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The tug-of-war on iron between plant and pathogen

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Abstract

Iron participates in various crucial metabolic processes as an essential cofactor of many enzymes, which are vital to the survival of plants and their pathogens. However, excessive iron is toxic to the cells of plants and pathogens. Iron plays a complex role in the interactions between plants and pathogens. Plants and pathogens have evolved sophisticated mechanisms to modulate iron status at a moderate level for maintaining fitness. Iron competition extensively exists on both sides of plants and pathogens during infection. Plants employ iron withholding, local iron accumulation, or iron deficiency to trigger resistance against pathogens. Pathogens counteract host-derived iron stress or interfere with plant iron homeostasis to ensure virulence during infection. This review focuses on the recent progress in understanding the roles of iron in plant-pathogen interactions and proposes prospects for future studies.

Keywords Iron homeostasis, Plant defense response, Iron signaling, Reactive oxygen species, Virulence, Extracellular siderophores

Background

Iron (Fe) is essential for most living organisms, including plants and pathogens (Philpott 2006). Iron exists as reduced, ferrous Fe^{2+} and oxidized, ferric Fe^{3+}, making them essential cofactors of enzymes that mediate redox reactions in a variety of key cellular metabolic processes such as respiration, tricarboxylic acid cycle, DNA and lipid synthesis, electron transfer, and cell proliferation (Aznar et al. 2015; Camprubi et al. 2017; Verbon et al. 2017).

Iron is mainly present in the Earth's crust as ferric hydroxides, which has extremely limited bioavailability due to its poor solubility under neutral aerobic conditions (Mori 1999). The growth and virulence of pathogens are defective under iron-deficiency conditions (Johnson 2008; Braun and Hantke 2011), as are chlorophyll synthesis and photosynthesis of plants, resulting in chlorosis and severe growth defects (Hänsch and Mendel 2009; Ravet et al. 2009). However, excess ferrous Fe^{2+} inside cells easily combines with oxides or peroxides to form toxic hydroxyl radicals via the Fenton reaction, causing damage to proteins, DNA, and lipids (Pierre and Fontecave 1999; Papanikolaou and Pantopoulos 2005; Dixon and Stockwell 2014). As a result, plants and pathogens have evolved various mechanisms for tightly regulating iron uptake, transport, and storage.

Competition for iron is a pivotal issue of plant-pathogen interactions (Verbon et al. 2017; Liu et al. 2021; Herlihy et al. 2020). For one thing, host plants redistribute iron at the cellular level during pathogen infection to initiate iron immunity, modulate reactive oxygen species (ROS) bursts, or directly activate the immune system (Weinberg et al. 2008; Kehl-Fie and Skaar 2010; Ganz and Nemeth 2015; Soares and Weiss 2015; Xing et al. 2021). For another, some pathogens counteract plant immunity by extracting iron from host iron storage proteins, switching iron uptake strategies to overcome host-derived iron stress, or secreting effectors to interfere

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with plant iron homeostasis during infection (Singh et al. 2016; Xing et al. 2021; Wang et al. 2022). These manipulations are primary participants in the iron tug-of-war between plants and pathogens. In this review, we focus on recent progress in the regulatory mechanism of iron homeostasis in plants and pathogens, as well as the fundamental role of iron on plant immunity and pathogen virulence, emphasizing the unique role of iron in plant-pathogen interactions.

Iron homeostasis in plants

Plants have developed sophisticated mechanisms to ensure an adequate supply of iron in a fluctuating environment. Plants sense iron status and modulate the transcription of iron uptake-associated genes to regulate iron uptake from soil to root.

Iron acquisition strategies in plants

To adapt to Fe-deficient environments, plants evolved two different iron uptake mechanisms, known as reducing (Strategy I) and chelating strategies (Strategy II) (Römheld and Marschner 1986). Non-grass plants employ Strategy I to mobilize and acquire iron, which includes acidification of the rhizosphere by root-released H^+ involving H^+-ATPase, such as AHA2 (Santi and Schmidt 2009). Fe^{3+} is reduced to Fe^{2+} by plasma membrane protein Ferric Reduction Oxidase 2 (FRO2) before being transported to the root epidermis by high-affinity iron transporter Iron-Regulated Transporter 1 (IRT1) (Eide et al. 1996; Robinson et al. 1999; Brumbarova et al. 2015). The grass family represents Strategy II plants, which release phytosiderophores (PS) from roots to solubilize and chelate Fe^{3+} in soil by Transporter of Mgineic Aid1 (TOM1) (Nozoye et al. 2011). Fe^{3+}-phytosiderophores chelates are then taken up by specific transporters, such as Yellow Sytripe1 transporter (YS1) or YS1-like (YSL) in plants (Curie et al. 2001; Kobayashi and Nishizawa 2012).

Regulation of iron homeostasis in plants

Iron uptake from the soil is essential for maintaining plant iron homeostasis, but it is not the sole mechanism involved in the above process. Plants have developed mechanisms for regulating gene expression in response to iron availability to maintain iron homeostasis. Multiple basic helix-loop-helix (bHLH) transcription factors are involved in regulating plant iron homeostasis. The FER-like Iron deficiency-induced Transcription factor (FIT) and POPEYE (PYE) modules are the two critical regulatory networks of iron homeostasis in the Strategy I plant (Long et al. 2010; Ivanov et al. 2012). Upon iron deprivation, the FIT (bHLH29) is activated at the transcriptional and post-translational levels after it interacts with the Ib subgroup of bHLH transcription factors (bHLH38/39/100/101) (Yuan et al. 2008; Sivitz et al. 2012; Wang et al. 2013) to activate downstream iron-uptake genes, such as AHA2, FRO2, and IRT1 (Colangelo and Guerinot 2004; Santi and Schmidt 2009). Independent of FIT, the expression of the IVb subgroup of bHLH transcription factor PYE/bHLH47 is also upregulated upon iron deficiency. Like FIT, PYE interacts with IVc bHLH transcription factor ILR3/bHLH115, activating FRO2/IRT1 or ferritins FER/nicotianamine synthase 4 (NAS4) to facilitate iron transportation (Long et al. 2010). E3 ubiquitin-protein ligase BRUTUS (BTS) interacts with ILR3/bHLH105 and bHLH115 to facilitate their degradation via the 26S proteasome pathway, negatively regulating the expression of FIT and PYE to prevent iron overload in Fe-sufficient environments (Long et al. 2010; Selote et al. 2015; Rodrı´guez-Celma et al. 2019). In addition, UPSTREAM REGULATOR OF IRT1 (URI/bHLH121) has been recently identified and characterized as a positive regulator of plant iron homeostasis that directly or indirectly regulates the expression of most of the known genes participating in FIT and PYE regulatory networks (Kim et al. 2019; Gao et al. 2020; Lei et al. 2020).

Iron homeostasis in rice, a model plant for studying the strategy II mechanism, is also regulated by the bHLH transcription factors. The rice OsbHLH156/*Oryza sativa* FER-Like Fe Deficiency Induced Transcription Factor (OsFIT), OsbHLH56/Iron Related Transcription Factor 2 (OsIRO2), and OsbHLH63/OsIRO3 directly regulate genes involved in the iron uptake of Strategy II plant (Ogo et al. 2007; Liang et al. 2020; Wang et al. 2020). OsbHLH56/OsIRO2 positively regulates phytosiderophore biosynthesis and the expression of iron (III)-Deoxymugineic acid transporter *YSL15* (Ogo et al. 2006); OsFIT/OsbHLH156 interacts with OsIRO2/OsbHLH56 and promotes its accumulation in the nuclear (Liang et al. 2020; Wang et al. 2020). In contrast, OsIRO3 negatively regulates iron deficiency responses (Zheng et al. 2010). Iron deficiency induces an increase in transcript abundance of OsIRO2 and OsIRO3, which is mediated by Positive Regulator of Iron Homeostasis OsPRI1/OsbHLH060, OsPRI2/OsbHLH058, and OsPRI3/OsbHLH059 (Zhang et al. 2017, 2020; Kobayashi et al. 2019). Two more transcription factors, the Iron Deficiency-Responsive Element-binding Factor 1 and 2 (IDEF1 and IDEF2) from the ABI3/VP1 and NAC families, are also vital in regulating iron homeostasis (Kobayashi et al. 2007, 2009). OsIDEF1 functions upstream of OsIRO2, forming a transcriptional cascade that enhances the expression of genes involved in Fe(III)-DMA uptake and translocation, whereas OsIDEF2 regulates iron transport by binding to the promoters of several genes involved in iron homeostasis (Kobayashi

et al. 2007, 2009). Haemerythrin Motif-containing Really Interesting New Gene (Ring) and Zinc-Finger Protein 1 and 2 (OsHRZ1 and OsHRZ2), two rice ubiquitin E3 ligases displaying high homology with BTS, have been reported as potential iron sensors that play a negative role in iron acquisition under iron-sufficient conditions (Kobayashi et al. 2013). The in-depth study of the transcriptional regulation of iron homeostasis in strategy II plants is mainly focused on rice, which remains to be further explored.

Plant signals and hormones are also involved in the regulation of iron homeostasis. Salicylic acid (SA), gibberellin (GA), nitric oxide (NO), and ethylene (ET) play key roles in the Fe-response signaling pathway (Graziano et al. 2002; Lingam et al. 2011; Meiser et al. 2011; Wild et al. 2016). SA has been found to upregulate the expression of Fe-responsive transcription factor genes *bHLH38*, *bHLH39*, and the Fe transport gene *YSL3* (Kang et al. 2003). The SA levels increase, and the expression of SA-responsive genes is upregulated in *Arabidopsis* under iron deficiency conditions (Chen et al. 2014; Shen et al. 2016). DELLAs, the repressors of the GA signal pathway, directly bind to FIT, thereby inhibiting the expression of the downstream *IRT1* gene under Fe-abundant conditions (Wild et al. 2016). Iron deficiency stimulates NO accumulation in plant roots, which upregulates iron uptake genes (Graziano et al. 2007). In tomato plants, treatment with an NO donor to Fe-deficient roots induces the upregulation of FRO1, IRT1, and FER (Graziano et al. 2007). Applying NO to maize mutants defective in Fe uptake can revert the chlorosis phenotype (Graziano et al. 2005). Furthermore, NO has also been identified as a stabilizing stimulus of FIT protein abundance implicated in post-translational regulation of FIT (Meiser et al. 2011). In *Arabidopsis*, tomato, and cucumber, supplementary ethylene induces the Fe deficiency response (Romera and Alcantara 1994; Lucena et al. 2006, 2015; Waters et al. 2007; Garcia et al. 2010). Ethylene induces physiological and morphological responses in plant roots under Fe-deficient conditions (Lucena et al. 2015). The addition of ethylene, ACC, or ethephon, plants show physiological changes, such as enhanced ferric reductase activity, Fe^{2+} uptake capacity, rhizosphere acidification, and flavin excretion (Romera and Alcántara 2004; Lucena et al. 2006; Waters et al. 2007; García et al. 2010). In addition to physiological responses, ethylene also regulates morphological responses to Fe deficiency, such as enhanced root hairs, surface area of root epidermal transfer cells, and cluster roots (Schmidt and Schikora 2001; Schikora and Schmidt 2002; Zaid et al. 2003; Romera and Alcántara 2004). Reciprocally, Fe deficiency influences ethylene biosynthesis and signaling pathways (Wu et al. 2011; Lucena et al. 2015; Ye et al. 2015). FIT promotes stability and assists iron acquisition by interacting with transcription factors EIN3 and EIL1 in the ET signaling pathway (Lingam et al. 2011). Thus, there is positive feedback between Fe deficiency responses and ethylene biosynthesis. Recently, it has been reported that Fe deficiency induces the high expression of *SAM1* and *SAM2* in a FIT-bHLH Ib module-dependent manner in plant roots (Lu and Liang 2023). These findings reveal that SA, NO, and ET are positive regulators of the Fe uptake, whereas GA is a negative regulator. The fact that hormones and signals contribute to iron homeostasis indicates that fine-tuning Fe transport, storage, and uptake is crucial for immunity. ROS and Ca^{2+} signals also play a vital role in the regulation of plant development and stress response (Castro et al. 2021; Dong et al. 2021; Luan and Wang 2021). ROS-inducible transcriptional regulator ZAT12 interacts with FIT to prevent FIT degradation (Brumbarova et al. 2015). Calcium-dependent protein kinase CIPK11 interacts with FIT and activates FIT via phosphorylation at Ser272, allowing for FIT-dependent Fe deficiency responses (Gratz et al. 2019). Under iron-deficient conditions, calcium-dependent protein kinases CPK21 and CPK23 interact with and phosphorylate IRT1, promoting the transport of Fe from the extracellular space to the intracellular space (Wang et al. 2023). These findings indicate that plants fine-tune iron homeostasis at transcriptional and post-transcriptional levels.

Iron homeostasis in plant pathogens

During pathogen infections, iron is closely combined with plant ferritin, which makes it extremely low and unable to be absorbed and utilized by pathogens. Pathogens have developed various iron uptake strategies to successfully uptake iron from host plants for infection. In addition, pathogens have evolved precise iron-responsive regulatory systems to maintain iron homeostasis to adapt to iron-scarce or abundant host environments.

Iron acquisition of plant pathogens

The iron uptake strategies of plant pathogens have classically been divided into low-affinity and high-affinity uptake pathways (Haas 2014). Low-affinity uptake pathways encompass iron-containing protein uptake pathways and ferrous iron absorption pathways, mainly employed when iron is sufficient. The high-affinity uptake pathways play essential roles in acquiring iron under iron deficiency conditions, among which the siderophore-mediated iron uptake pathway is the most well-studied (Haas et al. 2008).

The high-affinity uptake pathways play substantial roles in the iron acquisition of phytopathogenic fungi during infection, including the reductive iron assimilation (RIA) pathway and the siderophore-mediated iron assimilation

(SIA) pathway (Haas et al. 2008; Albarouki and Deising 2013). The RIA pathway is characterized by two redox steps at the plasma membrane. Iron reductases reduce the extracellular insoluble or chelator-complexed ferric Fe^{3+} to soluble ferrous Fe^{2+} (Dancis et al. 1992). Subsequently, Fe^{2+} is oxidized to Fe^{3+} and translocated into the cytoplasm by the synergistic complex multicopper ferroxidase (Fet3) and iron permease (Ftr1) (Marvin 2004; Albarouki and Deising 2013). Extracellular siderophores are a group of low molecular weight (ranging from 500 to 1500 Da) ferric-iron-specific chelators that positively influence the iron uptake of pathogens (Chu et al. 2010). Ornithine is catalyzed by the L-ornithine-N_5-monooxygenase SidA and the non-ribosomal peptide synthase NPS to synthesize siderophores (Philpott 2006; Haas et al. 2008; Johnson 2008). The Fe^{3+}-siderophore complexes are transported into the cell by the siderophore iron transporter (ARN/SIT) subfamily (Haas 2014).

Various extracellular siderophores are widespread in most phytopathogenic bacteria (Chu et al. 2010; Hider and Kong 2010). For Gram-negative bacteria, siderophores are secreted into the extracellular space and specifically bind to Fe^{3+} to form Fe^{3+}-siderophore complexes, delivered into the periplasm by TonB-dependent transporters (TBDTs) located in the outer membrane. Then, the Fe^{3+}-siderophore complex is transported into the cytoplasm via an ABC transporter in the inner membrane. For Gram-positive bacteria, due to the absence of the outer membrane system of the bacteria, the Fe^{3+}-siderophore complex uptake is implemented in one step, which is performed through an ABC-like transport system (Andrews et al. 2003; Pandey et al. 2023). For some Gram-negative bacteria, the ferrous iron uptake system is vital for iron acquisition in some anaerobic-microaerophilic environments. The ferrous iron is transported to the periplasm by Fe^{2+}-specific porins. Then, the FeoB complex (FeoABC) transporter transports the ferrous iron to the cytoplasm (Janakiraman and Slauch 2000; Marlovits et al. 2002; Hantke 2003).

Transcriptional regulation of iron homeostasis in plant pathogens

Regulation of iron homeostasis is indispensable to ensure optimal cellular metabolism and avoid iron toxicity in phytopathogenic fungi. A negative feedback loop consisting of transcription factors Sre and HapX tightly regulates iron homeostasis in plant fungal pathogens (Canessa and Larrondo 2013; John et al. 2021). GATA-type transcription factor Sre (Siderophore biosynthesis repressor) is a core transcriptional regulator of iron homeostasis in phytopathogenic fungi (Voisard et al. 1993; Chao et al. 2008). Under iron sufficiency conditions, Sre binds to the consensus sequence ATCWGA TAA and represses RIA and SIA pathways to avoid iron toxicity (An et al. 1997a, b; Chung et al. 2020). Under iron starvation conditions, the transcriptional repression by Sre is disinhibited in the pathogen, thereby initiating the iron uptake pathway to rapidly acquire iron from the host plant (Schrettl et al. 2010). The bZIP-type transcription factor HapX is highly conserved among phytopathogenic fungi and has a basic leucine zipper domain that specifically binds to the 5′-CCAAT-3′ motif (Schrettl et al. 2010; Wang et al. 2019). Under iron starvation conditions, HapX spares iron by repressing iron-consuming pathways involved in processes of respiration, amino acid metabolism, citric acid cycle, DNA replication, and DNA repair (Jung et al. 2010; Schrettl et al. 2010; Chen et al. 2011; Hsu et al. 2011; López-Berges et al. 2012). Sre represses the expression of *hapX* under iron sufficiency conditions, while HapX represses *Sre* under iron starvation conditions (Mercier et al. 2006, 2008; Jbel et al. 2009; Jung et al. 2010). Additionally, both Sre and HapX are regulated post-translationally with iron to inhibit HapX and activate Sre (Haas 2012). Recently, histone H2B deubiquitination (H2B deub1) and the deposition of histone variant H2A.Z and histone 3 lysine 27 trimethylation (H3K27 me3) have been found to be involved in the networks of HapX- and Sre-mediated iron homeostasis regulation. Under iron excess conditions, HapX activates iron storage by promoting H2B deub1 at the promoter of the responsible genes. Meanwhile, Sre inhibits iron acquisition by facilitating the deposition of H2A.Z and H3K27 me3 at the first nucleosome after the transcription start site (Sun et al. 2023).

Although Sre and HapX have been identified to be involved mainly in iron homeostasis regulation, they are also members of a larger transcriptional network in which other transcription factors modulate their expressions, and several of their targets are also subject to additional transcriptional regulation. Recent findings show that pH-responsive transcription factor PacC and nitrogen metabolism regulator AreA are involved in the regulation of iron homeostasis in phytopathogenic fungi (Gu et al. 2022; Wang et al. 2019). This finding indicates the potential existence of a regulatory network tandem between iron homeostasis, nitrogen metabolism, and pH response pathways in phytopathogenic fungi.

Fur (Ferric uptake regulator) is a global regulatory transcription factor that plays a core role in maintaining bacterial iron homeostasis, and its function depends on the availability of Fe^{2+} (Baichoo et al. 2002; Fuangthong and Helmann 2003). Under iron excess conditions, Fur dimer and its corepressor Fe^{2+} form a complex that binds to the conserved fur-box located in the promoter of many iron-uptake-related genes, including the biosynthetic genes of siderophores, to suppress their expression (Jittawuttipoka

et al. 2010; Troxell and Hassan 2013). In contrast, under iron deficiency conditions, Fur dissociates with Fe^{2+}, disengages from the promoter regions of target genes, and initiates iron uptake (Pandey 2023). XibR (*Xanthomonas* iron-binding regulator) is another novel iron-binding transcriptional repressor of siderophore-biosynthetic genes (Pandey and Chatterjee 2022). Under iron-replete conditions, the Fe^{3+}-XibR complex directly binds to the promoter region of genes involved in siderophore synthesis, thereby repressing gene expression. Meanwhile, under iron-deplete conditions, XibR transcriptionally activates the expression of genes related to iron storage and outer membrane receptors for enhancing iron uptake (Pandey et al. 2016). These findings indicate that the regulation of iron homeostasis in phytopathogenic bacteria is a complex system.

The role of iron in the interactions between plants and pathogens

Iron is a key microelement with multiple roles throughout plant-pathogen interactions. Both sides of the interaction have evolved a variety of strategies to limit the rival's iron availability or disrupt iron homeostasis.

Iron and plant immunity

A defense strategy in vertebrates is withholding Fe by ferritin to limit iron availability for pathogen proliferation (Soares and Weiss 2015). The growth and developmental restriction of pathogens conferred by plant iron availability is called "iron immunity" (Xing et al. 2021). Host plants hide iron with iron storage proteins and defensin to create a locally extremely deficient iron host environment, inhibiting pathogen growth, development, and virulence (Kieu et al. 2012; Hsiao et al. 2017). The iron-binding ferritin gene (*FER*) expression is upregulated in plants after pathogen infection (Dellagi et al. 2005). During the interaction between *Arabidopsis thaliana* and *Dickeya dadantii*, the iron content of infected sites is significantly lower than that of non-infected sites. The expression of the iron storage gene *FERRITIN1* (*AtFER1*) is upregulated to initiate iron immunity that sequesters free Fe^{3+} in the cytoplasm and prevents Fe^{3+} entering apoplasts against pathogen invasion (Kieu et al. 2012; Aznar et al. 2015). *Arabidopsis* plants deficient in *FER* expression are more susceptible to *D. dadantii* (Dellagi et al. 2005). The role of plant defensins (PDF1.1, 1.2, and 1.3) is consistent with FER in iron immunity (Thomma et al. 2002; Sels et al. 2007). The AtPDF1.1 is secreted into the apoplast to chelate Fe^{3+}, limiting the iron supply and reducing pathogen virulence (Hsiao et al. 2017). Moreover, multiple plant immune-signaling pathways commonly suppress the pathogenic bacterial iron acquisition pathway (Nobori et al. 2018). The above examples suggest that iron immunity is one of the essential defense responses in plant-pathogen interactions.

Local iron accumulation is also an iron-immune strategy in plants. Recruitment of iron in infection sites induces ROS bursts through the Fenton reaction, which is a critical immune response for plants, particularly poaceae. In wheat-*Blumeria graminis* pathosystems, Fe^{3+} accumulates and ROS bursts at cell wall appositions (CWAs) (Greenshields et al. 2007; Liu et al. 2007). In rice-*Magnaporthe oryzae* pathosystems, Fe^{3+} is over-accumulated at infectious sites, dramatically suppressing the pathogen's growth by host ROS bursts. Fe^{3+} and ROS bursts at infected sites and phytochemical accumulation significantly enhance host resistance with high iron treatment. In agreement with these findings, in the pathosystems of maize and *Colletotrichum graminicola*, sufficient iron induces ROS accumulation and enhances host resistance (Ye et al. 2014). In addition, in the incompatible rice-*M. oryzae* interaction, iron redistribution and ROS accumulation lead to iron- and ROS-dependent ferroptotic cell death, which is an important plant immune response (Dangol et al. 2019; Liang et al. 2021). These data indicate that the mechanistic connection between the recruitment of iron and a successful immune response is explained, at least in part, by ROS bursts dependent on iron.

Iron deficiency confers plant resistance as an important immune response. Under iron deficiency conditions, *A. thaliana* confers resistance to the bacterial pathogen *D. dadantii* and the necrotrophic fungus *Botrytis cinerea* (Kieu et al. 2012). The inoculation of *B. cinerea* activates the Fe deficiency response of plants, which further induces ethylene synthesis and then resistance to *B. cinerea* (Lu and Liang 2023). In addition, iron deficiency induces the production of secondary metabolites involved in plant immunity. Under iron-deficient conditions, *Arabidopsis* roots secrete coumarin with antimicrobial ability and function as defense compounds in host plants against pathogen infection (Verbon et al. 2017; Beyer et al. 2019). In rice, iron deficiency triggers the secretion of protocatechuic acid, which has antimicrobial activity and confers resistance to the fungal pathogen *C. circinans* in onions (Tzin and Galili 2010; Ishimaru et al. 2011). These data show that iron deficiency can trigger the plant immune system (Fig. 1).

In addition, plant iron homeostasis is inextricably linked to plant immunity. Pathogen infections significantly modulate the high expression of iron homeostasis genes in host plants. Meanwhile, the expression of *IRT1*, *FRO2*, and *AtNRAMP3* (an iron transporter located in vacuole membrane) is upregulated in roots by *D. dadantii* inoculation in *Arabidopsis* leaves (Dellagi et al. 2005; Segond et al. 2009; Aznar et al. 2014). In rice, *miR7695*

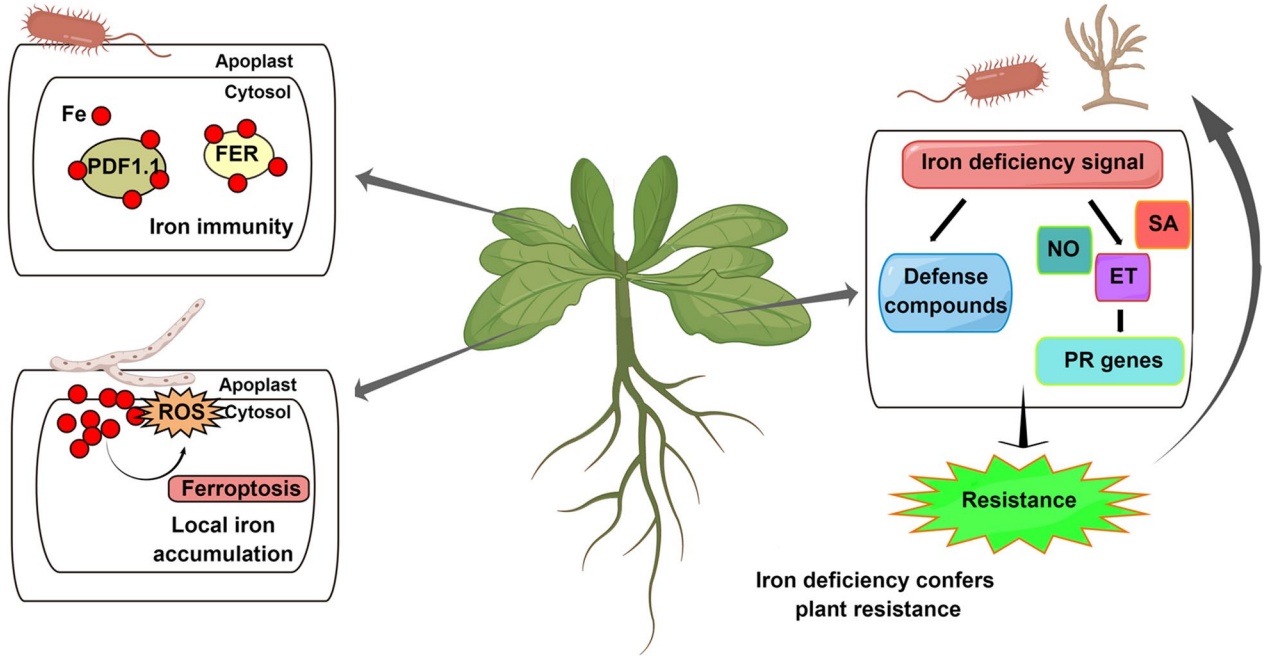

Fig. 1 Iron-mediated plant immunity. A strategy is to withhold Fe by chelating to limit iron availability necessary for pathogen proliferation (upper left). The second strategy is to suppress pathogens at infection sites by local iron accumulation, which induces ROS bursts (lower left). The third strategy is to induce the production of defense compounds or ethylene synthesis via iron deficiency to activate the expression of defense genes (right)

expression is regulated by *M. oryzae* infection, with subsequent downregulation of an alternatively spliced transcript of iron transporter *OsNramp6* (natural resistance-associated macrophage protein 6) (Li et al. 2019; Sánchez-Sanuy et al. 2019). These results suggest that IRT1, FRO2, and NRAMP are involved in plant immunity as positive regulators. PYE/ILR3 plays a key role in ROS accumulation by facilitating cluster shuttling between proteins in intracellular organelles and the cytosol via a conserved 2Fe-2S protein NEET (Nechushtai et al. 2012; Zandalinas et al. 2020). In addition, ILR3 also interacts with the Alfalfa mosaic virus coat protein and positively regulates accumulations of ROS, pathogenesis-related protein 1 (PR1), SA, and JA (Aparicio and Pallás 2017). BTS, an iron-binding E3 ligase, interacts with AtVOZ1 and AtVOZ2, which are NAC transcriptional regulators that activate the defense responses against fungal and bacterial infection in *A. thaliana* (Nakai et al. 2013; Selote et al. 2018). Thus, iron homeostasis has an intrinsic role in coordinating plant growth, development, and disease resistance.

Iron and virulence of plant pathogens

Siderophore-mediated iron uptake pathway is essential for the full virulence of many phytopathogenic bacteria, such as *D. dadantii*, *Erwinia amylovora*, *E. carotovora*, *Pseudomonas syringae* pv. *tabaci*, and *Xanthomonas oryzae* pv. *oryzicola* (Barnes and Ishimaru 1999; Franza et al. 2005; Taguchi et al. 2010; Rai et al. 2015; Müller et al. 2022). However, siderophores exhibit no obvious impact on virulence in some phytopathogenic bacteria, such as *P. syringae* pv. *tomato* DC3000, and *Ralstonia solanacearum* AW1 (Bhatt and Denny 2004; Jones and Wildermuth 2011). The ferrous iron uptake pathway also plays an important role in the virulence of some phytopathogenic bacteria. For example, the full virulence of *X. oryzae* pv. *oryzae* is dependent on the ferrous iron uptake pathway rather than on the siderophore-mediated iron uptake pathway (Pandey and Sonti 2010).

The ability to uptake iron from the host is indispensable to the virulence of phytopathogenic fungi. High-affinity iron assimilation pathways RIA and SIA are essential for full virulence. The RIA pathway is necessary for *U. maydis* and *Microbotryum violaceum* to ensure their full virulence (Birch and Ruddat 2005; Eichhorn et al. 2006). SIA pathway is essential for the full virulence of *C. miyabeanus*, *A. brasicicola*, *A. alternata*, *F. graminearum*, *M. grisea*, *C. graminearum*, and *Aspergillus fumigatus* (Oide et al. 2006; Greenshields et al. 2007; Hof et al. 2007, 2009; Chen et al. 2013; Haas 2014; Lu et al. 2021). In addition, the low-affinity iron assimilation pathway also plays a role in virulence (Grinter et al. 2018; Zheng et al. 2017; Yu et al. 2023).

A unique correspondence between the high-affinity uptake pathways and lifestyles exists in maize pathogenic fungi, and biotrophic and necrotrophic fungi have been found to rely on RIA and SIA pathways, respectively, for iron acquisition during pathogenesis (Mei et al. 1993; Eichhorn et al. 2006; Oide et al. 2006; Condon et al. 2014). Interestingly, the maize hemibiotrophic fungi utilize RIA and SIA pathways at biotrophic and necrotrophic stages, respectively (Albarouki et al. 2014). In typical maize biotrophic fungus *U. maydis*, the deletion of SIA pathway gene *Sid1* has no impact on virulence, while inactivation of the multicopper oxidase gene *Fer*1 and the iron permease gene *Fer2* in the RIA pathway results in virulence reduction (Mei et al. 1993; Eichhorn et al. 2006). In maize necrotrophic fungus *C. heterostrophus*, the siderophore biosynthesis gene *ChNPS6* is required for full virulence, while the iron permease gene *FTR1* is dispensable for virulence (Oide et al. 2006; Condon et al. 2014). Meanwhile, the two life stages of maize hemibiotrophic fungus *C. graminicola* coincide with the two distinct iron uptake pathways. Inactivation of the RIA pathway gene *fet1-3* in *C. graminicola* impairs the infection structure differentiation and the appressorial penetration in the biotrophic phase, while the deletion of SIA pathway genes *sid1* and *nps6*, results in necrotrophic hyphae expansion and virulence reduction (Albarouki and Deising 2013; Albarouki et al. 2014). These findings suggest a correlation between the iron assimilation pathways switch and the trophic style transition in hemibiotrophic fungi in maize.

Extracellular siderophores trigger plant immunity

In addition to contributing to pathogen virulence, extracellular siderophores are able to trigger plant immunity. Fungal extracellular siderophores initiate plant immunity in two different ways. Extracellular siderophores activate the salicylic acid pathway in *A. thaliana* by scavenging Fe, whereas siderophore-Fe complexes are ineffective (Dellagi et al. 2009). Similarly, treatments of barley leaves with deferrioxamine (DFO) upregulate the expression of PR and Fe homeostasis genes (Liu et al. 2007). These results indicate that iron scavenging is precisely a mechanism of immunity. Fungal extracellular siderophores also directly activate plant immune responses. Pretreatment with the coprogen primes maize defenses against the hemibiotroph pathogenic fungus *C. graminicola* (Albarouki et al. 2014). Pre-treated maize leaves enhance PR gene induction and ROS accumulation upon subsequent attack by pathogens. Similar results are obtained upon treatments with apo-coprogen or Fe-coprogen, indicating that priming, in this case, is independent of Fe scavenging. As the priming effect of coprogen on immune responses in maize does not rely on Fe scavenging, coprogen may be recognized by a receptor to activate downstream responses, as in the case of MAMPs that are recognized by pattern recognition receptors. In addition, extracellular siderophores modify Fe distribution at the cellular level in plants. Siderophores induce ROS production and activate immunity by directly transferring iron from apoplast to cell wall accumulation (Aznar et al. 2015).

Plant pathogens overcome "iron-related immunity" using diverse strategies

Well-adapted pathogens have evolved mechanisms for extracting iron from host iron storage proteins (Fig. 2a). *Verticillium dahliae* chelates iron from host plants through Asp-type CFEM family members in iron-deficiency xylem and Asn-type CFEM members to suppress immunity, for successful colonization and propagation in host plants (Wang et al. 2022). The *xfeA* (iron receptor gene) in *X. oryzae* pv. *oryzicola* senses extra-cytoplasmic iron by adenosine-to-inosine (A-to-I) RNA editing, suggesting that bacteria may use A-to-I editing as an alternative strategy to promote the uptake of metabolic iron and improve their competitiveness (Nie et al. 2021). This observation has revealed a new mechanism by which bacteria use A-to-I RNA editing to adjust iron concentrations. The hemibiotrophic pathogens shift lifestyle from biotrophs during the early stage of infection to the necrotrophic phase at the late stage. The lifestyle transition in their infectious cycle suggests that the hemibiotrophic fungi switch their iron uptake strategies to counteract host iron immunity during infection. *C. graminicola* utilizes the RIA pathway to efficiently acquire iron in the biotrophic stage and overcome host low iron stress for pathogens invasion and development (Albarouki and Deising 2013). Subsequently, pathogens secrete extracellular siderophores to chelate Fe^{3+}. Furthermore, extracellular siderophores plunder iron from host ferritin to limit oxidative stress caused by iron accumulation in plants (Albarouki et al. 2014). Biosynthetic genes of extracellular siderophores are specifically downregulated during the biotrophic phase, possibly regulating the production of siderophores at the early stages of infection to circumvent the elicitation of host immune responses.

Interfering with plant iron homeostasis is another mechanism by which pathogens counteract iron-regulated immunity (Fig. 2b). AvrRps4, an effector protein delivered by *P. syringae*, interacts with and targets the plant iron sensor protein BTS to facilitate iron uptake and pathogen proliferation in *A. thaliana*. AvrRps4 resulted in iron accumulation, especially in the plant apoplast (Xing et al. 2021). *M. oryzae* suppresses ROS accumulation by secreting effector AVR-Pii and interferes with ferroptosis to overcome host immunity (Singh et al. 2016). These findings suggest that secreting effector proteins is

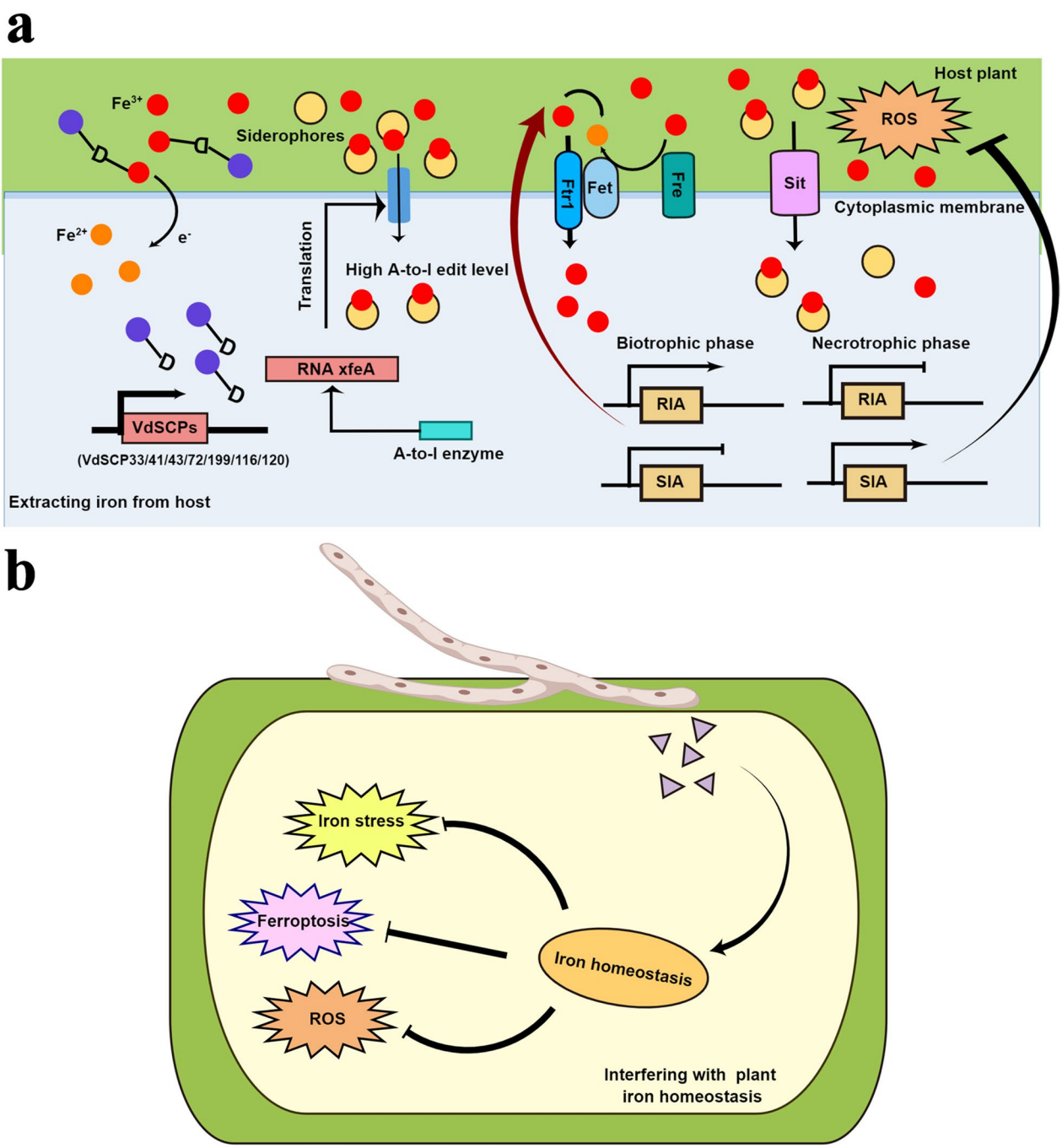

Fig. 2 Pathogens employ multiple mechanisms to overcome plant iron-regulated immunity. **a** One strategy is to extract iron from host iron storage proteins. For example, under plant iron-depleted conditions, *V. dahliae* employs the Asp-type CFEM-containing VdSCPs (VdSCP33, VdSCP41, VdSCP43, VdSCP72, VdSCP99, VdSCP116, and VdSCP120) to sequester iron to counteract host resistance; under iron-depleted conditions or *in planta*, *xfeA* in *Xanthomonas oryzae* pv. *oryzicola* senses extra-cytoplasmic iron and changes the hydrogen bonding network of ligand channel domains by adenosine-to-inosine (A-to-I) RNA editing; *C. graminicola* utilizes the RIA pathway to efficiently acquire iron in the biotrophic stage, overcomes host low iron stress. **b** Pathogens secrete extracellular siderophores to chelate Fe^{3+} to limit host oxidative stress. Another strategy is to interfere with plant iron homeostasis. For example, effectors delivered by pathogens interact with and target the plant iron homeostasis protein to facilitate iron uptake or inhibit ROS production

an important strategy by which pathogens interfere with plant iron homeostasis.

Conclusion and Perspectives

Iron should be considered as a crucial microelement with complex roles in plant-pathogen interactions. Many topics remain to be addressed about the role of iron in the interaction between plants and pathogens, which will influence future research directions.

Iron is a conserved factor as a microelement and signal that potentially modulates defense response against invaders in animal and plant kingdoms during evolution. Plant iron status is a key indicator of plant-pathogen interactions and particular defense responses. Fe supply modulation leads to different outcomes depending on the strategy of pathogen infection. In some cases, Fe directly contributes to the amplification of plant ROS production. Moreover, Fe supply indirectly affects plant metabolic activity, thereby allowing the production of antimicrobial compounds or other defenses that require Fe-dependent enzymes. However, Fe deficiency also causes the accumulation of antimicrobial compounds. These lines of evidence suggest that iron status has multiple effects on plant immunity depending on specific plant-pathogen interactions. However, studying how the host plants determine to defend the pathogens by withholding iron or over-accumulating iron is still needed.

Microbial extracellular siderophores initially secreted by pathogens to acquire Fe from their environment have been shown to trigger defense responses. Depending on the host, defense responses by extracellular siderophores are involved in either their Fe scavenging property or as MAMPs (microbe-associated molecular patterns). In the soil environment, plants are exposed to a variety of beneficial or pathogenic microorganisms, all of which are likely to produce extracellular siderophores. A better understanding of how extracellular siderophores affect plant immunity holds promise for designing new crop protection strategies.

Hemibiotrophic pathogens switch their iron uptake strategies to adapt to host iron status. For example, maize plants recruit free iron to the infection site, which induces ROS accumulation during *C. graminicola* infection (Ye et al. 2014). The iron assimilation pathway of *C. graminicola* switches from RIA to SIA in response to host iron status changes (Albarouki and Deising 2013; Albarouki et al. 2014). This evidence shows that the iron status of host plants substantially determines iron assimilation pathways utilized by fungal pathogens. A comprehensive study of biotrophic, hemibiotrophic, and necrotrophic pathogens would allow a better understanding of the link between the pathogen lifestyle and plant iron status. In addition, it would be interesting to know whether the plant Fe status affects pathogen lifestyle, which could also affect pathogenesis. In addition, it is meaningful to study how the pathogens sense the intracellular and extracellular iron status. Iron homeostasis genes are considered crucial elements with complex roles in plant immunity, whereby iron homeostasis genes could be underlying resistance-related genes in crops. Crops could be engineered to overexpress Fe homeostasis genes that positively affect plant disease resistance without yield loss.

Iron-limiting soils are widespread, causing significant losses in plant growth and productivity. Rhizosphere microbes have great potential for improving plant iron nutrition under iron-limited conditions. Under iron-limited conditions, plant-secreted coumarin compounds are beneficial mediators of plant-microorganism interactions. These specialized metabolites alter the composition of root microbiota and are necessary for microbiota-mediated plant iron uptake and immune regulation (Verbon et al. 2017; Schmidt et al. 2020). In *Arabidopsis*, variation in coumarin production has been shown to correlate with performance under iron limitation (Siwinska et al. 2014; Tsai et al. 2018). Rhizosphere microbes improve the performance of iron-limited plants dependent on plant iron import and secretion of the coumarin (Harbort et al. 2020). These findings show that the root microbiota is an integral component of plant edaphic adaptation to growth in iron-limiting soil. Root-secreted coumarins are inducible under iron starvation and mediate an interaction between the host and commensals that improves host iron nutrition. A better knowledge of these complex interactions and their monitoring will aid the improvement of crop production in iron-limiting soil.

Abbreviations

CWAs	Cell wall appositions
DFO	Deferrioxamine
ET	Ethylene
GA	Gibberellin
PS	Phytosiderophores
RIA	Reductive iron assimilation pathway
ROS	Reactive oxygen species
SA	Salicylic acid
SIA	Siderophore-mediated iron assimilation pathway

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Author contributions

CSX conceived the concept. JYS participated in writing the manuscript and submitted pictures. CSX and SQX revised and finalized the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding authors on request.

Declarations

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Not applicable.

Consent for publication
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