabidopsis* NahG plants that are unable to accumulate SA provided genetic evidence that *P. fluorescens* WCS417r-ISR is mediated by an SA-independent signaling pathway and does not coincide with enhanced SA levels (112, 113). The same appeared to be true for the ISR-inducing PGPR *Pseudomonas putida* WCS358r (165). It was thus concluded that rhizobacteria-mediated ISR and SA-dependent SAR are regulated by different signaling pathways. This was supported by observations that although both rhizobacteria-mediated ISR and pathogen-induced SAR are effective against a broad spectrum of attackers, their ranges of effectiveness are partly divergent (151). Van Loon & Bakker (157) reviewed the cases of rhizobacteria-mediated ISR in which a role for SA had been functionally tested. They concluded that the ability to activate an SA-independent ISR pathway is common for beneficial microbes and occurs in a broad range of plant species. Although the terms SAR and ISR are officially synonymous (51), for pragmatic reasons

we refer to SAR when the induced resistance is triggered by a pathogen or demonstrated to be SA dependent and to ISR when the induced resistance is triggered by a beneficial microbe or demonstrated to be SA independent.

Jasmonic Acid and Ethylene in Control of Induced Systemic Resistance

Along with SA, the plant hormones JA and ethylene (ET) are also important regulators of the plant immune system (145). By using *Arabidopsis* mutants impaired in JA or ET signaling, it was demonstrated that JA and ET are central players in the regulation of rhizobacteria-mediated ISR (114). JA signaling mutants *jar1*, *jin1*, and *coi1* and diverse ET signaling mutants, including *etr1*, *ein2*, *ein3*, and *eir1*, were shown to be defective in *P. fluorescens* WCS417r–ISR (66, 114, 119). For many other PGPR, such as *Serratia marcescens* 90–166, *Pseudomonas protegens* CHA0, and *P. fluorescens* Q2-87, and PGPF, such as *Penicillium* sp. GP16-2, *Trichoderma harzianum* T39, and *P. indica*, genetic evidence in *Arabidopsis* pointed to a role for JA and/or ET in the regulation of ISR (1, 56, 58, 67, 132, 143, 181). The same holds true for other plant species, such as tomato and rice (36, 52, 154, 185), supporting the notion that JA and ET are dominant players in the regulation of the SA-independent systemic immunity conferred by beneficial soilborne microbes (**Figure 2**).

In accordance with its dependency on JA and ET signaling, rhizobacteria-mediated ISR was shown to be effective against attackers that are sensitive to JA/ET-dependent defenses, including necrotrophic pathogens and insect herbivores (reviewed in 116, 166). However, negative effects of beneficial microbes on plant-insect interactions have been reported as well (115).

Beneficial Microbes Triggering the Systemic Acquired Resistance Pathway

Although ISR by beneficial microbes is often regulated through SA-independent mechanisms, several PGPR have been reported to trigger an SA-dependent type of ISR that resembles pathogen-induced SAR. For instance, an SA-producing mutant of PGPR strain *Pseudomonas aeruginosa* 7NSK2 was shown to confer enhanced disease resistance in wild-type bean and tomato but not in SA-nonaccumulating NahG tomato (6, 33). Also PGPR *P. fluorescens* P3 overexpressing the SA-biosynthesis gene cluster of *P. aeruginosa* PAO1 was demonstrated to elicit SA-dependent SAR (85). Although many rhizobacteria have the capacity to produce SA, it is usually not the causal agent of the observed systemic resistance (6, 40, 120, 123). This is likely caused by the fact that rhizobacteria-produced SA is often not released in the rhizosphere but becomes incorporated into SA moiety-containing siderophores that are produced under iron-limiting conditions to improve uptake of ferric iron (Fe^{3+}), which makes SA unavailable for triggering the SAR pathway (6, 9). Examples of wild-type PGPR that have been demonstrated to induce SA-dependent SAR are *Paenibacillus alvei* K165 (147) and *P. fluorescens* SS101 (152). Also a role for SA in the induction of systemic resistance has been established for several *Trichoderma* PGPF (29, 82, 83). In the cases that beneficial microbes trigger SA-dependent SAR, reactive oxygen species that accumulate at the site of tissue colonization seem to be important elicitors (6). Because SA-dependent signaling triggered by beneficial microbes is likely to follow the SAR signaling pathway, we refer the reader to the above section on pathogen-induced SAR.

NPR1: A Common Regulator of Systemic Acquired Resistance and Induced Systemic Resistance

Since its discovery in 1994 (21), the essential role of the transcriptional coregulator NPR1 in SA-dependent SAR has been well characterized (43, 102, 171). NPR1 was shown to be required

for JA/ET-dependent ISR triggered by *P. fluorescens* WCS417r (114) and many other PGPR and PGPF as well (1, 56, 58, 131, 133, 143, 181). While in SAR, NPR1 functions as a transcriptional coactivator of SA-responsive *PR* genes; rhizobacteria-mediated ISR typically functions without *PR* gene activation. Hence, the role of NPR1 in ISR seems to be different from that in SAR (**Figure 2**). In SA signaling, NPR1 is clearly connected to a function in the nucleus (43). In contrast, evidence is accumulating for a cytosolic function of NPR1 in JA/ET signaling and ISR (111, 122, 140, 143). Interestingly, simultaneous activation of SAR and ISR leads to an additively enhanced defensive capacity (163). Whether this is based on the notion that SAR and ISR do not seem to compete for the same subcellular pool of NPR1 is as yet unknown, as the exact molecular mechanism by which NPR1 functions in JA/ET-dependent ISR remains to be established. It is, however, interesting to note that the *NPR1*, *NPR3*, and *NPR4* genes are highly expressed in *Arabidopsis* roots (39), suggesting a role in the regulation of root-associated immune responses.

Priming: sensitization of the whole plant for enhanced defense; characterized by a faster and stronger activation of cellular defenses upon invasion

PRIMING: INVISIBLE PREPARATION FOR COMBAT

Ever since the discovery that SA-independent ISR is not associated with the accumulation of PR proteins or *PR* transcripts in systemic tissues (54, 113), alternative hallmarks for ISR have been sought. In the search for a functional explanation for the role of JA and ET in ISR, the production of these hormones was analyzed in ISR-expressing plants. Surprisingly, colonization of *Arabidopsis* roots by ISR-inducing PGPR did not enhance the production of these hormones in systemic tissues, nor did they induce the expression of JA/ET-responsive genes, suggesting that ISR is based on an enhanced sensitivity to these hormones rather than on an increase in their biosynthesis (112, 164). Experiments in which ISR-expressing *Arabidopsis* plants were challenged with the bacterial pathogen *P. syringae* revealed that ISR was associated with enhanced pathogen-induced expression of the JA-responsive gene *VSP* (164). Similarly, the JA/ET-responsive genes *PDF1.2* and *HEL* showed a potentiated expression pattern in ISR-expressing *Arabidopsis* plants that were challenged with the ISR-sensitive generalist insect herbivore *Spodoptera exigua* but not when the leaves were damaged by the ISR-insensitive specialist herbivore *Pieris rapae* (161). Large-scale analysis of the ISR transcriptome of *Arabidopsis* before and after pathogen challenge confirmed that ISR is associated with potentiated expression of JA/ET-regulated genes that are induced upon subsequent attack (169) (**Figure 2**).

This preparation of the whole plant to better combat pathogen or insect attack is called priming and is characterized by a faster and/or stronger activation of cellular defenses upon invasion, resulting in an enhanced level of resistance (28). Since the observation by Van Peer et al. (162) that ISR in carnation is associated with augmented accumulation of phytoalexins at the site of pathogen infection, a large number of studies with PGPR (1, 3, 14, 22, 64, 166, 177) and PGPF (56, 74, 83, 133, 137) have supported the notion that ISR by beneficial microbes is commonly based on priming. Several studies showed that the transcriptome changes that occur in systemic tissues upon colonization of the roots by beneficial microbes are, in general, relatively mild, especially in comparison to the massive transcriptional reprogramming that occurs during pathogen attack (3, 74, 119, 166, 169, 177). Because the primed state is often invisible in unchallenged plants, this hallmark of ISR is best studied in combination with a challenging pathogen or insect to unveil the enhanced transcriptional changes in primed plants that become apparent only after pathogen or insect attack.

Defense priming emerged as an important cellular process in many types of biologically and chemically induced systemic immunities (28, 47). By studying the costs and benefits of priming, it was shown that the fitness costs of priming are lower than those of constitutively activated defenses (156, 172, 174). The fitness benefits of priming were shown to outweigh its costs under

pathogen pressure, suggesting that priming functions as an ecological adaptation of the plant to reduce damage in a hostile environment. Several excellent reviews have been published on the molecular mechanisms underlying defense priming (27, 47, 104), so we only highlight the most relevant issues below.

Closing the Gates: Augmenting Structural Barriers

In addition to potentiation of defense-related gene expression, augmenting structural barriers has also been implicated in priming by beneficial microbes. Ultrastructural and cytochemical studies of pea roots bacterized with *P. fluorescens* 63-28R showed enhanced cell wall appositions at the site of infection by *Pythium ultimum* (14). Similarly, *P. fluorescens* WCS417r-induced *Arabidopsis* showed an increased frequency of callose depositions at the site of entry of the downy mildew pathogen *Hyaloperonospora arabidopsidis*, which effectively arrested pathogen ingress (153). This priming for enhanced callose deposition was impaired in the abscisic acid (ABA)-related mutant *ibs3*, indicating that this phenomenon is regulated by plant hormone ABA (149, 153). A role for ABA in the activation of primed defense responses in systemic tissue was recently also demonstrated for herbivore-induced resistance (173). The biotrophic pathogen *H. arabidopsidis* is insensitive to JA/ET-dependent defenses; hence the ABA-dependent priming for callose deposition during ISR provides an additional layer of protection that extends the spectrum of effectiveness of ISR (**Figure 2**).

Many foliar pathogens invade plants by entering through stomata on the leaf surface. In *Arabidopsis*, infection of the leaves by *P. syringae* results in attraction of *Bacillus subtilis* FB17 to the root system, where it triggers ISR that protects noninfected plant parts against *P. syringae* infection (128). Interestingly, *B. subtilis* FB17-ISR was shown to mediate accelerated closure of the stomata in response to pathogen attack (69). This PGPR-induced priming for enhanced stomatal closure represents yet another structural barrier that can delay disease progression in ISR-expressing plants.

Transcription Factors Involved in Priming

Because priming is clearly expressed at the transcriptional level, research has focused on signaling proteins and transcriptional regulators that accumulate after induction of the primed state. These factors are thought to remain inactive in enemy-free conditions but provide the plant with the capacity to react with an accelerated defense response upon perception of a pathogen- or insect-derived stress signal. In *Arabidopsis*, the ISR-primed state was shown to be associated with elevated transcript levels of a set of transcription factor genes in which the AP2/ERF family was notably overrepresented (153). Several members of the AP2/ERF family have been implicated in the regulation of JA- and ET-dependent defenses (88), which is in agreement with the observation that JA/ET-regulated genes, in particular, show a primed expression pattern in challenged ISR-expressing plants (169). Pozo et al. (119) analyzed the promoter sequences of all JA-responsive *Arabidopsis* genes with a primed expression pattern in ISR-expressing plants. In silico analysis revealed that the promoters of the ISR-primed genes are significantly enriched for a *cis*-acting G-box-like motif. This motif is a binding site for MYC2 that functions as a key transcriptional regulator of JA-dependent defenses (88). MYC2-impaired *Arabidopsis jin1* mutants were unable to mount *P. fluorescens* WCS417r– or *P. indica*–mediated ISR and were affected in PGPR-induced priming of JA-dependent defenses (119, 143), highlighting MYC2 as an important transcriptional regulator of priming during ISR (**Figure 2**).

Priming: A Molecular Memory of Immunization?

Other signaling molecules implicated in defense priming are mitogen-activated protein kinases (MAPKs). Inactive forms of the MAPKs MPK3 and MPK6 were shown to accumulate after treatment of plants with low concentrations of the SAR-inducing SA-analog benzothiadiazole (BTH), which induces priming (13). After pathogen infection, the enhanced levels of these latent signaling components were activated, resulting in potentiated *PR-1* gene expression and the development of systemic immunity (**Figure 2**). Evidence is accumulating that priming is also associated with chromatin modifications in the promoters of WRKY transcription factor genes that regulate SA-dependent defenses, thereby facilitating potentiated expression of these defense-regulatory genes upon pathogen attack (60) (**Figure 2**). Recently, epigenetic regulation of pathogen- and β-aminobutyric acid (BABA)-induced priming for SA-dependent defenses and herbivore-induced priming for JA-dependent defenses was shown to be inherited by the next generation via chromatin remodeling or DNA methylation (78, 124, 138). Hence, plants seem to have the capacity to memorize a stressful situation and subsequently immunize not only themselves but also their offspring against future attacks (104). It should be noted that MAPK and epigenetic regulatory mechanisms have so far not been demonstrated for ISR by beneficial microbes.

Epiphytes: beneficial microbes living on the plant surface, e.g., in the rhizosphere

Endophytes: beneficial microbes living inside the plant

THE ROOTS OF INDUCED SYSTEMIC RESISTANCE: EARLY SIGNALING EVENTS

Root Colonization

Initiation of ISR requires beneficial microbes to efficiently colonize the root system of host plants (77). For the establishment of a successful mutualistic association, host plants and microbes need to respond to reciprocal signals and accordingly prioritize their responses so as to develop a lifestyle that provides mutual benefits. In the well-studied mycorrhizal and rhizobial symbioses, host-secreted strigolactones and flavonoids stimulate the production of symbiotic Sym and Nod factors by the microbes, which in turn activate a common symbiosis (Sym) signaling pathway in plant roots that is necessary for the establishment of a successful symbiotic relationship (100). How nonsymbiotic PGPR and PGPF establish a prolonged mutualistic interaction with plant roots is less well characterized, but a picture is emerging that a molecular dialog is also essential for these mutualistic interactions (77, 136, 188).

Many free-living PGPR actively respond to root exudates by adjusting their transcriptional program toward traits involved in chemotaxis, root colonization, and energy metabolism (44, 81, 84, 98). Once established on the root epidermis, PGPR epiphytes typically form biofilms in which multicellular communities are enclosed within an extracellular matrix of self-produced polymeric substances, mainly exopolysaccharides (EPS), and mucilage (128) (**Figure 3**). Biofilm formation is essential for the colonization of roots by *B. subtilis* and was recently shown to be stimulated by polysaccharides derived from host cell walls that function as signaling molecules for the expression of bacterial genes involved in matrix production (12). Within the EPS matrix, bacterial cells integrate host and self-derived signals and function in unison to coordinate the production and release of compounds related to plant growth promotion, nutrition, and ISR. Conceptually, this matrix can be considered as the mutualistic interface through which host plants and beneficials exchange solutes and chemical information. PGPR endophytes commonly enter the root interior through cracks in the newly emerged lateral roots or utilize root hairs and the apical zone as entry points (**Figure 3**). This mode of entry is facilitated by cell wall–degrading exo-enzymes, such as cellulase and pectinase (125).

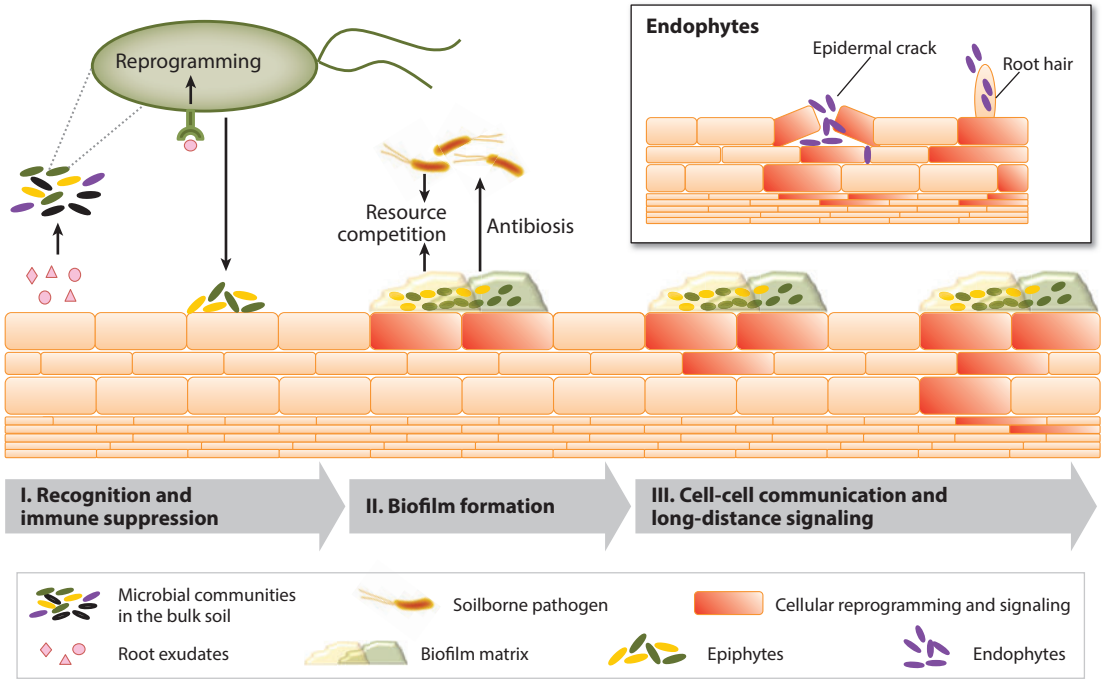

Figure 3

Diagram of the main phases involved in root colonization by beneficial soilborne bacteria and their functions. (I) Plant roots selectively secrete organic compounds that function as semiochemicals for the assembly of the root microbiome. Selected bacterial strains from the bulk soil communities specifically respond to host signals and reprogram to express traits related to root colonization. Microbes that have evolved as endophytes commonly enter the root interior through cracks in the root epidermis or through root hairs (*inset*). In phase I, local immune responses in host roots are transiently suppressed by epiphytic or endophytic plant growth–promoting rhizobacteria (PGPR), allowing bacteria to propagate on the root epidermis or intracellularly. (II) Once PGPR are established on the root, cell wall polysaccharides from the host function as environmental cues to promote biofilm formation on the root surface. Within the biofilm matrix, individual members and/or microbial consortia integrate host and self-derived signals to activate processes in the plant that lead to enhanced plant growth and induced systemic resistance (ISR). In addition, root microbiota protect root tissues against soilborne pathogens via the production of antibiotics and competition for nutrients and niches. (III) Early root responses to beneficial microbes are locally expressed in the epidermis and are subsequently communicated to the inner cell layers and to the aboveground plant parts via yet elusive long-distance molecules, where these signals confer ISR.

Although well known for their ability to adapt in the rhizosphere of various hosts, endophytic PGPF have evolved sophisticated strategies to colonize the intercellular space of the epidermal cortical root layer (97, 136). The fungal endophyte *P. indica* is a typical generalist with the unique ability to colonize the inter- and intracellular space of a wide range of mono- and dicotyledonous plants. In order to adapt to highly variable host environments, this fungus can adopt alternative lifestyles that are determined by host-specific metabolic cues (70). Endophytic *Trichoderma* spp. preferentially colonize the root hairs, where they typically form structures analogous to the appressorium of plant-pathogenic fungi (97). In the *Trichoderma virens* Gv29-8-maize interaction, it was shown that plant-derived sucrose and a sucrose-dependent signaling network in the fungus are crucial for the establishment of a mutualistic association (167, 168).

Upon root colonization, *Pseudomonas*, *Bacillus*, and *Trichoderma* strains have been shown to initiate an auxin-dependent root developmental program that results in abundant lateral root formation, increased root hair length, and enhanced plant biomass production (30, 101, 187, 189)

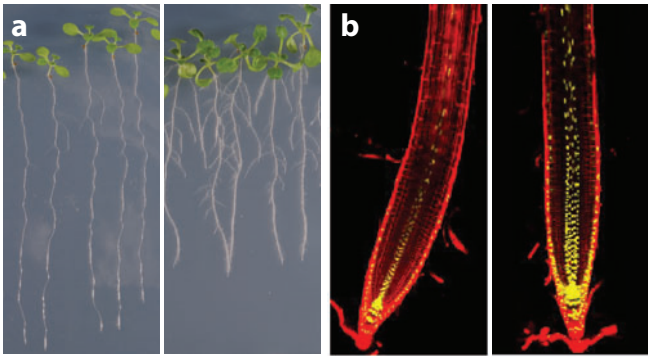

Figure 4

Plant growth–promoting effect of plant growth–promoting rhizobacteria (PGPR) strain *Pseudomonas fluorescens* WCS417r on *Arabidopsis*. (*a*) Colonization of *Arabidopsis* roots by *P. fluorescens* WCS417r increases shoot biomass and stimulates lateral root formation and root hair development. (*b*) *P. fluorescens* WCS417r–induced changes in root architecture are stimulated via auxin-dependent responses in the *Arabidopsis* root. Shown are confocal images of nonbacterized (*left*) and bacterized (*right*) roots (*red*) expressing the auxin-sensitive reporter *DR5::venusYFP* (*yellow*). Images are reproduced with permission from Reference 187.

(**Figure 4**). Although this trait clearly contributes to the plant growth–promoting activity of these beneficial microbes, its relation to ISR is often unclear. Recently, however, it was shown that *Arabidopsis* wild-type and ISR-defective mutants show similar PGPR-elicited alterations in the root architecture (187), suggesting that the capacity of PGPR to promote growth and to trigger ISR can function independently.

Modulation of Root Immunity

Like pathogens, beneficial microbes need to overcome or evade plant immune responses in order to establish a prolonged and intimate mutualistic interaction with the host. Molecules and strategies commonly used by pathogens to suppress host immunity are also employed by soilborne ISR-inducing microbes (176, 188). For instance, the ISR-inducing arbuscular mycorrhizal fungus *Rhizophagus intraradices* utilizes the symbiotic effector SP7 to suppress ET-mediated immune responses and promote fungal biotrophy (65). Similarly, the ectomycorrhizal fungus *Laccaria bicolor* produces the symbiosis effector MiSSP7, which is translocated into the plant cell nucleus, where it promotes the expression of auxin-responsive genes, possibly to suppress SA-dependent defenses (117). Additionally, the PGPF *P. indica* activates the JA signaling pathway in *Arabidopsis* roots to suppress both early and late defense responses (59). Transcriptome analyses of *P. indica* during root colonization revealed a large number of genes encoding small secreted proteins that may function as immune suppressive effectors (191). Downregulation of root immune responses has also been described for *Trichoderma* PGPF (17) and for ISR-inducing PGPR, such as *B. subtilis* FB17 and *P. fluorescens* WCS417r (71, 91, 169). The latter was shown to suppress activation of defense genes in *Arabidopsis* roots that are triggered by the MAMP flg22 (91). Possibly, colonization of the roots requires local suppression of PTI to protect the PGPR against MAMP-triggered production of antimicrobial compounds (**Figure 3**).

Many bacterial pathogens deliver immune-suppressive effectors in the plant cell via a type III secretion system. Despite the fact that many PGPR are equipped with a similar type III secretion

AUTOREGULATION OF MUTUALISM

Despite their net fitness benefit, mutualistic plant-microbe interactions also come with a fitness cost. In the rhizobial and mycorrhizal symbioses, costs and benefits of the symbiosis are balanced via a sophisticated long-distance signaling process called autoregulation, which controls the level of infection by the symbiont (95, 142). In the *Rhizobium*-legume symbiosis, autoregulation is initiated in the roots, where primary *Rhizobium* infections trigger the production of Clavata3/endosperm-surrounding region (CLE) glycopeptides (99). CLE glycopeptides are then loaded into the xylem and systemically transported to the shoot, where they bind to a leucine-rich repeat receptor-like kinase. A second, yet elusive, signal is generated in the shoot and is translocated back to the roots to restrict nodulation. Interestingly, several autoregulation mutants are hypersusceptible to pathogen infection, suggesting that systemic defense signaling may be an intrinsic part of the autoregulation phenomenon (188). It is tempting to speculate that beneficial associations with nonsymbiotic PGPR and PGPF are controlled by a similar autoregulation strategy, resulting in the ISR phenomenon that provides systemic protection in roots and shoots against a broad spectrum of pathogens. The recent finding that colonization of *Arabidopsis* roots by *P. indica* inhibits secondary colonization of distal roots (107) supports this hypothesis.

machinery and produce functional effectors (75, 86), their role in mutualistic plant-microbe interactions is still unclear. Along with suppressing local host defenses to facilitate colonization, PGPR effectors may also function as host-range specificity determinants under control of host resistance (R) proteins, as in the case of the *Rhizobium*-legume symbiosis (186, 188). This would allow host plants to utilize components of their immune system to select for their mutualistic partners. The observation that ISR is genetically determined by the host-microbe combination (148, 150, 165) supports this hypothesis.

Microbial Elicitors of Induced Systemic Resistance

Although beneficial microbes seem to actively suppress local host defense responses in the roots, ISR-inducing beneficial microbes must also produce elicitors that are responsible for the onset of systemic immunity. It has been proposed that ISR is the resultant of a long-distance signaling mechanism that in rhizobial and mycorrhizal symbiosis is responsible for autoregulating the colonization density of the symbionts (142, 188) (see sidebar, Autoregulation of Mutualism). In this scenario, local immune suppression and systemic activation of defense priming would balance the costs and benefits of mutualism.

Early reports on MAMPs and other elicitors of ISR-inducing PGPR focused on the involvement of lipopolysaccharides (LPS) and the iron-regulated metabolites pyoverdin and SA (37, 159). In the past years, many other ISR elicitors have been identified, including antibiotics, such as 2,4-diacetylphloroglucinol (DAPG) and pyocyanin; flagella; *N*-acyl homoserine lactones; iron-regulated siderophores; and biosurfactants (reviewed in 37). In addition, volatile organic compounds, such as 2R,3R-butanediol produced by *B. subtilis* GB03 (130) and a C13 volatile emitted by *Paenibacillus polymyxa* (73), were demonstrated to elicit ISR (**Figure 2**). Several of these ISR elicitors were shown to act redundantly (10). For example, LPS-containing cell walls, flagella, and the siderophore pyoverdine of *P. putida* WCS358 elicit ISR in *Arabidopsis* when applied exogenously to the roots (90). However, *P. putida* WCS358 mutants lacking pyoverdine, flagella, or the immunizing O-antigenic side chain of LPS were still capable of triggering ISR, indicating that multiple bacterial elicitors of this strain can trigger systemic immunity. This resembles PTI in

DAPG: 2,4-diacetylphloroglucinol

plant-pathogen interactions, where recognition of multiple PAMPs is funneled into the same PTI signaling pathway (16, 190).

In PGPF, several elicitors with defense-activating properties have been identified (135). These include enzymatic proteins, such as xylanases and cellulases, but also proteins and peptides with more specific defense-eliciting functions, such as Sm1 from *T. virens*. (41). However, in most cases functional evidence for a role in ISR in vivo, e.g., via gene-knockout experiments, is lacking. Recent comparative genomics of *Trichoderma* spp. and mycorrhizal fungi revealed the presence of many genes that encode putative effectors and elicitors, which offers a great potential to further investigate their role in the elicitation of ISR (97, 146).

MYB72: root-specific R2R3-type MYB transcription factor; functions during the onset of ISR by beneficial microbes and is associated with the iron-deficiency response

MYB72: An Early Root-Specific Regulator of Induced Systemic Resistance

ISR elicited by beneficial microbes involves long-distance signaling that starts at the root-microbe interface. Very few studies have investigated signaling components of the plant root that are important for the initiation of ISR. Using the *Arabidopsis* mutant *eir1*, which is insensitive to ET in the roots only, it was shown that ET signaling in the roots is required for the expression of ISR in the leaves and possibly facilitates the generation or translocation of a yet elusive systemic ISR signal (66). Furthermore, the R2R3-type MYB transcription factor gene *MYB72* was identified as one of the significantly induced genes in *Arabidopsis* roots in response to *P. fluorescens* WCS417r (169). In uninduced plants, *MYB72* is little expressed in the root vascular bundle but becomes highly expressed in root epidermis and cortical cells upon colonization by ISR-inducing PGPR (**Figure 5**). Knockout *myb72* mutants of *Arabidopsis* are impaired in their ability to express ISR against different foliar pathogens upon treatment with *P. fluorescens* WCS417r or *P. putida* WCS358r, indicating that this root-specific transcription factor is essential for the onset of ISR. *MYB72* is also induced in *Trichoderma*-colonized *Arabidopsis* roots and shown to be crucial for *Trichoderma* ISR (4, 17, 133), suggesting that MYB72 is a node of convergence in the ISR signaling pathway triggered by different beneficial microbes. Overexpression of *MYB72* does not confer enhanced resistance to foliar pathogens (155), suggesting that MYB72 acts in concert with one or more other signaling components.

MYB72 is specifically induced in roots under iron-limited conditions or conditions that distort iron uptake, such as high zinc concentrations (34, 103), pointing to a link between iron homeostasis and the onset of ISR (**Figure 5**). This notion is supported by the fact that the expression of the iron-deficiency marker genes *FRO2* and *IRT1*, coding for a Fe^{3+} chelate reductase and a Fe^{2+} transporter, respectively, are coregulated with *MYB72* in *Arabidopsis* roots colonized by ISR-inducing *Pseudomonas* strains but not in roots colonized by the ISR-noninducing *P. fluorescens* strain WCS374r (C. Zamioudis & C.M.J. Pieterse, unpublished results). Detailed genome-wide transcriptional profiling in roots of *Arabidopsis* wild-type and mutant *myb72* confirmed that MYB72-associated root transcriptional responses to ISR-inducing rhizobacteria are dominated by genes associated with the iron-deficiency response. Because many *Pseudomonas* spp. produce iron-chelating siderophores to take up iron from the environment, induction of the iron-deficiency response in the roots may be caused by bacterially inflicted iron stress. However, siderophore mutants of *P. fluorescens* WCS417r were still able to induce *MYB72* and the iron uptake genes *FRO2* and *IRT1*. Moreover, these genes were induced by volatile organic compounds produced by ISR-inducing PGPR and PGPF (189). Hence, the iron-deficiency response is activated even though plants do not physically experience iron limitation (**Figure 2**). How the iron-deficiency response functions in the communication between beneficial microbes and the plant root is currently unknown. It may be required at the root-microbe interface for the production of semiochemicals or for the generation and/or translocation of a long-distance ISR signal (**Figure 5**).

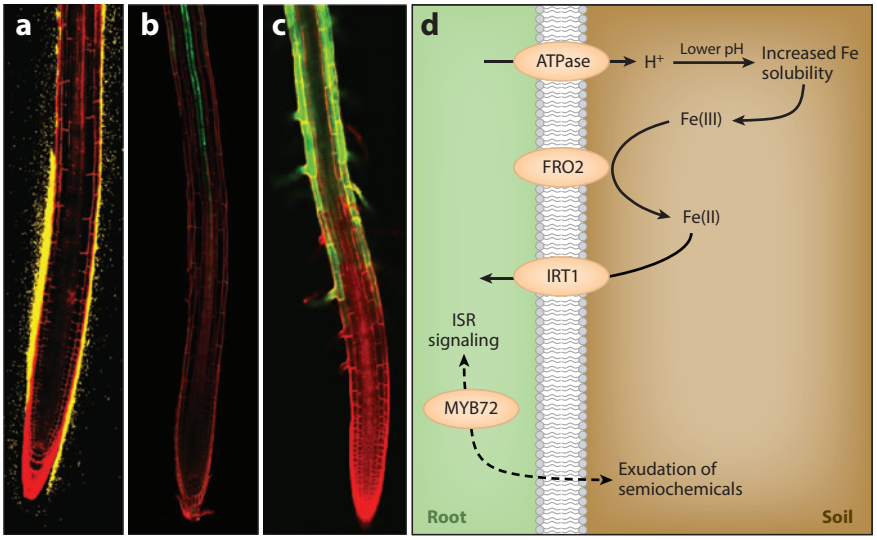

Figure 5

(*a*) Confocal image of *Arabidopsis* root epiphytically colonized by induced systemic resistance (ISR)-inducing *Pseudomonas fluorescens* WCS417r bacteria expressing yellow fluorescent protein (YFP) (*yellow*). Bacterial cells that are in contact with the root form a biofilm, whereas cells in the root vicinity retain the planktonic state (*red color in panels* a–c *indicates propidium iodide–stained* Arabidopsis *root*). (*b*) Nonbacterized *Arabidopsis* root of *pMYB72::GFP* reporter line expressing green fluorescent protein (GFP) under the control of the *MYB72* promoter. In nonbacterized roots, *MYB72* is mainly expressed in the xylem parenchyma cells (*green*). (*c*) Root colonization by *P. fluorescens* WCS417r and conditions of iron (Fe) deficiency activate *MYB72* expression in the root epidermal and cortical cell layer (*green*). (*d*) Schematic representation of the iron-deficiency response in *Arabidopsis* roots. During the iron-deficiency response, roots acidify the soil environment via proton extrusion to solubilize Fe(III), which is then reduced to Fe(II) by the action of the ferric chelate reductase FRO2. Fe(II) is then imported in the root via the iron transporter IRT1. Upon colonization of the roots by ISR-inducing rhizobacteria, *MYB72* is coordinately upregulated with *FRO2*, *IRT1*, and several other iron deficiency–regulated genes (*not shown*). MYB72 may function in the generation or translocation of long-distance ISR signals. Alternatively, MYB72 may act in the production and/or secretion of root semiochemicals that stimulate plant growth–promoting rhizobacteria to produce signals that trigger ISR.

Microbiome: communities of commensal, mutualistic, and pathogenic microorganisms that live in close association with a host

Rhizosphere effect: effect of root secretions in the rhizosphere on microbial biomass, activity, and community composition as compared with the bulk soil

THE RHIZOSPHERE MICROBIOME AND INDUCED SYSTEMIC RESISTANCE

Engaging a Social Network with the Underground

Beneficial microbes with ISR-eliciting properties have often been selected from large screens of the root microbiome for members that have biological control activities (37, 64, 136, 175). The rhizosphere microbiome contains a mesmerizing diversity of microbes that interact with each other in a positive or negative manner (15, 89). In most soils, growth of microbes is limited by carbon availability, a commodity of which photosynthesizing plants have plenty. Plants deposit up to 40% of the photosynthetically fixed carbon via their root system (rhizodeposition), where it becomes accessible for microbiota in the rhizosphere (7). This causes a 10–100-fold increase in the microbial density in the rhizosphere and a microbial community composition that is significantly distinct from the surrounding bulk soil, a phenomenon called the rhizosphere effect (8) (**Figure 3**). As the gut and skin microbial communities affect human health, the composition

PLANT AND HUMAN MICROBIOMICS

New opportunities offered by next-generation sequencing techniques have inspired a renewed interest in microbiomics, especially in the medical field. Large-scale studies, such as the Human Microbiome Project, have shown that specific microbial communities that reside in or on body parts, such as the gut or the skin, can have a decisive influence on human health. Particular microbial communities have been associated with obesity, psoriasis, asthma, inflammatory bowel disease, colorectal cancer, cardiovascular disease, and other human conditions (25). Although different in many aspects, plant and human microbiomes share important similarities (15). Not only do both host microbiomes competitively exclude pathogens from their hosts, they also modulate host immunity and assist in nutrient uptake and utilization. However, whereas the human microbiome is limited in its phylogenetic diversity, plants are colonized by extremely diverse communities, especially on their roots (25, 89). Nonetheless, to gain a thorough understanding of the biological mechanisms that control the structure of plant and human microbiomes, essentially similar questions need to be addressed. Answers to these questions will ultimately lead to innovative ways of regulating the health of any host.

of microbial communities in the rhizosphere can have significant effects on plant health (15, 25, 110) (see sidebar, Plant and Human Microbiomics).

Recently, next-generation sequencing technologies have made it feasible to study the immense microbial diversity in the rhizosphere in detail. These studies confirmed that the rhizosphere microbiota consist of a subset of the total diversity of the bulk soil in which plants are grown (19, 79, 108). Being the reservoir from which rhizosphere inhabitants are selected, soil type is an important factor in determining rhizosphere microbial community composition. Nonetheless, in the same soil different plant species select distinct microbial communities, presumably because of differences in root exudates (50). Although soil is the decisive factor in structuring root-associated microbial communities, there is overlap in the bacterial species that are selected by genotypically similar plants across different soils (19, 79, 108). This suggests the existence of coevolutionary relationships between plant-inhabiting bacteria and their hosts.

Evidence is accumulating that plants can modulate the composition of their root microbiome, a capacity that can provide important fitness benefits to the plant (15, 110). Plants can specifically select and enrich certain bacterial groups or species through the secretion of compounds that selectively stimulate or repress microbial growth (15). The PGPR *P. putida* KT2440 is recruited by maize plants through the secretion of benzoxazinoids, antimicrobial compounds that inhibit most microbes but to which KT2440 is insensitive (98). Another example of recruitment was demonstrated upon infection of foliar parts of *Arabidopsis* by pathogenic *P. syringae*. In plants under pathogen attack, the roots intensify active secretion of malic acid, which increases abundance of, and biofilm formation by, the ISR-eliciting *B. subtilis* strain FB17 in the rhizosphere (128). Such pathogen-induced recruitment of beneficials is in line with the observation that exogenous application of the defense hormone JA to the leaves of *Arabidopsis* changed the rhizosphere abundance of several taxa that have been associated with disease suppression (23).

Disease-suppressive soils: soils in which a pathogen does not establish or persist, or in which it causes disease at first but then disease declines with successive cropping of the host

Disease-Suppressive Soils

A striking example that coevolution of plant-beneficial microbe interactions for the benefit of plant health occurs in nature is evidenced by the existence of disease-suppressive soils (180, 182). The disease suppressiveness of these soils is generally based on specific microbial populations that antagonize pathogens. Disease-suppressive soils occur worldwide, and some develop following

prolonged monoculture of a specific crop (110, 182). Microorganisms that have been demonstrated to contribute to the disease suppressiveness of soils include *Trichoderma*, *Fusarium*, *Streptomyces*, *Bacillus*, and *Actinomyces* spp.; however, bacteria from the genus *Pseudomonas* have most often been identified as important players (89, 182). Possible mechanisms of disease suppression include competition for space and (micro)nutrients; hyperparasitism; antagonism via microbial production of secondary metabolites, such as iron-chelating siderophores, antibiotics, and lytic enzymes; and elicitation of ISR (75, 110, 182) (**Figure 3**).

Among the best-characterized examples of disease suppressiveness are *Fusarium* wilt–suppressive soils and take-all decline in wheat monocultures (2, 87, 110, 180, 182). The basis of *Fusarium* wilt suppressiveness includes the activity of nonpathogenic *Fusarium* spp. that compete for carbon with pathogenic *Fusarium* spp., and *Pseudomonas* spp. that antagonize the pathogen via the production of siderophores and the antibiotic phenazine (87). Take-all disease caused by the soilborne pathogen *Gaeumannomyces graminis* gradually declines during consecutive years of wheat monoculture because of the buildup of populations of *Pseudomonas* spp. that produce the antibiotic DAPG, for which the fungal pathogen is highly sensitive (180).

Many *Pseudomonas* spp. strains that have been isolated worldwide for their excellent plant-protective properties appear to be genetically very closely related (R.L. Berendsen, C.M.J. Pieterse, P.A.H.M. Bakker, unpublished results). This suggests not only that plants select for specific bacteria with biocontrol activity but also that similar strains are present globally in different soils. Some of these closely related strains were isolated from different plant species and thus might embody a group of universal PGPR, whereas others were isolated from the same plant species and could represent plant species-specific beneficials. This also became evident from studies on disease-suppressive soils. Although at least 18 genotypically different DAPG producers have been found in disease-suppressive soils across Europe and the United States, some of the same genotypes have been found in different locations (32). Furthermore, it was demonstrated that in side-by-side fields with long histories of either monocultures or crop rotations with wheat or flax, DAPG producers were only found in the monoculture fields of both crops and that the prevalent DAPG producers in flax monoculture fields were genotypically different from those in wheat monoculture fields (72).

Is Induced Systemic Resistance Constitutively Active in the Field?

The microbial community in the rhizosphere is extremely diverse, and members of many genera have the potential to elicit ISR. On top of that, many different microbial determinants have been implicated in eliciting ISR. Thus, the question of whether all plants in the field are already in the state of ISR seems reasonable, and it may explain some observations of inconsistent performance of induced resistance in the field. However, there are many examples of PGPR or PGPF that induce ISR under field conditions when introduced to soil or planting material (64, 175). This suggests that untreated plants do not constitutively express ISR or at least that they are not induced up to their full potential. This apparent contradiction may be explained by the relatively high population densities of introduced bacteria that are required for effective elicitation of ISR. For example, the threshold population density of *P. fluorescens* WCS374r required to elicit ISR in radish is 10^5 colony-forming units per gram of root (121). The occurrence of such a high density of a single bacterial genotype in the rhizospheres of field-grown plants seems unlikely, with the exception of the situation in some disease-suppressive soils. For example, in take-all decline soil, population densities of DAPG-producing *Pseudomonas* spp. are consistently above the 10^5 threshold (182). Given the observation that DAPG production by *P. fluorescens* is a major determinant of ISR (181), ISR may be operative in take-all decline soils in which DAPG-producing *Pseudomonas* spp. play a

prominent role. A demonstration that suppressive soils not only control a single target soilborne pathogen or disease but also stimulate the plant immune system would greatly enhance their standing as an important approach to managing diseases and insects in conventional and organic crop production systems.

CONCLUDING REMARKS

Since the discovery that selected beneficial soilborne microbes can stimulate plant immunity, now more than 20 years ago, a wealth of knowledge has accumulated on the mechanisms underlying ISR. The plant immune system plays a central role in the social network of plants that, on the one hand, can be activated to ward off enemies and, on the other hand, can be suppressed to accommodate mutualists. Both aspects of host immune modulation are operative in the ISR phenomenon, and their interplay will definitely be a subject of future studies. A major gap in our knowledge is how recognition of beneficial microbes at the root-soil interface drives the whole plant body toward enhanced growth and elevated stress resistance. The first steps toward unraveling the molecular dialog between roots and ISR-eliciting microbes have been made, but major questions still need to be resolved. For instance, how are signals from ISR-eliciting microbes perceived in the roots and translated into specific plant responses that mediate enhanced defense in foliar tissues? Do plant roots produce one or more long-distance ISR signals, and if yes, what is their nature? Long-distance signaling molecules may be generated and/or modified in the outermost root cell layer, as indicated by the expression pattern of *MYB72*, which is required for the onset of ISR in the roots. As is the case with the establishment of SAR and herbivore-induced resistance (24, 57), signaling cascades in the xylem parenchyma cells of the vascular bundle may also be critical for the establishment of ISR in foliar tissues. As plant roots respond to ISR-eliciting microbes in a cell type–specific manner, the analysis of root cell type–specific transcriptome and metabolome profiles in response to beneficial microbes will be highly informative.

We have also become much more aware of the fact that the beneficial microbes that are studied as elicitors of ISR are part of a large microbiome that is structured at the root-soil interface and within the root compartment. Although the importance of the root microbiota in improving nutrient availability, antagonizing soilborne pathogens, promoting plant growth, and priming the plant's immune system is well established and abundantly used in biocontrol strategies (76, 175), we are still ignorant about how plants are able to shape the composition of the root microbiome to their own benefit. What are the plant traits and corresponding genes that enable plants to maximize profitable and protective functions from their root microbiota? Exciting new discoveries combining metagenomic analysis and quantitative plant genetics have revealed a core root microbiome of plants, including that of *Arabidopsis* (15, 19, 79, 89, 108, 110), which will greatly facilitate future studies on the relation between the root microbiome and plant health.

The major societal challenge to produce more food with less fertilizer and agrochemical inputs in crop protection has greatly increased the awareness of the importance of the root microbiome in plant health for current agricultural and horticultural practices. In natural ecosystems, plants have evolved in the context of complex microbial communities that fulfill important plant functions related to plant growth, vigor, and defense. However, these traits provided by the plant's second genome have not been major targets of classical plant-breeding programs. Hence, the continuous increase in our knowledge on the molecular and genetic basis of plant-beneficial microbe communication in the context of its evolutionary and ecological relevance will be highly instrumental for the development of sustainable future crops that are better able to maximize profitable and protective functions from beneficial microbes in their root microbiome. Indeed, roots and their plant health–supporting microbiome may hold the key to the next green revolution.

SUMMARY POINTS

1. Beneficial microbes produce different MAMPs and elicitors that can trigger ISR.
2. Local suppression of root immune responses is a common feature of ISR-eliciting beneficial microbes that possibly aids in root colonization.
3. The root-specific transcription factor MYB72 is an early signaling factor that functions as a node of convergence in ISR elicited by diverse beneficial microbes.
4. ISR triggered by beneficial soilborne microbes is often regulated by a JA/ET-dependent signaling pathway, but beneficial microbes that elicit the SA-dependent SAR pathway exist as well.
5. Priming for enhanced defense, rather than direct activation of resistance, is a common feature of systemic immunity elicited by beneficial microbes.
6. Plants have mechanisms by which they enrich their microbiome with beneficial microbes that provide protection against diseases.
7. ISR is a plant immune function mediated by the root microbiome.
8. Disease-suppressive soils are enriched with beneficial microbes that promote plant health.

FUTURE ISSUES

1. To what extent does beneficial plant-microbe communication at the root-soil interface facilitate microbial colonization and drive the whole plant body toward enhanced growth and elevated immunity?
2. What is the role of the MYB72-controlled gene regulatory network and other root cell type–specific signaling components in the onset of ISR?
3. What is the identity of the ISR long-distance signal(s), and does autoregulation of mutualism play a role in ISR by nonsymbiotic PGPR and PGPF?
4. What is the role of NPR1 in the regulation of ISR elicited by beneficial microbes?
5. Is priming induced by beneficial microbes mediated via epigenetic mechanisms, and can it, as SAR and herbivore-induced resistance are, be transgenerationally inherited?
6. How do plants structure their root microbiome, and can they modulate its composition to improve plant immune functions?
7. Do disease-suppressive soils play a broader role in plant defense against pathogens and insects through ISR activity?
8. What are the microbial functions and matching plant genes involved in microbiome-mediated beneficial effects on plant growth and protection, and how can we utilize this information in designing sustainable next-generation crops?

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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Contents

Errata

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