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Iron and Immunity

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Abstract

Iron is an essential nutrient for most life on Earth because it functions as a crucial redox catalyst in many cellular processes. However, when present in excess iron can lead to the formation of harmful hydroxyl radicals. Hence, the cellular iron balance must be tightly controlled. Perturbation of iron homeostasis is a major strategy in host-pathogen interactions. Plants use iron-withholding strategies to reduce pathogen virulence or to locally increase iron levels to activate a toxic oxidative burst. Some plant pathogens counteract such defenses by secreting iron-scavenging siderophores that promote iron uptake and alleviate iron-regulated host immune responses. Mutualistic root microbiota can also influence plant disease via iron. They compete for iron with soil-borne pathogens or induce a systemic resistance that shares early signaling components with the root iron-uptake machinery. This review describes the progress in our understanding of the role of iron homeostasis in both pathogenic and beneficial plant-microbe interactions.

INTRODUCTION

Iron is an essential element for most organisms and is abundantly present in the Earth's crust. However, its bioavailability is limited because iron is mainly present as ferric oxide, which is poorly soluble at neutral and high pH. Iron ions can exist in both the ferric (Fe^{3+}) and the ferrous (Fe^{2+}) form, allowing them to function as the catalytic component of enzymes that mediate redox reactions in key cellular processes, such as DNA replication and energy production. Although iron scarcity hampers the growth of many organisms, iron overload can also be harmful. Excess Fe^{2+} inside a cell leads to the formation of hydroxyl radicals via the so-called Fenton reaction (38, 48), which can cause damage to proteins, DNA, and lipids (84). Therefore, most organisms have evolved sophisticated mechanisms that tightly regulate iron uptake, transport, and storage. These mechanisms emerged as important players in the arms race between hosts and pathogens. In the mammalian innate immune system, iron-withholding strategies play a central role in preventing invading pathogens from entering the host (13, 43, 128). In plant-pathogen interactions, similar strategies have been described (37, 41, 77). Interestingly, the role of iron in plant immunity is even more complex, as it involves the tripartite interaction among host, pathogen, and plant-beneficial microbiota in the rhizosphere (4, 104).

In the 1980s, it was shown that addition of exogenous iron to disease-suppressive soils counteracted the suppressiveness of Fusarium wilt–suppressive soils and of a soil suppressive to *Gaeumannomyces graminis* var. *tritici*, the fungus that causes take-all disease of wheat (64, 76). Competition for iron between the soil-borne pathogens and their antagonistic microorganisms was considered to be the mechanism of disease suppression (81, 116). This highlighted iron as a central player in the tripartite interaction among beneficial microbes, pathogens, and plants. Iron-chelating siderophores, which under iron-limiting conditions are produced in the rhizosphere by plant growth–promoting rhizobacteria, emerged as important actors in this process. These siderophores were found to inhibit growth of soil-borne pathogens by depriving them of iron (81, 116, 146). Seminal work of Expert and coworkers showed that bacterial plant pathogens, such as *Dickeya dadantii* (formerly *Erwinia chrysanthemi*) and *Erwinia amylovora*, secrete siderophores as virulence factors. These siderophores either facilitate iron uptake from the host (37) or protect the pathogen from plant-derived toxic hydroxyl radicals produced at the site of infection (23). In addition to the role of iron in the interaction between plants and microbes, it recently became evident that the signaling pathways regulating plant iron uptake interact directly with the plant immune signaling network (104). For instance, the defense-related hormones salicylic acid, jasmonic acid, and ethylene affect important steps in the iron-uptake response in plant roots (4). Moreover, components of the iron-uptake signaling pathway in host roots appear to be required for the onset of induced systemic resistance (ISR), which is triggered by selected plant growth-promoting rhizobacteria and fungi (153, 154). Recent advances in our understanding of iron homeostasis mechanisms in both plants and microbes and the emerging link between iron and both plant immunity and pathogen virulence prompted us to thoroughly review these respective fields and provide an outlook for future research.

Ferric iron: Fe^{3+} ion, abundantly present in most soils but generally in an insoluble form

Ferrous iron: Fe^{2+} ion, transported into root epidermal cells, can react with H_2O_2 to produce highly reactive free radicals via the Fenton reaction

Fenton reaction: the reaction of ferrous iron with H_2O_2 ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{-}OH + {}^{\bullet}OH$), leading to the formation of toxic hydroxyl radicals that are harmful to biomolecules

Microbiota/microbiome: community of commensal, mutualistic, and pathogenic microorganisms that live in close association with plants

Rhizosphere: the narrow soil layer around a plant's root system that is influenced by the root and its exudates and contains a multitude of microorganisms

Disease-suppressive soils: soils in which the activity of a pathogen is suppressed, generally because of specific microbial populations that antagonize pathogens

PLANT IRON HOMEOSTASIS

Iron Acquisition Strategies in Plants

In most soils, iron is poorly available. To enable iron uptake under these conditions, non-grass and grass plant species evolved distinct iron-uptake responses, called Strategy I and Strategy II, respectively (111). The molecular mechanisms underlying both iron-uptake strategies have been thoroughly described in a number of excellent reviews (21, 46, 57, 65, 98, 143), so we highlight

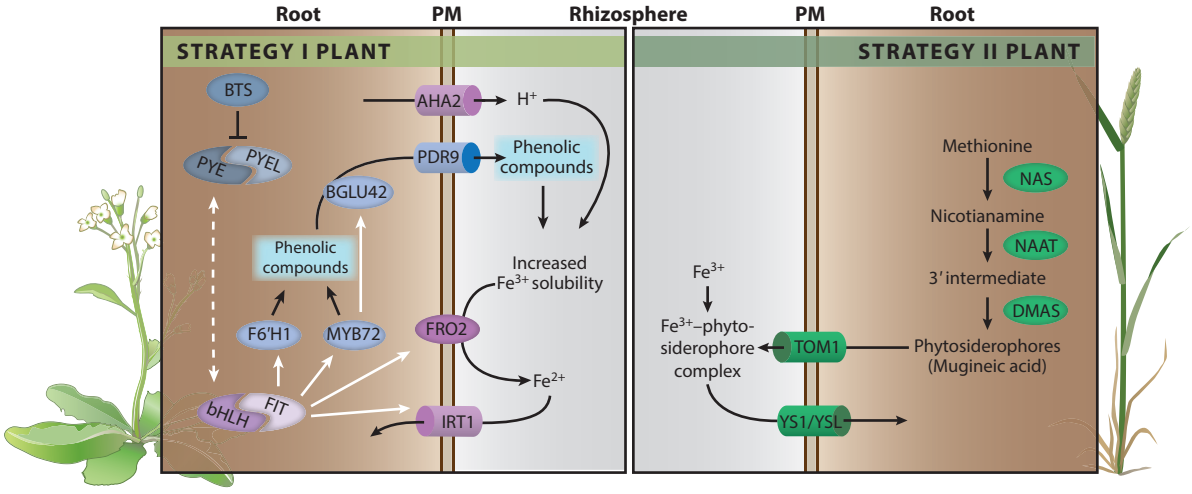

Figure 1

Iron-uptake strategies by non-grass (Strategy 1) and grass plants (Strategy II). Under iron-limiting conditions, Strategy I plants upregulate transcription of the bHLH transcription factor gene *FIT*. FIT interacts with other bHLH proteins to enhance the expression of *AHA2*, *FRO2*, and *IRT1* (16, 57). AHA2, FRO2, and IRT1 localize to the plasma membrane (114, 115, 140). There, H^+-ATPase AHA2 extrudes protons into the rhizosphere, which lowers soil pH and increases Fe^{3+} solubility (114). FRO2 reduces Fe^{3+} to Fe^{2+} (107), which is transported into the root epidermis by IRT1 (34). The bHLH transcription factor gene *PYE* is also upregulated upon iron deficiency. PYE interacts with PYEL bHLHs (80), aiding iron homeostasis through an as yet unknown mechanism. PYE and PYEL are negatively regulated by BTS (123). Iron availability is further enhanced by the release of iron-mobilizing phenolic compounds. This is mediated by the transcription factor MYB72, the coumarin biosynthesis protein F6′H1, the glucose hydroxylase BGLU42, and the ABC transporter PDR9 (39, 118, 153). In Strategy II grass plants, iron deficiency induces the biosynthesis of the iron scavenger nicotianamine (NA) from its precursor methionine after which iron-chelating phytosiderophores are produced by the action of NAAT and DMAS (8, 95). Phytosiderophores are released into the rhizosphere by the transporter TOM1 (94). After binding Fe^{3+} in the rhizosphere, the complexes are transported back into the root by specific transporters, including YS1 and YSL (20, 55, 65). Solid lines indicate established interactions; dashed lines indicate hypothetical interactions. Black arrows indicate a positive effect; white arrows indicate transcriptional activation. Abbreviation; PM, plasma membrane.

only the main characteristics here. Non-grass plants, such as the model plant *Arabidopsis thaliana* (hereafter, *Arabidopsis*), activate a coordinated set of responses in root cells when exposed to iron-limiting conditions (**Figure 1**). During this Strategy I response, solubility of Fe^{3+} in the soil is increased by the activity of the H^+-ATPase AHA2, which secretes protons into the rhizosphere that lower the pH (114). Solubilized Fe^{3+} is reduced to Fe^{2+} by the plasma membrane protein FERRIC REDUCTION OXIDASE 2 (FRO2), after which it is transported from the soil environment to the root epidermis by the high-affinity IRON-REGULATED TRANSPORTER1 (IRT1) (34, 107).

Grass plants, such as maize and wheat, make use of an iron chelation–based strategy to mobilize and acquire iron under iron-limiting conditions (**Figure 1**). In these so-called Strategy II plants, iron deficiency triggers the conversion of methionine into nicotianamine (NA), which is subsequently converted into phytosiderophores by NICOTIANAMINE AMINOTRANSFERASE (NAAT) and DEOXYMUGINEIC ACID SYNTHASE (DMAS) (8, 95). Phytosiderophores are released into the rhizosphere by TRANSPORTER OF MUGINEIC ACID1 (TOM1) (94). Upon binding iron in the rhizosphere, the phytosiderophores are taken up by the plant by specific transporters, such as YELLOW STRIPE1 (YS1) or YS1-like (YSL) (20, 55, 65).

Both Strategy I and II are activated in roots upon sensing low iron availability. In addition, iron-stressed plants initiate a number of root surface–enlarging morphological changes in the root

Siderophores: high-affinity ferric iron–chelating compounds produced by plants and microorganisms to increase iron availability

Induced systemic resistance (ISR): broad-spectrum enhanced defensive capacity of the entire plant, acquired upon local induction by beneficial root-colonizing microbes

architecture. These changes include increased root branching and root hair formation, which aid in the plant's capacity to take up iron (59, 119). Interestingly, as yet unidentified systemic signals from the shoot can also upregulate iron-uptake responses in the roots, e.g., when iron-demanding processes such as photosynthesis call for enhanced iron availability in the shoots (141).

Molecular Regulation of Iron-Uptake Components in Strategy I Plants

The molecular regulation of Strategy I has been elucidated in detail, predominantly in *Arabidopsis*. The basic helix-loop-helix (bHLH) transcription factor FER-LIKE IRON DEFICIENCY INDUCED TRANSCRIPTION FACTOR (FIT) emerged as the central regulator of the Strategy I iron-uptake response (16, 58, 152). Upon iron deprivation, FIT is activated at the transcriptional and post-translational levels, after which it interacts with other members of the bHLH transcription factor family (bHLH38/39/100/101) (127, 144, 151) to activate downstream iron-uptake genes, such as *AHA2*, *FRO2*, and *IRT1* (**Figure 1**) (16, 57, 114). Independent of FIT, another bHLH transcription factor called POPEYE (PYE) is upregulated upon iron deficiency. Like FIT, PYE interacts with other bHLH transcription factors, such as PYE-like (PYEL), to regulate iron homeostasis (80). PYE and PYEL are negatively regulated by the E3 ubiquitin-protein ligase BRUTUS (BTS) (123). Because *pye* and *fit* single mutants of *Arabidopsis* become chlorotic under iron-limiting conditions (16, 80), both networks are apparently necessary for efficient iron uptake in Strategy I plants.

Iron Transport and Storage

In addition to *AHA2*, *FRO2*, and *IRT1*, FIT upregulates the transcription factor genes *MYB72* and *MYB10* (99). Together, MYB72 and MYB10 induce the production of the iron scavenger NA by upregulating the NA synthase gene *NAS4* (99). NA is important for plant survival in alkaline soil where iron availability is greatly restricted. NA is thought to play a role in the distribution of iron within the plant via the transporter YELLOW STRIPE-LIKE2 (YSL2), but the molecular mechanisms involved are largely unknown (27, 63, 66).

Iron transport and storage are further regulated by iron transporters called natural resistance-associated macrophage proteins (NRAMPs) (19) and iron storage proteins called ferritins (10, 131). NRAMPs coordinate iron distribution across the cell (19) and organize iron transport out of vacuoles (71). Ferritins play an important role in averting oxidative stress by storing it away from other molecules with which it can react. Moreover, prior to storage, ferritins convert iron to its nonreactive ferric form, which ensures that the phytotoxic Fenton reaction with oxygen does not occur (22, 73). Iron-bound ferritins are mostly located in chloroplasts and mitochondria (93).

Iron-Mobilizing Phenolic Compounds

Plant roots also enhance iron availability in the rhizosphere through the secretion of iron-mobilizing, phenylpropanoid-derived secondary metabolites (**Figure 1**). MYB transcription factors are central regulators in the biosynthesis of these fluorescent phenolic compounds (30, 79). In iron-deprived *Arabidopsis* roots, the FIT-regulated MYB transcription factor MYB72 controls a gene module that regulates the biosynthesis and secretion of a specific subclass of fluorescent phenylpropanoids that belongs to the coumarin family (**Figures 1** and **2**) (153). These coumarins are synthesized via FERULOYL-COA 6′-HYDROXYLASE1 (F6′H1) in the phenylpropanoid pathway and secreted into the rhizosphere by the iron deficiency–regulated ABC transporter

Strategy I: adaptive root response of non-grass plant species to iron deficiency characterized by rhizosphere acidification, reduction of Fe^{3+} to Fe^{2+}, and increased iron transporter activity

Strategy II: adaptive root response of grass plant species, characterized by iron uptake via iron-chelating phytosiderophores

FRO2: a ferric chelate reductase that transfers electrons across the plasma membrane to reduce ferric iron chelates to form soluble ferrous iron

IRT1: iron transporter protein mediating transport of ferrous iron into root epidermal cells under iron-deficient conditions

Nicotianamine (NA): iron-chelating siderophore that functions in iron uptake and/or transport in both Strategy I and Strategy II plants

FIT: transcription factor with central role in the regulation of iron uptake in plant roots

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

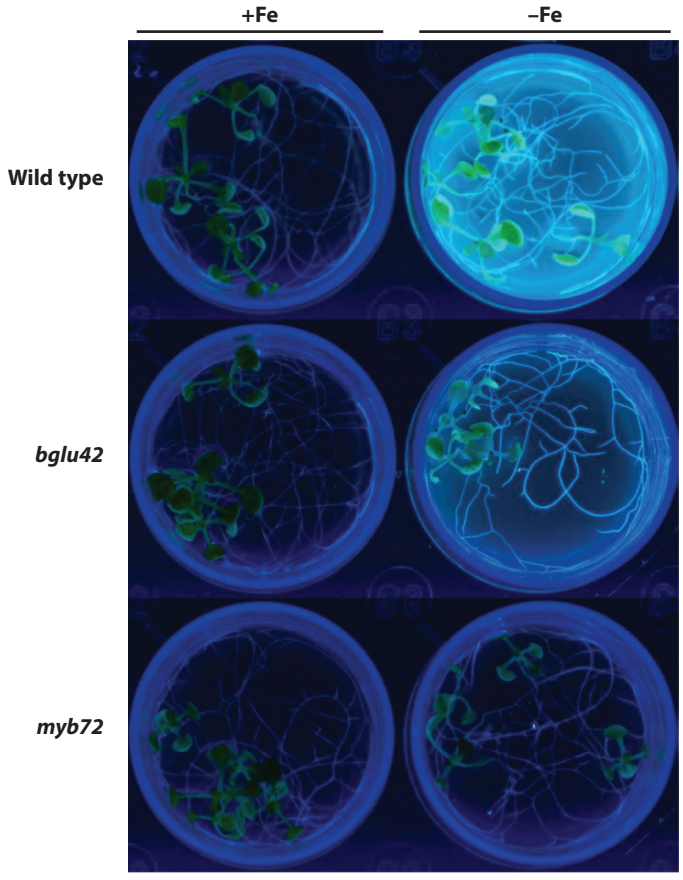

Figure 2

The role of MYB72 and BGLU42 in the production and secretion of iron-mobilizing fluorescent phenolic compounds in *Arabidopsis* roots in response to iron deficiency. Iron limitation (−Fe) increases the production and secretion of fluorescent phenolic compounds in roots of wild-type *Arabidopsis* Col-0 plants. In roots of mutant *bglu42* plants, these compounds are still produced (fluorescence in the roots) but hardly secreted (reduced fluorescence in the culture medium). Mutant *myb72* plants are incapable of producing the fluorescent compounds. Shown are two-week-old *Arabidopsis* seedlings grown in liquid Hoagland medium with (+Fe) or without (−Fe) iron, as described in Reference 153. Pictures were taken under UV light (365 nm) to visualize fluorescent phenolic compounds.

PLEIOTROPIC DRUG RESISTANCE9 (PDR9) (**Figure 1**) (39, 108, 117, 118). Upon release in the rhizosphere, coumarins can chelate and mobilize Fe^{3+} and make it available for reduction and uptake by the roots (40, 117).

MYB72 also activates the expression of *β-GLUCOSIDASE 42* (*BGLU42*) (44, 153). Mutant *bglu42* plants are still able to produce fluorescent phenolic compounds upon iron starvation, but their secretion into the rhizosphere is severely hampered (**Figure 2**). This suggests that the glucose hydrolase activity of BGLU42 is involved in processing the fluorescent phenolic compounds to enable their secretion into the rhizosphere (153). This function is consistent with the general role of β-glucosidases in chemical destabilization and release of stress-induced secondary metabolites (92).

Coumarins: a subclass of phenolic compounds synthesized by plants under stress situations that can facilitate iron uptake

Effects of Plant Hormones on Iron-Uptake Responses

In plants, the iron-deficiency response is regulated at both the transcriptional and the post-translational levels (7, 17, 53, 126). The plant hormones auxin, ethylene, nitric oxide, cytokinin, and gibberellic acid emerged as important players in the regulation of this process (53, 124, 147). In *Arabidopsis*, ethylene and gibberellic acid increase *FRO2* and *IRT1* expression in the root epidermis, leading to increased iron uptake (44, 109, 147). Furthermore, ethylene and auxin stimulate the accumulation of nitric oxide production in iron-deficient roots. Both ethylene and the accumulated nitric oxide result in stabilization of FIT and enhanced iron uptake (89, 110). In addition, auxin stimulates formation and elongation of lateral roots, enabling the plant to take up more iron (45). Cytokinin, in contrast, decreases root growth and suppresses genes involved in the iron-deficiency response (122).

The major defense hormones salicylic acid and jasmonic acid also influence plant iron acquisition. In *Arabidopsis*, salicylic acid affects auxin and ethylene signaling, thereby positively affecting the expression of the iron-uptake genes *FRO2* and *IRT1* (124). In contrast to salicylic acid, jasmonic acid negatively affects iron acquisition by downregulating *FRO2* and *IRT1* in a FIT-independent manner (87). Salicylic acid, jasmonic acid, ethylene, and auxin play key roles in the regulation of the plant immune signaling network (102). Hence, the fact that these hormones also affect iron-uptake responses in plant roots pinpoints a potentially important link between iron availability and immunity.

MICROBE IRON HOMEOSTASIS

Like plants, bacteria and fungi need iron for their development and growth, whereas high iron concentrations can be toxic. In microbes, sufficient iron uptake is ensured by several iron-uptake strategies. One of the most common strategies employed by both bacteria and fungi is analogous to the iron chelation–based Strategy II in plants, as it depends on the production and secretion of siderophores. Microbial siderophores are low-molecular-weight organic compounds (500–1,500 kDa) that are produced under iron-limiting conditions (91). Most microbial siderophores are synthesized by members of a large family of modular multienzymes called nonribosomal peptide synthetases (NRPSs) (52, 91). The iron-chelating moieties in bacterial siderophores can be catecholate, carboxylate, and/or hydroxamate groups (52, 91). In contrast, all fungal siderophores identified so far contain hydroxamate groups, with the exception of the carboxylate siderophore rhizoferrin, which is produced by certain zygomycetes (47). After secretion into the environment, siderophores chelate iron (**Figure 3**). In bacteria and fungi, the resulting iron-siderophore complex is recognized and taken up by specific receptors and their associated siderophore transporters (9, 47, 81, 91). In fungi, iron can also be taken up through reductive iron assimilation, during which Fe^{3+} is reduced to Fe^{2+} prior to direct uptake (47).

In many bacteria, iron uptake is downregulated via the ferric uptake regulator (Fur) protein, which dimerizes when intracellular iron excess is perceived. The resulting Fur dimer functions together with Fe^{2+} as a corepressor of genes involved in iron uptake (36, 133). In *Pseudomonas* spp., these genes include transcription factor genes involved in the activation of siderophore production, such as extracytoplasmic function (ECF) sigma transcription factors (18).

Iron bound to microbe-secreted siderophores might be utilized by plants. Tomato, cucumber, barley, and oat can use iron bound to rhizoferrin, a fungal siderophore produced by *Rhizopus arrhizus*, as efficiently as a common iron source (Fe-EDTA or Fe-EDDHA) (150). Similarly, soybean and oat can use iron chelated to siderophores from compost microorganisms at least as efficiently as Fe-EDDHA (15), tomato can use iron chelated to *Chryseobacterium* siderophores (106), *Arabidopsis* can use the iron bound to the *Pseudomonas* siderophore pyoverdine, resulting in

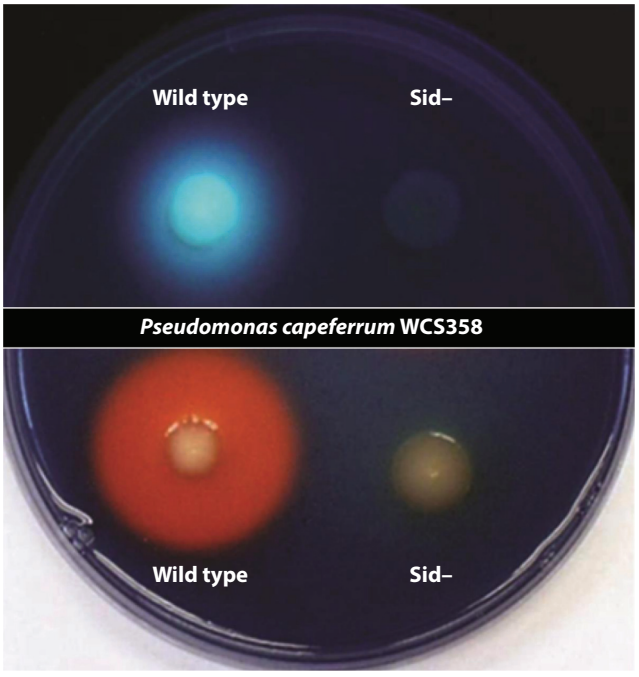

Figure 3

Visualization of the production (*top*) and iron-chelating capacity (*bottom*) of the fluorescent siderophore pyoverdin by wild-type *Pseudomonas capeferrum* WCS358 and its siderophore-deficient (Sid–) mutant. Shown are bacterial colonies cultivated on low-iron King's B (KB) medium (*top*) and chrome azurol sulfonate (CAS) medium (*bottom*). On KB medium, the pyoverdine siderophore fluoresces when illuminated with UV light. On CAS medium, the blue-colored chrome azurol S/iron(III)/hexadecyltrimethylammonium bromide turns orange when a strong chelator removes the iron from the dye.

improvement in growth (137), and barley can use iron chelated to the pyoverdine siderophore of *Pseudomonas capeferrum* WCS358 (formerly known as *Pseudomonas putida* WCS358) (9), resulting in stimulated chlorophyll synthesis (31). How plants obtain iron bound to microbial siderophores is not fully understood (1). Interestingly, microbe-produced apo-siderophores, i.e., iron-free siderophores, can also improve plant growth. Apo-pyoverdine, for example, can partly reduce iron-deficiency symptoms of *Arabidopsis* growing in low-iron conditions, possibly because it enhances the expression of the iron-uptake genes *IRT1*, *FRO2*, and *NAS4* in the roots (132).

ROLE OF IRON IN PATHOGEN VIRULENCE AND HOST DEFENSE

Because iron homeostasis is essential to the survival of both plants and microbes, it is not surprising that iron availability affects the outcome of plant-pathogen interactions (4). In fact, iron is known to affect virulence and resistance across all kingdoms of life (see sidebar titled Iron and Immunity Across Kingdoms of Life).

Pathogen Virulence and Iron

Siderophore-mediated iron acquisition is essential for full virulence of many plant pathogens. Pathogens that reside in the soil first need to compete with other members of the soil microbial community for the scarce available iron necessary for growth before a host plant can be

IRON AND IMMUNITY ACROSS KINGDOMS OF LIFE

Iron homeostasis is linked to immunity across all kingdoms of life. In the fungal kingdom, the wheat pathogen *Fusarium graminearum* responds to bacterial microbe-associated molecular patterns (MAMPs) by upregulating iron acquisition responses, possibly preparing the fungus for further interaction with mycopathogenic bacteria (56). In animal innate immunity, iron sequestration is an ancient host defense against invading pathogens (97). In this process, iron-storing FERRITINS and iron-transporting NRAMPs keep iron out of reach of pathogens while keeping it available to the host (97, 145). Also in humans, iron withholding is a crucial part of the innate immune response to microbial infection. Well-adapted microbes have in turn evolved mechanisms to extract iron from host storage proteins or to interfere with host iron sequestration (13, 43). Given that iron acquisition is fundamental to the virulence of many pathogens, microbial infections can sometimes be successfully treated by using iron-chelating drugs that prevent pathogen access to iron (67).

infected (**Figure 4*a***). Microbial siderophores play a key role in this underground warfare for iron. The outcome of siderophore-mediated competition for iron depends on the iron affinity of the siderophores, the quantity of siderophores produced, and the species specificity of the siderophores. Highly specific siderophores are recognized only by the receptors of the producing organism, whereas heterologous siderophores are recognized and taken up by different microorganisms (81). A rhizosphere-competent microbe ideally produces large amounts of specific siderophores with a high affinity for iron, in addition to having multiple receptors for heterologous siderophores (9). Plant growth–promoting rhizobacteria that produce such specific, high-affinity siderophores can effectively deprive soil-borne pathogens of iron and thereby suppress plant disease (77). Successful soil-borne pathogens clearly evolved ways to cope with such antagonistic microbes in the rhizosphere. The soil-borne vascular wilt pathogen *Fusarium oxysporum* f. sp. *lycopersici* produces the transcription factor HapX, which is an important regulator of fungal adaptation to iron starvation and excess. HapX-regulated iron-uptake responses are implicated in successful iron competition with siderophore-producing beneficial *P. putida* bacteria in the rhizosphere (82). Apart from competition with antagonistic microorganisms in the soil, plant pathogens also evolved ways to cope with iron-related host plant defense mechanisms. In the case of *F. oxysporum* f. sp. *lycopersici*, HapX was shown to be essential for full fungal virulence on not only its host plant tomato but also immune-suppressed mice. Because HapX is conserved throughout the fungal kingdom, it is likely a central regulator of iron-related survival strategies of many fungi (82).

The capacity to acquire iron from the host is also an important pathogenicity factor of foliar pathogens. Virulence of diverse plant-pathogenic ascomycete fungi, with host ranges varying from wheat, barley, and maize to rice and *Arabidopsis*, was shown to depend on the pathogen's capacity to secrete siderophores (96). An exogenous supply of iron relieved this siderophore dependency, highlighting the iron-scavenging function of siderophores as an important virulence factor in plant-pathogen interactions (96). A similar virulence function has been described for siderophores of bacterial pathogens, such as *D. dadantii*, which secretes these iron-sequestering compounds during interaction with its hosts, *Arabidopsis* and African violet (24, 42) (**Figure 4*b***). Although iron uptake is also essential for pathogenicity of the smut fungus *Ustilago maydis* on maize, this pathogen does not depend on siderophores for full virulence (88). Instead, a permease-based iron-uptake system is required for full virulence (33) (**Figure 4*b***). Also, in the hemibiotrophic maize pathogen *Colletotrichum graminicola*, siderophores are required for full virulence. However, their production is specifically downregulated during the biotrophic phase, possibly to circumvent elicitation of

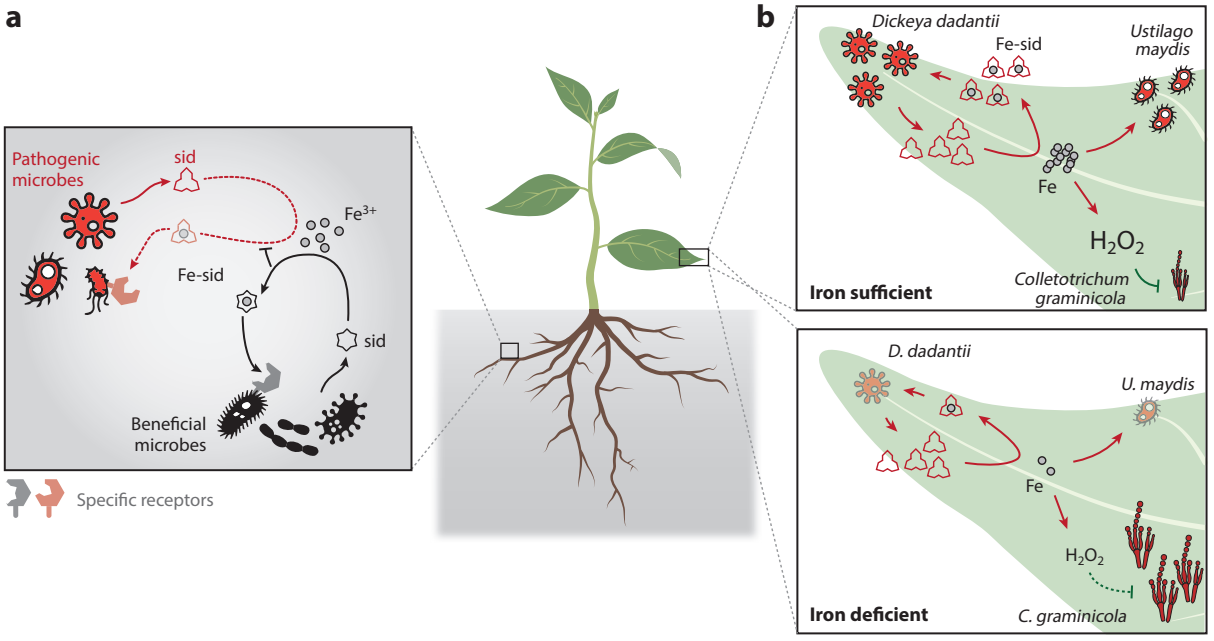

Figure 4

Effects of iron availability on pathogenic microorganisms. (*a*) In soil, bacteria and fungi compete for available iron (*gray circles*) by secreting iron-chelating siderophores (sid). Siderophores can be taken up upon recognition by specific receptors once they have bound iron (Fe-sid). By producing siderophores with high iron affinity, beneficial microbes can outcompete pathogenic microbes that produce siderophores with a lower iron affinity, resulting in suppression of disease (81, 116). (*b*) Iron availability influences the interaction between plants and foliar pathogens. Sufficient iron uptake is essential for virulence of pathogens such as *Dickeya dadantii* and *Ustilago maydis*. As a result, these pathogens cause more disease on plants grown under high-iron conditions (*top panel*) than on plants grown under iron-deficient conditions (*bottom panel*) (33, 62). However, high iron availability in the host can favor the development of oxidative stress (symbolized by the size of H_2O_2), thereby promoting defense against pathogens such as *Colletotrichum graminicola* (149). Solid lines and arrows indicate stronger activity of the indicated process than do dotted lines and arrows. Black, red, and green lines and arrows indicate processes mediated by beneficial microbes, pathogens, or plants, respectively.

host immune responses (2). These examples illustrate that microbial iron homeostasis is essential for maximum virulence on their hosts.

Host Iron Status and Pathogen Virulence

Because iron acquisition is essential for the virulence of many plant pathogens, one could assume that iron-starved host plants are less susceptible to pathogen infection. Indeed, iron-starved *Arabidopsis* plants were more resistant to attack by the bacterial pathogen *D. dadantii* and the necrotrophic fungus *Botrytis cinerea* than plants grown under iron-sufficient conditions (62). The enhanced resistance of the iron-starved plants to *D. dadantii* was not correlated with activation of plant immune responses, suggesting that iron deprivation of the pathogen per se affects pathogen virulence in this plant-pathogen interaction (**Figure 4*b***) (62). In other cases, iron starvation promotes susceptibility to certain pathogens. For example, the soil-borne fungal pathogen *Verticillium dahliae* caused more disease in peanut, eggplant, and a resistant tomato line when the plants were grown in iron-deficient soils (6, 68, 85). Likewise, the maize pathogen *C. graminicola* was better able to infect iron-starved than iron-sufficient plants, likely because iron-deprived plants developed a weaker oxidative burst at the site of pathogen infection (149) (**Figure 4*b***).

Oxidative burst: a rapid formation of reactive oxygen species, used as a defense strategy

Increased production of toxic compounds by iron-starved pathogens may also contribute to the enhanced susceptibility phenotype of iron-deficient plants. In the opportunistic human pathogen *Pseudomonas aeruginosa*, the production of the virulence factor exotoxin is dependent on the secretion of the iron-starvation regulated siderophore pyoverdine (70). Similarly, pyoverdine produced by the tobacco pathogen *Pseudomonas syringae* pv. *tabaci* 6605 controls the production of tabtoxin, a toxin that induces chlorosis in the leaves of its host (130). Thus, depending on the host-pathogen interaction, the iron status of the host plant can positively or negatively affect pathogen virulence and the development of local defense responses, with major consequences for disease development.

Hydrogen peroxide (H_2O_2): involved in the defensive oxidative burst employed by plants to defend themselves against pathogen attack

Plant Defense via Changes in Host Iron Homeostasis

In specific plant-pathogen interactions, pathogen-induced changes in plant iron homeostasis mechanisms affect host immunity. In *Arabidopsis*, bacterial siderophores of *D. dadantii* induce the expression of the iron storage gene *FERRITIN1* (*FER1*) (24). Mutant *fer1* plants are more susceptible to *D. dadantii* (24), suggesting that iron sequestration by ferritins is part of an iron-withholding defense strategy that is induced in response to pathogen invasion. Alternatively, FER1 plays a role in the protection of cells against the high amounts of iron that are released from the cell walls upon pathogen infection (5). In the same pathosystem, the pathogen's siderophore chrysobactin stimulates the production of the defense hormone salicylic acid in the host, resulting in induction of the *PATHOGENESIS-RELATED* defense marker gene *PR-1*, callose deposition along the leaf veins, and accumulation of H_2O_2 (3, 24, 25). These iron-related defense responses are likely caused by pathogen-inflicted changes in iron distribution at the site of pathogen infection (5, 121). Interestingly, application of this leaf pathogen or its siderophores to shoots also induced the expression of *FRO2* and *IRT1* in the roots, suggesting that microbe-induced changes in iron homeostasis mechanisms can be expressed systemically throughout the plant (3, 25, 121). Redistribution of iron upon pathogen attack is also observed in other plant species. Attack of wheat leaves by the powdery mildew fungus *Blumeria graminis* f. sp. *tritici* leads to redistribution of Fe^{3+} to the apoplast of epidermal leaf cells, where it induces the production of H_2O_2, resulting in a defensive oxidative burst. The ensuing iron deficiency in the cytosol of the epidermal cells induces the expression of *PR-1* (78). These examples show that pathogen-induced iron redistribution in the host can contribute to disease resistance at different levels, directly by withholding iron from the pathogen and indirectly by triggering defense responses.

BENEFICIAL MICROBES AFFECT PLANT RESISTANCE VIA IRON

Plant iron homeostasis is affected not only upon pathogen infection but also root colonization by specific beneficial soil microbiota. Among these are plant growth–promoting rhizobacteria and fungi that are known to trigger ISR. ISR by beneficial rhizosphere microbes is a plant-mediated systemic immune response that primes plant tissues for enhanced defense against a broad spectrum of pathogens (83, 104). A connection between iron homeostasis and ISR was found in 1996 when Leeman and coworkers (75) reported that the elicitation of ISR against Fusarium wilt in radish by beneficial *Pseudomonas* spp. was more effective under low-iron conditions. Siderophores secreted by *Pseudomonas* spp. under such low-iron conditions were subsequently shown to act as elicitors of ISR in tomato (90) and rice (26). Interestingly, other beneficial microbes, such as the beneficial fungi *Piriformospora indica* and *Trichoderma* spp., stimulate both plant iron uptake and plant disease resistance (51, 100). However, the molecular mechanism behind the association between iron and immunity remained obscure in these studies.

MYB72 Links Induced Systemic Resistance and the Iron-Deficiency Response

The molecular basis of triggering, signaling, and expression of ISR has been extensively studied in the interaction between *Arabidopsis* and the plant growth–promoting rhizobacterium *Pseudomonas simiae* WCS417 (formerly known as *Pseudomonas fluorescens* WCS417) (9, 103, 104, 135). Using this model system, the plant hormones jasmonic acid and ethylene were found to be required for the enhanced resistance phenotype of ISR-expressing plants. However, ISR triggered by beneficial microbes is often not associated with enhanced biosynthesis of these hormones or with massive changes in defense-related gene expression in the leaves. Instead, ISR-expressing plants are primed for a faster and stronger expression of cellular defense responses after pathogen or insect attack (86, 104).

Although leaf tissues of *Arabidopsis* plants colonized by *P. simiae* WCS417 do not display major transcriptome changes, roots respond massively to the colonization (105, 139). *MYB72*, described above for its role in the biosynthesis and secretion of iron-mobilizing phenolic compounds under iron-limiting conditions, is among the genes induced in roots upon colonization by *P. simiae* WCS417 (139). In colonized *Arabidopsis* roots, *MYB72* is specifically activated in the epidermal and cortical cells (**Figure 5*a***) (154). Other ISR-inducing beneficial microbes, such as *P. capeferrum* WCS358, *Trichoderma harzianum* T-78, and *Trichoderma asperellum* T-34, trigger a similar *MYB72* expression pattern, while the non-ISR-inducing strain *Pseudomonas defensor* WCS374 (formerly known as *P. fluorescens* WCS374) (9) does not (120, 152). Knockout mutants of *MYB72* are unable to establish ISR upon root colonization by either *P. simiae* WCS417 or *T. asperellum* T-34. Thus, the transcription factor MYB72 is required for the onset of ISR triggered by different types of beneficial microbes (120, 136).

Among the genes regulated by MYB72 in WCS417-colonized *Arabidopsis* roots are *BGLU42* and *PDR9*. Both BGLU42 and PDR9 are involved in the secretion of iron-mobilizing phenolic compounds under iron-limited conditions (153). Interestingly, similar phenolic compounds are produced in response to root colonization by the plant growth–promoting rhizobacteria *P. fluorescens* SS101 and *Paenibacillus polyxyma* BFKC01 (134, 157). *Arabidopsis bglu42* mutants are unable to mount WCS417-ISR and overexpression of *BGLU42* confers a broad-spectrum resistance to *P. syringae* pv. *tomato*, *B. cinerea*, and *Hyaloperonospora arabidopsidis* (153). Because expression of BGLU42 is essential and sufficient for the onset of ISR and is part of the iron-deficiency response, it is tempting to speculate that the fluorescent phenolic compounds produced in an MYB72-dependent manner and metabolized by the glucose hydrolase activity of BGLU42 function as long-distance ISR signals (**Figure 5*b***).

Dual Activation of Iron Uptake and Immunity by Microbes

Not only *MYB72* and *BGLU42* but 20% of all the genes that are differentially expressed in *Arabidopsis* roots upon colonization by *P. simiae* WCS417 under high-iron conditions are shared with the iron-deficiency response (28, 154). These include important plant iron homeostasis genes such as *FIT*, *FRO2*, and *IRT1* (154). The activation of the iron-deficiency response genes is likely not simply caused by local iron deprivation by bacterial siderophores around the root, as a siderophore mutant of *P. simiae* WCS417 activates their expression to the same extent as wild-type WCS417 bacteria (154).

Several microbial determinants have been shown to induce iron acquisition responses. For example, the plant growth–promoting rhizobacterium *P. polyxyma* BFKC01 produces auxin, which is associated with BFKC01-mediated upregulation of *FIT*, *IRT1*, and *FRO2* in *Arabidopsis* roots (157). Other beneficial rhizobacteria, including *P. simiae* WCS417, trigger endogenous auxin responses in plant roots. This results in morphological changes in the root architecture, such as

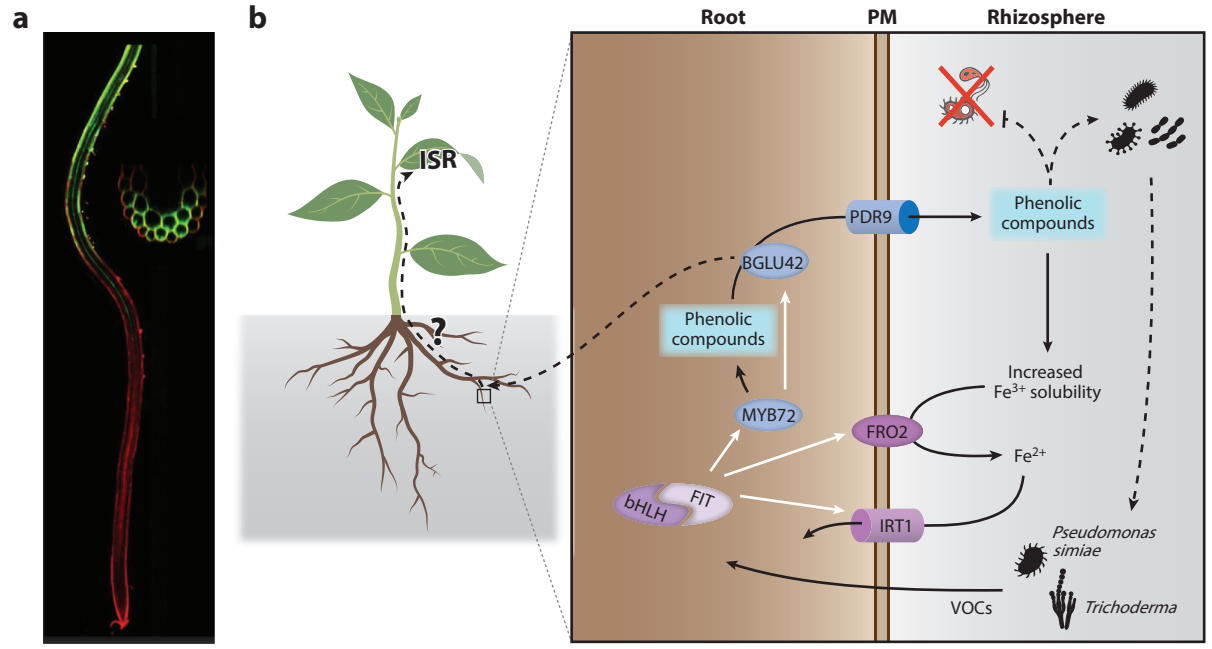

Figure 5

(*a*) Confocal image of a root of an *Arabidopsis MYB72*$_{pro}$*:GFP* reporter line expressing green fluorescent protein (GFP) under the control of the *MYB72* promoter after two days of treatment with the induced systemic resistance (ISR)-eliciting rhizobacterium *Pseudomonas simiae* WCS417 (red indicates propidium iodide–stained *Arabidopsis* root). On the right, a transverse optical section of the root. Image reproduced with permission from Reference 154. (*b*) Schematic representation of root-specific molecular changes related to the onset of ISR and plant iron (Fe) acquisition as triggered by beneficial ISR-inducing microbes in the rhizosphere. Colonization of the root by ISR-inducing microbes activates the transcription factor gene *MYB72* and the iron-uptake genes *FRO2* and *IRT1* in a FIT-dependent manner. Microbial volatiles are determinants in the activation of this process (154). MYB72 regulates the biosynthesis of fluorescent phenolic compounds and the root-specific expression of the glucose hydrolase gene *BGLU42* and the ABC transporter gene *PDR9*, resulting in the secretion of the phenolic compounds (153). In the rhizosphere, the fluorescent phenolics chelate and mobilize Fe^{3+} and make it available for reduction and uptake by the root. The antimicrobial activity of some phenolic compounds may play a role in shaping the rhizosphere microbial community. BGLU42 is required for rhizobacteria-mediated ISR and when overexpressed confers resistance against a broad spectrum of plant pathogens (153). Hence, MYB72-dependent BGLU42 activity in roots is speculated to play a role in the generation of a mobile ISR signal that is systemically transported throughout the plant. Solid lines indicate established processes; dashed lines represent predicted processes. Black arrows indicate a positive effect; white arrows indicate transcriptional activation. Abbreviations: PM, plasma membrane; VOCs, volatile organic compounds.

enhanced lateral root formation and elongation of root hairs, which resemble those observed in response to iron starvation and are known to increase the plant's capacity to take up iron (138, 155). Interestingly, volatiles produced by the beneficial microbes *Bacillus subtilis* GB03 and *P. simiae* WCS417 were shown to both induce ISR and activate the expression of *FIT*, *IRT1*, and *FRO2* in *Arabidopsis* roots, even when plants were grown under conditions of sufficient iron (113, 154, 156).

Exudates: compounds secreted into the rhizosphere by plant roots that are thought to affect plant nutrient uptake and rhizosphere microbiome composition

Effect of Iron-Mobilizing Phenolics on Microbial Community

Root exudates have a major impact on the composition of the microbial community in the rhizosphere. The plant iron nutritional status can strongly influence both the root exudation pattern and the rhizosphere microbial community structure (12, 39, 118). For example, in barley plants grown in an iron-deficient soil, manipulation of the plant iron nutrition status by a foliar spray

significantly influenced the composition of the microbial community structure in the rhizosphere (148). This shift in community structure can be correlated with a shift in microbial community function, as observed in the rhizosphere microbial community of iron-stressed red clover plants, which is enriched in siderophore-producing microbes (60). This observation is in line with the current idea that modification of exudation patterns by plants in response to various environmental stimuli results in the enrichment of specific microbial species in the rhizosphere microbial community that, in turn, can perform beneficial functions for the host plant (11, 74, 101, 112). For example, in *Arabidopsis*, infection of the leaves with the bacterial pathogen *P. syringae* results in the production of specific root exudates that attract the ISR-inducing rhizobacterium *B. subtilis* FB17 (69). Invasion of the sugar beet rhizosphere by the necrotrophic pathogen *Rhizoctonia solani* caused a shift in the microbiota that was related to the production of oxalic acid by the pathogen (14). Iron availability may play a role in this shift in the microbiota, as oxalic acid production by fungi increases iron availability (32).

The phenylpropanoid-derived metabolites secreted in response to iron starvation are major components of root exudates (108, 118). Several of them, such as the coumarin phytoalexin scopoletin, have antimicrobial activity and act as chemical defense components against pathogen infection (29, 35, 61, 125, 129, 142). The secretion of these antimicrobial phenolics in response to stimulation by specific rhizosphere microbiota may be part of the selection process that is involved in rhizosphere microbial community assembly. Possibly, rhizosphere microbes that induce the root iron-deficiency response are less sensitive to the subsequently produced antimicrobial exudates than other members of the rhizosphere microbial community (**Figure 5*b***). This scenario results in mutual benefits by which the plant selectively supports growth of protective ISR-inducing microbes in the rhizosphere.

CONCLUDING REMARKS

Where organisms compete for the same limited resources, the struggle for survival fosters the evolution of sophisticated life strategies in all the interacting partners. In this review, we focused on the role of iron in the interaction between plants and their associated beneficial and pathogenic microbes. However, other minerals and nutrients have impacted the coevolution between plants and microbes in their own way. The role of phosphate scarcity in the interaction between plants and pathogenic and endophytic *Colletotrichum* spp. is a nice example of this (49, 54). Many *Colletotrichum* spp. are plant pathogenic, but *Colletotrichum tofieldiae* developed a plant-beneficial lifestyle by which it aids in plant phosphorus uptake under phosphorus-deficient conditions. Hence, nutrient scarcity facilitated the development of both pathogenic and beneficial life strategies in plant-associated microbiota, but we are only at the beginning of unraveling the underlying molecular and ecological details.

Over the past decades, iron availability has been a recurrent theme in the research field of plant-microbe interactions. An effect of iron on plant-microbe interactions was first observed in disease-suppressive soils, where siderophore-mediated competition for iron between beneficial microbes and soil-borne pathogens was identified as an important mechanism of disease suppressiveness (64, 76). Later, iron homeostasis in both the host and the pathogen was shown to play a role in specific plant-pathogen interactions (37). More recently, it became evident that ISR triggered by beneficial microbes in the rhizosphere shares important signaling components with the iron-deficiency response in plant roots (153, 154), which raises exciting new questions about the molecular ecology of plant-microbe interactions. From the plant side, the benefits of the interaction with ISR-inducing microbes are obvious. The plant mounts a systemic immune response that is effective against a broad spectrum of plant pathogens. Moreover, its capacity to acquire

iron increases, which may enable increased plant growth. However, many questions remain about the benefits of the interaction for the microbes. Does the resulting secretion of iron-mobilizing phenolic compounds affect assembly of the microbial community to their advantage? Does altered root exudation activate microbial functions that are mutually beneficial? And what are the nature and role of microbial volatiles in this process? Recent advances in next-generation sequencing technology boosted the field of host-microbe research and provided new insights into the underlying principles of how plant genotype, microbial community composition, and soil characteristics such as nutrient availability affect the delicate ecological balance between mutualists and pathogens in the rhizosphere and impact fitness parameters of the host plant (12, 50, 72, 101). These new developments will increase our knowledge of how fierce competition for scarce nutrients, such as iron, has led to the evolution of sophisticated interactions between plant hosts and their associated microbes. Ultimately, this will aid in the development of sustainable future crops that can maximize protective and plant growth–promoting functions provided by the beneficial microbes in their root microbiomes.

SUMMARY POINTS

1. Iron homeostasis mechanisms in plants, pathogens, and beneficial microbes play key roles in plant-microbe interactions.
2. Several plant defense hormones also function in the maintenance of iron homeostasis.
3. Iron withholding is a plant defense mechanism that can reduce pathogen virulence.
4. Local plant iron excess stimulates the development of a defensive oxidative burst that inhibits pathogen invasion.
5. Beneficial microbes in the rhizosphere antagonize soil-borne pathogens through siderophore-mediated competition for iron.
6. The ISR and the iron-uptake signaling pathways interact in plant roots via the transcription factor MYB72, which controls the biosynthesis of iron-mobilizing phenolics.
7. MYB72-dependent BGLU42 activity is required for the secretion of iron-mobilizing phenolics into the rhizosphere and the onset of ISR.
8. Fluorescent iron-mobilizing phenolics in root exudates play a role in rhizosphere microbial community assembly.

FUTURE ISSUES

1. How does nutrient scarcity facilitate the development of pathogenic or beneficial life strategies in plant-associated microbiota?
2. How does the activation of the iron-deficiency response in the roots result in systemic immunity in the shoots?
3. What is the nature of the (volatile) microbial determinants that activate the iron-deficiency response in plant roots and how do they function?

4. What is the identity of the mobile ISR signal that is postulated to be generated by the activity of BGLU42 in roots upon stimulation by ISR-inducing microbes in the rhizosphere?
5. How do ISR-inducing microbes profit from the induction of the iron-deficiency response in plant roots?
6. Do phenylpropanoid-derived metabolites in root exudates play a role in rhizosphere microbial community assembly?

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Errata

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