IRIS AperTO

UNIVERSITÀ DEGLI STUDI DI TORINO

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Signals from chloroplasts and mitochondria for iron homeostasis regulation

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IRIS AperTO

UNIVERSITÀ DEGLI STUDI DI TORINO

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ron (Fe) is an essential element for human nutrition. Given that plants represent a major dietary source of Fe worldwide, it is crucial to understand plant Fe homeostasis fully. A major breakthrough in the understanding of Fe sensing and signaling was the identification of several transcription factor cascades regulating Fe homeostasis. However, the mechanisms of activation of these cascades still remain to be elucidated. In this opinion, we focus on the possible roles of mitochondria and chloroplasts as cellular Fe sensing and signaling sites, offering a new perspective on the integrated regulation of Fe homeostasis and its interplay with cellular metabolism.

Highlights

► The understanding of plant iron homeostasis must be fully elucidated. ► We review the knowledge of metabolic adaptation in response to altered iron availability. ► Mitochondria and chloroplasts are proposed to act as cellular iron sensing and signaling sites.

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Metabolic adaptation to the Fe status of a plant

Fe is essential for most living organisms, and plants represent the main dietary source of Fe in human nutrition. Consequently, Fe uptake by roots, its distribution throughout organs, tissues and subcellular compartments (Boxes 1 and 2), the synthesis of prosthetic groups, such as heme or Fe–sulfur (S) clusters, and Fe storage were major focuses of scientific research during the past decade (for overview see [1]). Fe is essential for vital metabolic reactions in organelles, such as respiratory and photosynthetic electron transport chains (RET and PET, respectively); thus, its imbalance affects the entire cellular metabolism. To optimize effective Fe acquisition, distribution, and utilization, plants react to changes in Fe availability in their environment by adapting their metabolism and by tightly regulating Fe homeostasis. Despite the wealth of knowledge that has been gained concerning the processes by which plants can respond to Fe deficiency, the mechanisms of Fe sensing and signaling are not yet fully understood. So far, several key players in the major transcriptional networks that control Fe homeostasis have been identified, as well as several different Fe-responsive signaling pathways [2] (Box 1).

Box 1

Plant Fe-transport mechanisms and transcriptional control

In plants, the main obstacle to overcome concerning Fe nutrition is related to its low availability in the soil. In fact, notwithstanding its abundance, Fe exists in well-aerated soils mainly as scarcely soluble Fe(III)-oxides and oxi-hydroxides and therefore is not freely available for uptake by plants. To overcome with this situation, plants have evolved efficient mechanisms to acquire Fe from the soil. Dicots and nongrass plants developed the so-called 'Strategy I' mechanism, by which Fe acquisition is mediated via a reduction-based mechanism [2]: a ferric chelate reductase converts the Fe in Fe(III)-chelates to free Fe^{2+} and, subsequently, an Fe^{2+} transporter (IRT1, IRON-REGULATED TRANSPORTER 1) moves Fe across the plasma membrane into the cell. Additionally, in most of the Strategy I plants studied so far, there is an associated increase in the activity of a plasma membrane H^+-ATPase, which actively extrudes protons. Extracellular protons in turn are necessary both for decreasing rhizospheric pH to solubilize Fe(III) and for generating the electrochemical proton gradient to drive Fe uptake.

By contrast, in grasses (Strategy II plants), a group that includes most of the staple grain crops worldwide, a distinct mechanism for Fe uptake has evolved. These plants produce molecules of the mugineic acid family called phytosiderophores (PSs). PSs are secreted into the rhizosphere by the TOM1 (transporter of mugineic acid family phytosiderophores 1) transporter where they chelate and help to solubilize Fe^{3+}. The Fe(III)–PS complex is then taken up into root cells through the action of YELLOW STRIPE 1 (YS1) proteins [2,15,77].

To sustain Fe uptake, plants reprogram the entire metabolism. In particular, in Strategy I plants, Fe deficiency strongly affects mitochondrial functionality and, therefore, cells induce alternative energetic pathways, such as glycolysis, oxidative pentose phosphate pathways, or fermentation [36]. In addition, in Strategy II plants, Fe deficiency increases some substitute energetic pathways, although no specific data are available concerning the effect on mitochondria [11]. To increase Fe availability and acquisition, as well as production of mugineic acids (Strategy II), synthesis of phenols (Strategy I) and of organic acids (both Fe-uptake mechanisms) is induced.

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Progress has been made in identifying and characterizing several transcription factors (TFs) that regulate plant Fe-deficiency responses and which have been reviewed recently [2,15,78]. These TFs act by trans-activating primary target genes, such as Fe(III)-chelate reductases, biosynthetic enzymes of the mugineic acid Fe-chelators, and transporters. Briefly, in dicotyledonous plants, the regulation of Strategy I genes is under the control of two main and independent transcriptional pathways: the FER-LIKE IRON-DEFICIENCY-INDUCED TRANSCRIPTION FACTOR (FIT) and the POPEYE-mediated networks. The FIT-mediated network is mainly required for the regulation of the Fe-deficiency response at the epidermal cell level, whereas the POPEYE-mediated network occurs in the vasculature and regulates genes implicated in metal homeostasis. In grasses, the regulation of Strategy II genes requires the TFs OsIDEF1 (IDEF, iron deficiency-responsive element-binding factor) and OsIDEF2, as well as OsIRO2, as positive regulators of the Fe-deficiency response in rice.

Box 2
Organellar Fe transport

Once Fe enters the plant cell, it may be either integrated in cytoplasmic proteins or diverted to chloroplasts, mitochondria, or vacuoles. PERMEASE IN CHLOROPLASTS 1 (PIC1) is involved in Fe transport to chloroplasts [79,80], whereas the MITOCHONDRIAL IRON TRANSPORTER (MIT) loads cytoplasmic Fe to mitochondria [19,81]. Vacuoles, serving as additional Fe pools, acquire Fe through the VACUOLAR IRON TRANSPORTER 1 (VIT1; [82]). For chloroplasts, nuclear genes of primary photosynthesis are reciprocally regulated in Arabidopsis knockout and overexpressing mutants of the Fe-uptake protein PIC1 [79,80]. Interestingly, although photosynthesis-associated transcripts accumulate in PIC1-overexpressing lines, plants suffer from chlorosis and reduced growth, most likely due to plastid-internal Fe toxicity. Thus, PIC1ox plants show an antagonist effect of photosynthetic activity and regulation of gene expression, similar to the mentioned reciprocal Fe-deficiency regulation of mitochondrial RET activity and transcript and/or protein abundance (see main text). It is therefore tempting, but still preliminary, to speculate whether organellar retrograde signals, which might be generated by metabolic and/or activity changes in key proteins, might compete with cytosolic Fe sensing, which would trigger an anterograde pathway (Box 3).

Plants could sense Fe deficiency and/or toxicity in the cytosol, and excess Fe could either be diverted into the vacuole or into plastids, where it could be stored in the Fe-storage protein ferritin. An indication for cytosolic and nonplastid Fe sensing is provided by knockout mutants of PIC1, which show a strong increase in ferritin transcripts and proteins [79], possibly reflecting a rise in cytosolic Fe, while Fe uptake into chloroplasts is blocked. A reduction in mitochondrial Fe uptake in rice is suggested to induce Fe excess in the cytoplasm as well as the upregulation of OsVIT1[19], additionally supporting cytosolic Fe perception. However, the mechanism of this sensing is not clearly understood. The importance of transporter-mediated Fe trafficking between the various subcellular compartments has been further documented in Arabidopsis seeds. Manipulation of Fe levels by overexpression of AtVit1 or knocking out Nramp3 and Nramp4 (two transporters responsible for Fe unloading from the vacuole) result in a decrease in ferritin abundance in the plastids [83], in this case arguing for cytosolic Fe sensing and thus anterograde signals.

In short, cellular transporters are regulated in response to Fe deficiency and/or excess and work in close coordination to manage changes in Fe availability, and to tune the appropriate delivery of the metal. Therefore, they represent important targets and tools for future studies on the signaling of plant Fe-homeostasis regulation.

In response to Fe deficiency, plants initiate several metabolic changes to bring about increased Fe acquisition capacity, as extensively reviewed previously [3–5]. On the one hand, a low Fe content leads to a high energy request to sustain the increased rate of Fe acquisition; on the other hand, it limits the functioning of mitochondria and chloroplasts, which are Fe-dependent energy-producing organelles. To address this energetic emergency, cells must increase the rate of energy-producing alternative pathways. These increases have been observed in both Strategy I [6–10] and Strategy II plants [11] (Box 1). Because the photosynthetic apparatus is strongly affected under Fe deficiency, the existence of a carbon flow from root to leaf in the form of carboxylates has been observed in Fe-deficient plants [12,13].

The metabolic reprogramming under Fe deficiency relates to the functional alteration of essential cell compartments, such as mitochondria and chloroplasts. Organellar processes could therefore be involved in Fe sensing. Among them, Fe distribution among the various subcellular compartments is crucial and is controlled by organellar Fe transporters [14–16], as described in Box 2.

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Fe deficiency-induced changes in plant mitochondria and chloroplasts

Mitochondria are a major subcellular compartment for Fe metabolism, because Fe is an essential cofactor for several proteins belonging to RET and the tricarboxylic acid (TCA) cycle. Moreover, part of Fe–S cluster and heme biosynthesis is located in the mitochondria and is strictly linked to Fe homeostasis. Hence, alteration of the cellular Fe status dramatically influences mitochondrial functionality and thereby cellular metabolism [3,4,17–19].

Fe deficiency decreases RET activity [20]. However, Fe-deficient Arabidopsis (Arabidopsis thaliana) roots show accumulation of some respiratory transcripts and proteins [21,22], suggesting the existence of antagonistic levels of regulation under Fe starvation. Furthermore, several authors have reported that, under Fe deficiency, induction of TCA cycle activity leads to the strong production of organic acids, which are intermediate compounds of the TCA cycle [4]. Because succinate dehydrogenase and aconitase are Fe–S proteins, it has recently been hypothesized that, under Fe deficiency, the TCA cycle might shift to a linear mode, bypassing the affected enzymes [4]. Furthermore, it appears that aconitase is affected by metal-induced damage [23] and that inhibition of aconitase activity by reactive oxygen species (ROS, see below) leads to mitochondrial citrate export [24].

Similarly to mitochondria, chloroplasts also have several Fe-containing proteins located in all plastid subcompartments, with the most prominent functioning in PET [5]. Fe shortage thus induces a decrease in the pigment content (chlorophyll and carotenoids) and in proteins belonging to the photosynthetic apparatus. As a result, the photosynthetic rate diminishes, as well as the amount of the photosystem II (PSII) antennae, which exhibit an altered aggregation, concomitant with a decrease in xanthophyll content [25–29]. Accordingly, in the green algae Chlamydomonas (Chlamydomonas reinhardtii) a decrease in the amount of photosystem I (PSI), as well as a remodeling of the PSI-associated light-harvesting complex I (LHCI), were observed [30,31]. Other photosynthesis-related proteins also decrease in abundance, such as components of inorganic carbon assimilation, plastocyanin, proteins associated with the light reaction, and enzymes belonging to the Calvin cycle [32], suggesting that Fe deficiency affects the protein abundance of the photosynthetic apparatus both at the thylakoid as well as the stromal and lumenal levels [30,33].

Mitochondria and chloroplasts in Fe-dependent oxidative stress signal production and nitric oxide-mediated control of Fe homeostasis

Iron imbalance is known to induce oxidative stress in cells by promoting the generation and accumulation of ROS, causing oxidation of cellular components, hindering metabolic activities, and affecting organelle integrity [34]. Indeed, Fe is a cofactor of many antioxidant enzymes, including catalase, peroxidases, ascorbate peroxidase, and Fe-superoxide dismutase. These enzymes are strongly affected by Fe deficiency, leading to a consistent unbalance of the detoxification processes in plants, which thus accumulate ROS [35,36]. Fe is also a pro-oxidant factor that can catalyze free radical production in the presence of reductants and peroxides. In particular, Fe-mediated ROS production is involved in the transcriptional regulation of the expression of ferritin genes, encoding chloroplast proteins storing Fe when in excess [37].

PET and RET activities determine the redox states of their respective organelles, being associated with reducing power or energy-carrying metabolites, such as NAD(P)H and ATP [38–40]. The organellar redox state can be monitored by the production of ROS, which in turn is associated with changes in nuclear gene expression (NGE) [41]. The role of ROS as retrograde signals has been questioned, because they are probably too short lived to reach the nucleus and too unspecific to act as information carriers. Nevertheless, it has been hypothesized that ROS might act indirectly by generating specific peptides from the proteolytic breakdown of oxidized proteins that might have signal function, contributing to retrograde signaling and gene regulation, as observed in mitochondria [42]. Furthermore, under Fe deficiency, the altered RET and PET could lead to ROS overproduction and, thus, to protein oxidation (Figure 1) [43–45]. Alteration of the assembly of the protein complexes of RET and PET under Fe deficiency (see above) could produce peptides hosting Fe–S clusters, which might be oxidized and/or degraded and then function as signals.

Hypothetical retrograde signals produced by mitochondria and chloroplasts under…

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Figure 1. Hypothetical retrograde signals produced by mitochondria and chloroplasts under iron (Fe) stress conditions and their possible implication in Fe sensing and signaling systems in plants. Fe-stress conditions affect both respiratory (RET) and photosynthetic (PET) electron transport chains in mitochondria and chloroplasts. Furthermore, these conditions lead to the production of reactive oxygen species (ROS), which in turn might oxidize peptides. These

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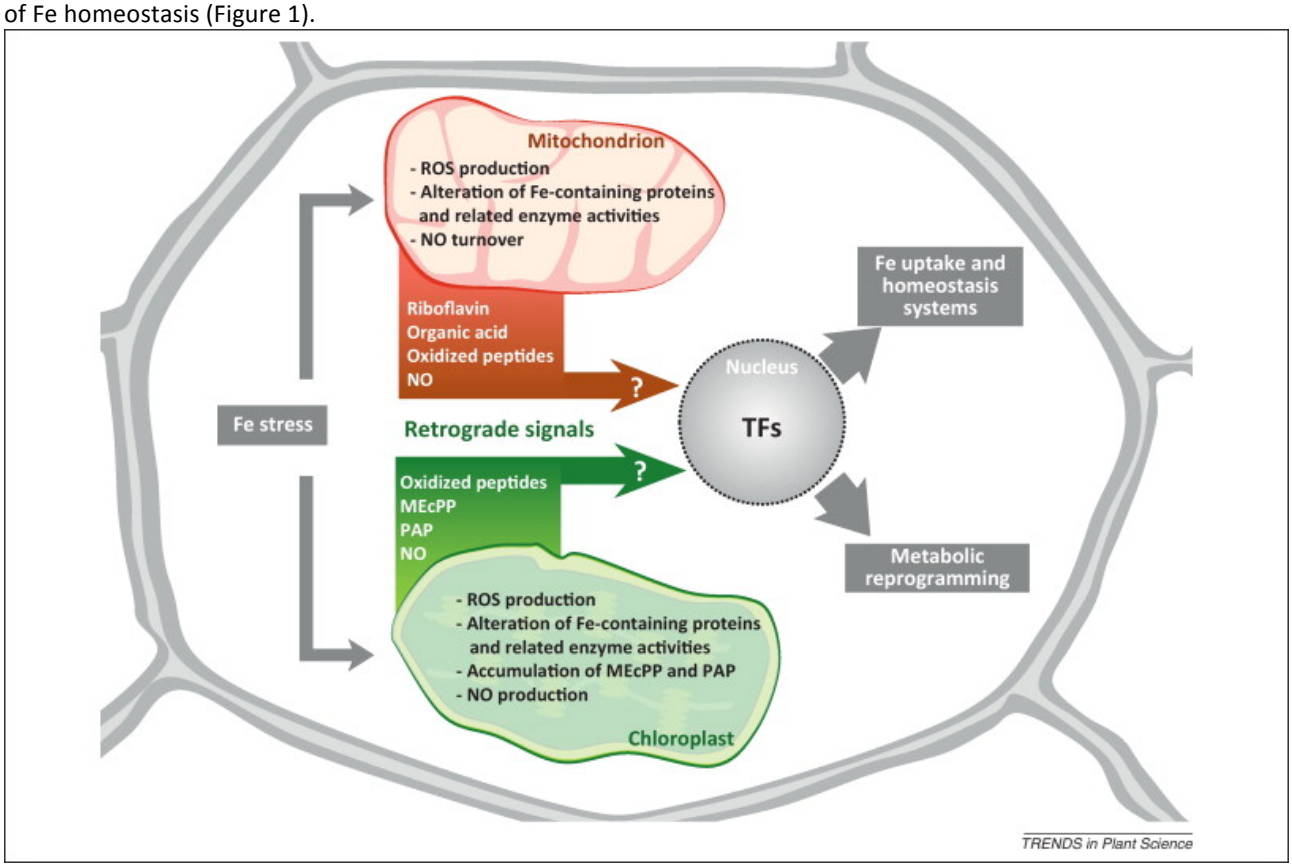
oxidized peptides could function as specific retrograde signals. As described in the main text, in both organelles, Fe-containing proteins and enzymes can be affected by Fe stress. Furthermore, an accumulation of methylerythritol cyclodiphosphate (MEcPP) and 3′ -phosphoadenosine 5′ -phosphate (PAP) in chloroplasts, and export of riboflavins and organic acids in mitochondria might occur in response to Fe stress. Nitric oxide (NO) represents another important signal molecule involved in the adaptation of Fe homeostasis. In chloroplasts, Fe excess promotes NO production, whereas in mitochondria, NO turnover is most likely to be involved in regulation. Furthermore, mitochondria and chloroplast metabolism might act directly as cellular Fe sensors via modification of enzymes. Subsequently, they could produce retrograde signals responsible for the recruitment and/or activation of the transcription factor (TF) cascades responsible for the regulation of Fe uptake and homeostasis systems and for tuning of cellular metabolism.

An important signal molecule involved in the establishment of Fe homeostasis in plants is nitric oxide (NO), which acts downstream of the Fe transcription factor FIT [46–50]. Cellular NO production involves both mitochondria and chloroplasts. Plant mitochondria participate in NO turnover by the interconversion of nitrite and NO at the site of complex IV [51], and plastids are important players in regulating NO levels in plant cells [52]. Furthermore, Fe excess induces NO production within the chloroplasts before the upregulation of expression of the ferritin AtFer1 gene [46,53], thereby reinforcing the idea that retrograde signaling by organelles could play a crucial role in the regulation of Fe homeostasis (Figure 1).



Putative retrograde signals from Fe-stressed plastids and mitochondria

The coordination between organelle gene expression (OGE) and NGE requires both anterograde and retrograde signals [54] (Box 3). The retrograde pathway communicates changes in the metabolic status of the organelles to the nucleus and consequently changes the anterograde signals. Changes in the metabolic status of chloroplasts and/or mitochondria (e.g., in response to an altered Fe nutritional status) have profound effects on the rest of the plant cell, and involve massive changes in the transcript profiles of nuclear genes. Despite the evidence that the main cellular targets under Fe deficiency are mitochondria and chloroplasts, no specific study has yet investigated the role of these organelles in Fe sensing and signaling in plants. It is therefore timely to investigate hypothetical retrograde signals from chloroplasts and mitochondria as a result of Fe stress.

Box 3

Anterograde and retrograde signaling pathways

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In response to endogenous and environmental stimuli that are perceived by the nucleus, an anterograde mechanism transmits signals originating from the nucleus to coordinate gene expression in organelles. The regulation of OGE mostly occurs through post-transcriptional mechanism and involves nuclear-encoded proteins, acting as regulators. By contrast, retrograde mechanisms transmit signals originating in the organelles to regulate NGE, which can then alter anterograde control. These mechanisms allow the communication of the functional and developmental state of organelles to the nucleus, which can thus modulate cellular metabolism [84]. In photosynthetic organisms, this regulation is more complex owing to crosstalk between mitochondria and chloroplasts. Tight coordination between the nucleus and organelles is crucial to the survival of eukaryotic cells: not only are chloroplasts and mitochondria of great bioenergetic importance, but they also synthesize many different cellular metabolites, including amino acids, fatty acids, isoprenoids, nucleotides, vitamins, and porphyrins.

For example a 'biogenic' retrograde signal is used by plastids as they develop into chloroplasts in young photosynthetic tissue. When chloroplast development is blocked, the expression of nuclear genes involved in photosynthesis and chloroplast biogenesis is greatly reduced. Arabidopsis genomes uncoupled (gun) mutants still express these nuclear genes even when chloroplast development is impaired ([85] and references therein). gun mutants demonstrate the implication of the branch point of the heme–chlorophyll biosynthesis pathway in the plastid as source of retrograde signals. The protoporphyrin IX precursor for heme is known to exit the plastid and is a mitochondrial retrograde signal in yeast. However, the mechanisms of its transport to the cytoplasm and of its interaction with signaling pathways are unknown. 'Operational' retrograde signals are also produced by plastids in response to external cues and stress. In contrast to gun signals, operational signals control nuclear genes to limit and repair damage from ROS generated by abiotic stresses, such as excess light and drought [54,85].

Plastid retrograde signals could derive from various sources, including the tetrapyrrole pathway, the level of ROS, or the redox state of the plastids [55]. All these signals are thought to converge on the regulator GENOMES UNCOUPLED 1 (GUN1) [56]. Recently, a new circadian Fe-sensing system located within chloroplasts has been identified in Arabidopsis[57,58]. It is independent of GUN1, requires an uncharacterized plastid-encoded protein, and depends on both the functional state of the chloroplast and the phytochromes [57]. On the one hand, these findings suggest that the known retrograde signals do not directly participate in Fe sensing mechanisms in plants. On the other hand, they emphasize the role of plastids in Fe sensing and signaling in a retrograde way. This raises the need to identify retrograde signal molecules potentially involved in plastid-to-nucleus signaling for tuning Fe homeostasis.

In this context, new plastid retrograde signals have been recently identified, such as the metabolites methylerythritol cyclodiphosphate (MEcPP) [59], and 3′ -phosphoadenosine 5′ -phosphate (PAP) [60]. MEcPP is an intermediate of the plastid methylerythritol phosphate (MEP) pathway, suggested to act as an NGE regulator [59]. 1-Hydroxy-2-methyl-2-(E)-butenyl4-diphosphate synthase (HDS) is a bottleneck enzyme in this pathway. In an Arabidopsis mutant defective in the CEH1 gene encoding HDS, MEcPP accumulates, the expression of selected stress-responsive genes increases, and salicylic acid accumulation occurs. Abiotic stresses, such as high light or wounding, also elevate MEcPP levels. It was proposed that the increased level of MEcPP serves as a specific and critical retrograde signal eliciting the expression of selected stress-responsive nuclear-encoded and plastid-localized proteins. Because HDS is a Fe–S cluster protein [61], it can be postulated that Fe-deficiency conditions could lead to MEcPP accumulation and, thus, the MEP pathway could be a metabolic stress sensor during Fe deficiency (Figure 1).

PAP is known to accumulate in Arabidopsis plastids in response to high light or drought stress and was able to regulate stress-responsive nuclear genes [60]. It accumulated in a sal1 mutant deficient in the enzyme able to dephosphorylate PAP to AMP. The mode of action of PAP could be inhibition of 5′ to 3′ exoribonucleases. Transcriptome analysis of Arabidopsis sal1 and xrn4 mutant plants (supplemental material in [60]) further revealed that the ferritin genes AtFer1, AtFfer3, and AtFer4 are upregulated in these genetic backgrounds, thus establishing a link between the PAP retrograde signaling pathway and the regulation of Fe homeostasis genes (Figure 1).

Mitochondrial retrograde regulation in plants is poorly understood and few signaling pathways have been identified [62]. As stated above, mitochondria are a crucial cellular site for the synthesis of Fe–S clusters, both for themselves and for Fe–S proteins from the cytosol and the nucleus [63]. Thus, impaired Fe–S cluster assembly in the mitochondria could influence or could be used as a sensor to signal alterations in Fe homeostasis. Some evidence supporting this hypothesis is found in yeast. In Saccharomyces cerevisiae, the expression of Fe uptake and storage genes is controlled by the Fe-responsive transcription factors Aft1 and Aft2 [64,65], which accumulate in the nucleus under Fe deficiency

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and activate the Fe regulon. The activation of Aft1/2 is mediated by the so-called 'Fra–Grx iron signaling pathway', which includes: (i) the mitochondrial Fe–S cluster biosynthesis machinery; (ii) the glutaredoxines Grx3 and Grx4; and (iii) an aminopeptide P-like protein named Fe repressor of activation-1 (Fra1) [66,67]. Under Fe-replete conditions, the Fra–Grx signaling pathway inhibits the Aft1/2 activity. By contrast, under Fe-deprived conditions, the affected mitochondrial Fe–S cluster biogenesis leads to the deactivation of the Fra–Grx pathway, allowing the Atf1 transcription factor to activate the Fe regulon [68]. Furthermore, frataxin, a mitochondrial protein involved in Fe homeostasis, might act as a mitochondrial sensor of the Fe content, regulating the rate of Fe–S biogenesis [69,70]. These findings suggest that molecules deriving from mitochondria, such as Fe–S clusters, are components of a retrograde pathway operating under Fe deficiency. Moreover, it has been suggested that some Fe-dependent metabolites (such as those provided by Fe-dependent enzymes) and/or heme contents are key regulators of central transcription factors, inducing the Fe regulon in yeast [71]. Furthermore, in Fe-deficient plants, accumulation of riboflavins has been observed [9,72]. These compounds are cofactors of complexes I and II of RET. It was therefore postulated that, by affecting RET-complexes, Fe deficiency allows the unused riboflavins to be transported outside the mitochondria [4,73]. Considering that riboflavins are also Fe3+-chelate reductase cofactors and that their accumulation is controlled by transcription factors regulating Fe assimilation [74], they might be considered as signal molecules of the physiological mitochondrial status under low Fe.

Concluding remarks and outlook

Despite great progress in understanding Fe homeostasis in plants, little insight has been gained concerning the effects of Fe nutritional status on the metabolism of organelles, and the consequences for Fe signaling.

Both Fe-deficient or Fe-excess conditions are known to affect mitochondrial and chloroplast metabolism through post-transcriptional and/or translational modifications of key enzymes. Such modifications are fast and enable a quicker response to environmental changes than via transcriptional activation. In particular, in the case of Fe deficiency, activity of Fe-containing enzymes is negatively regulated and, consequently, corresponding metabolite pools could be modified. Thus, we hypothesize that organelle retrograde signals could be produced from these post-transcriptional and/or post-translational-mediated metabolic changes, and transduced for subsequent regulation of nuclear genes that are important for Fe uptake and homeostasis, via the activation of the already established cascade of transcription factors (Figure 1). According to this scenario, long-term cellular metabolic reprogramming would accompany and follow adaptation of Fe uptake and homeostasis.

A challenge is to answer the question of whether Fe-mediated modifications of mitochondrial and chloroplast metabolism in response to alteration of the Fe status represent a source of retrograde signals, necessary to regulate the NGE involved in Fe stress responses. Therefore, there is a need to document kinetically the metabolic changes occurring in mitochondria and chloroplasts in response to Fe deficiency or excess, and the crosstalk between these organelles during these changes. Furthermore, it would also be interesting to study the organellar crosstalk in root cells, where nonphotosynthetic plastids are present, and compare it with crosstalk in leaf cells. Indeed, in root cells, where the plant manages the acquisition of Fe, plastidial–mitochondrial crosstalk would generate a root-specific signal pool able to regulate NGE of the roots. In addition, in leaf cells, where the plant manages the synthesis of organic compounds, chloroplast–mitochondria crosstalk would generate a leaf-specific signal pool. Whether the integration of these root and leaf signal pools contributes to the long-distance signaling of Fe deficiency [75] is an attractive question for future research. Whether sugars, or other molecules of general metabolism, which are transported in the phloem, participate in this systemic signal [75], is still unknown. However, in roots of some Fe-deficient plants, a change in the carbohydrate metabolism was observed with an increase in the raffinose family of oligosaccharides (RFOs) [9]. It has been reported that oligosaccharides, mainly generated from cell wall damage, might act as signaling molecules under some stress conditions [76] and that the RFOs might act as long-distance Fe-deficiency signals via phloem sap transport [9].

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