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Molecular Mechanisms for Iron Uptake and Homeostasis in Marine Eukaryotic Phytoplankton

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Abstract

The micronutrient iron is essential for phytoplankton growth due to its central role in a wide variety of key metabolic processes including photosynthesis and nitrate assimilation. As a result of scarce bioavailable iron in seawater, marine primary productivity is often iron-limited with future iron supplies remaining uncertain. Although evolutionary constraints resulted in high cellular iron requirements, phytoplankton evolved diverse mechanisms that enable uptake of multiple forms of iron, storage of iron over short and long timescales, and modulation of their iron requirement under stress. Genomics continues to increase our understanding of iron-related proteins that are homologous to those characterized in other model organisms, while recently, molecular and cell biology have been revealing unique genes and processes with connections to iron acquisition or use. Moreover, there are an increasing number of examples showing the interplay between iron uptake and extracellular processes such as boundary layer chemistry and microbial interactions.

Contents

1. INTRODUCTION

Nutrient availability in the ocean has immense influence on global primary productivity and microbially mediated biogeochemical cycling. In this context, the role of iron (Fe) as a micronutrient that limits phytoplankton growth has garnered significant interest over the past several decades. Although reviews from the 1950s and 1960s in this very journal describe early recognition of the universal requirement for iron to support life (127), uncertainty remained surrounding its significance in controlling phytoplankton growth in the natural environment (89, 150). Following the first accurate measurements of dissolved iron in seawater in the 1980s that revealed surface concentrations less than 0.5 nmol/kg (57, 82, 83) and experiments demonstrating increases in phytoplankton biomass after iron enrichment (31, 107, 108), the high importance of iron as a control on phytoplankton abundances and productivity in the ocean began to be more fully recognized.

With extensive and ongoing efforts to obtain high-quality iron measurements in the ocean, namely via the GEOTRACES program (3), dissolved iron concentrations in the surface ocean are now known to typically be in the 0.1 to 0.6 nM range but may be as low as 0.01 nM (52, 163) contributing to widespread limitation of growth in large areas of the ocean (115). Moreover, iron has been found to simultaneously colimit eukaryotic phytoplankton growth with nitrogen (26), the other trace metal Mn (25), and light in subsurface chlorophyll maxima layers (66) and in the Southern Ocean (21). Furthermore, there are interactive effects between iron and other micronutrients, such as vitamin B_{12} (14, 15), copper (125), and Zn (38). The availability of silicic acid and iron may also have interactive effects on diatoms, a lineage of phytoplankton belonging to the Stramenopile clade, as they require silicic acid to produce their cell walls (27, 69, 106).

Micronutrient: a chemical element or compound that is required for growth in relatively small quantities

Dissolved iron: iron species that can pass through a 0.2- or 0.4-µm filter, thus including both soluble iron species (less than 0.02 µm) and colloidal iron species (nanoparticulate species that are not truly dissolved)

Iron limitation in phytoplankton is traced to their early evolutionary history, most notably with the evolution of oxygenic photosynthesis. In phytoplankton, iron has essential roles as a cofactor for several proteins in diverse cellular processes, namely photosynthesis and nitrate assimilation (103). Oxygenic photosynthesis emerged approximately three billion years ago when dissolved iron concentrations were significantly higher, and phytoplankton made use of this abundant iron to irreversibly incorporate it into their photosynthetic electron transport chain and other key enzymes (11, 171). Following widespread and persistent oxygenation of surface waters 1,850–1,250 Mya (2), iron in seawater formed insoluble ferric oxyhydroxides that precipitated, resulting in the low dissolved iron concentrations observed today (11, 94). In addition to biological uptake, dissolved iron adsorbs onto particle surfaces or forms colloidal authigenic particles that may aggregate into larger particles and sink, further contributing to iron removal from the surface ocean, although these processes are somewhat reversable (22, 162).

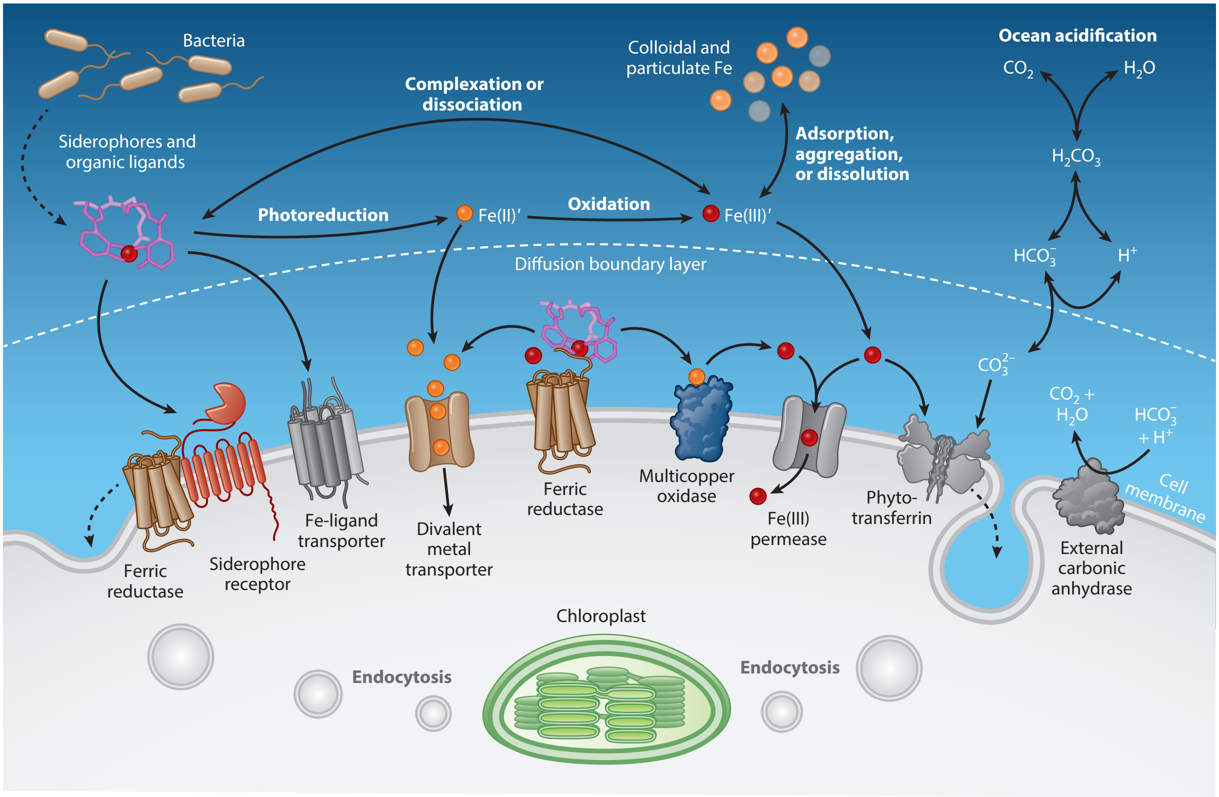

Figure 1

Cell surface view of iron uptake and processes that influence iron bioavailability in seawater. Figure adapted from images created with BioRender.com.

Iron removal is balanced by inputs that vary regionally (161). On global scales, iron supply is dominated by continental margin sediments where lateral advection transports iron beyond coastal waters. Iron released from hydrothermal vents is also a significant source as it is transported long distances and eventually upwelled, particularly in the Southern Ocean (5). In contrast, atmospheric dust deposition is relatively important in low-latitude regions (161), and on regional scales, rivers, glaciers, and sea ice melt also contribute to iron inputs (53, 129, 135). Following biological uptake, rapid recycling can further sustain iron in the euphotic zone (22).

Iron bioavailability is further influenced by its complex physicochemical speciation in seawater (**Figure 1**). It exists in two oxidation states: the more soluble ferrous iron (Fe(II)) and less soluble ferric iron (Fe(III)) that forms Fe(III) oxyhydroxide precipitates (28, 77). Fe(II) generally exists in relatively low concentrations as it undergoes oxidation to Fe(III) within minutes to hours (138), although at times, Fe(II) can account for a high percentage of total dissolved iron (67). Within the dissolved iron pool, less than 1% is presumed to exist as soluble inorganic Fe(II) or Fe(III), the sum of which is referred to as Fe′. The remainder is usually bound to organic ligands such as bacterial siderophores, humic acids, proteins, and exopolysaccharides. With a range of relatively strong to weak affinities for iron, these organic ligands allow dissolved iron concentrations to persist above the solubility limits of its inorganic species (55). Transformations among these chemical species are influenced by pH, temperature, oxygen, and photochemistry, including the dissolution of particulate iron (48, 96, 160). The result is a spectrum of iron bioavailability, from the most

Siderophore: microbially produced low-molecular-weight molecule that has a high-affinity for iron

Particulate iron: iron within or attached to particles greater than 0.2 or 0.4 μm available but least abundant being Fe′ to the least available generally being iron bound to certain strong organic ligands (92).

In response to iron stress or limitation, phytoplankton exhibit a range of physiological responses that in conjunction with the physiological aspects of iron uptake are reviewed by Marchetti & Maldonado (103). Photophysiological responses to iron stress are further detailed by Behrenfeld & Milligan (11). Briefly, intracellular iron contents, or quotas, decrease. Maximal uptake rates of both Fe′ and organically complexed iron increase, suggesting the upregulation of various cell surface iron transporters (65, 98). Cell sizes may also decrease, thus reducing overall nutrient requirements and improving nutrient uptake kinetics (103). Phytoplankton remodel their photosynthetic architecture, including decreases in their pigment inventories, leading to observable changes in their fluorescent properties (11, 41, 137). In diatoms, iron limitation also affects their elemental stoichiometry. Specifically, diatoms show increased silicon (Si) relative to carbon and nitrogen (68), which appears to be driven by reductions in cellular carbon and nitrogen rather than increases in Si (102).

Here we describe molecular mechanisms underlying iron uptake, cellular iron demand, and responses to iron stress in marine eukaryotic phytoplankton. Due to their prominence and ecological importance, previous studies, and therefore this review, largely focus on diatoms (Bacillariophyta) that alone comprise considerable diversity (20). However, many diatom proteins are homologous to those found in other phytoplankton lineages, suggesting that some of these mechanisms translate to different taxa. Studies on marine green algae (Prasinophyta), haptophytes (Haptophyta), dinoflagellates (Dinoflagellata), and other eukaryotic organisms are also included.

2. IRON UPTAKE MECHANISMS AND TRANSPORTERS

Corresponding to the wide variety of iron species available in seawater, eukaryotic phytoplankton evolved to possess a variety of iron uptake mechanisms enabling uptake of multiple iron sources, thus combating low iron availability and diffusion limitation (**Figure 1**) (155, 170). The evolutionary history of eukaryotic phytoplankton is complex and diverse, ranging from primary endosymbiotic events that created the green and red algal lineages to secondary and tertiary endosymbioses (74). Genetic origins within these lineages are further complicated by extensive horizontal gene transfer with bacteria (46). Diatoms, for example, are secondary endosymbionts with a mosaic of genes derived from both red and green algal endosymbionts, horizontally transferred genes of bacterial origin, and the retention of metazoan-type genes from their heterotrophic exosymbiont ancestor (20). This amalgamation of genes allows certain eukaryotic phytoplankton to possess diverse functional repertoires where iron-related genes are no exception.

2.1. Inorganic Iron Uptake and Intracellular Transport

As normally less than 1% of the dissolved iron pool, soluble inorganic iron (Fe′) exists in picomolar concentrations, yet it is the most bioavailable species and a primary source of iron for marine phytoplankton (55, 116). Inorganic iron uptake systems characterized in terrestrial organisms have affinities for iron in the micromolar range suggesting that marine phytoplankton must have novel mechanisms for inorganic iron acquisition under low concentrations (158). One such mechanism is the protein phytotransferrin (pTF), an outer membrane receptor that allows cells to import individual Fe(III) atoms via endocytosis (112) (**Figure 1**). This protein family includes the genes previously known as *ISIP2A* in diatoms (1) and *FEA1* in green algae (86) that are found widely across phytoplankton lineages (117) and upregulated under low iron availability (12, 35).

The evolution of pTF is a remarkable example of convergent evolution with transferrins that are found in metazoans and certain photosynthetic organisms, such as land plants and the green algae *Dunaliella salina*. Specifically, both families convergently evolved a requirement for carbonate (CO_3^{2-}) to coordinate Fe(III) ion binding, resulting in a second-order dependence on the concentrations of both Fe′ and CO_3^{2-} (7, 112). These second-order kinetics allow pTF to leverage high concentrations of CO_3^{2-} to acquire trace quantities of iron; however, in environments with low iron concentrations, carbonate ion concentrations may also be insufficient, leading to iron-carbonate colimitation with respect to pTF-mediated iron uptake (112).

Additionally, carbonate ion concentrations are declining due to ocean acidification (60), further decreasing the ability to bind inorganic iron. Acidification also makes iron less likely to dissociate from certain organic ligands, further lowering concentrations of Fe′ (143). Collectively, these effects may explain the negative impacts of acidification on iron-stressed phytoplankton (79, 154, 166), although changes in both pH and carbonate chemistry at the cell surface via photosynthesis and extracellular enzymes, such as carbonic anhydrases, may allow phytoplankton to overcome some of these effects (93) (**Figure 1**).

Prior to the discovery of pTF, kinetic models for iron uptake suggested that dissolved iron species, including soluble inorganic ferric iron, or Fe(III)′, required reduction at the cell surface (142). This model was based on the reductive iron uptake system in baker's yeast (*Saccharomyces cerevisiae*) and supported by similar genes found in the genome of the diatom *Thalassiosira pseudonana* (6), as well as physiological experiments with *Thalassiosira* spp. (97). This system includes cell surface ferric reductases that generate free ferrous iron, or Fe(II)′, from both Fe(III)′ and organically complexed iron. Fe(II)′ is then reoxidized by a multicopper oxidase that is coupled to a ferric iron permease (FTR) for transport across the cell membrane (**Figure 1**). This process enables selective iron transport, thus avoiding the uptake of unwanted metals (17); however, as previously described, the affinities for iron uptake with this system are likely in the micromolar range (88). While experiments suggest that diatoms exhibit extracellular Fe(II) oxidation that is impacted by copper availability (97), it is unknown whether or not this system is viable and functions at the cell surface as opposed to within endosomes. Additionally, while FTRs in *T. pseudonana* are localized to the cell surface, the localization of the multicopper oxidase remains unclear, leading to the alternative hypothesis that FTR functions as an independent transporter for Fe(III)′ uptake (A.B. Kustka, personal communication).

Direct uptake of inorganic ferrous iron, or Fe(II)′, has been observed in different microalgae (157) and likely occurs via nonspecific divalent metal transporters (103) that may also take up iron following ferric reductase activity (158) (**Figure 1**). Several families of proteins may perform this function, including ZIP (Zrt, Irt-like protein), NRAMP (natural resistance-associated macrophage protein), and CDF (cation diffusion facilitator) family transporters where they have been characterized in nonmarine model organisms (17). Once intracellular, iron must be trafficked to different sites and transported across organelle membranes; therefore, transporters in these families may also perform this function (**Figure 2**). To transport iron across the mitochondrial inner membrane, phytoplankton likely use proteins in the mitochondrial carrier family (SLC25A28 and SLC25A37, also referred to as mitoferrins) (17). Phytoplankton also possess homologs in the Ccc1/VIT1 (Ca(II)-sensitive cross-complementer 1/vacuolar iron transporter 1) family that transport intracellular iron in fungi and plants; however, while *VIT1* transcripts are iron-responsive in green alga *Ostreococcus tauri* (86), they do not appear to be so in diatoms (81). Rather, VIT1 in diatoms has been proposed to serve a role in cadmium detoxification (23), although its specific function remains unclear. Lastly, diatoms and the pelagophyte *Pelagomonas calceolata* possess ferroportins that export iron and other divalent metals in multicellular organisms (113, 172); in microalgae, they are hypothesized to export iron from endosomes (61).

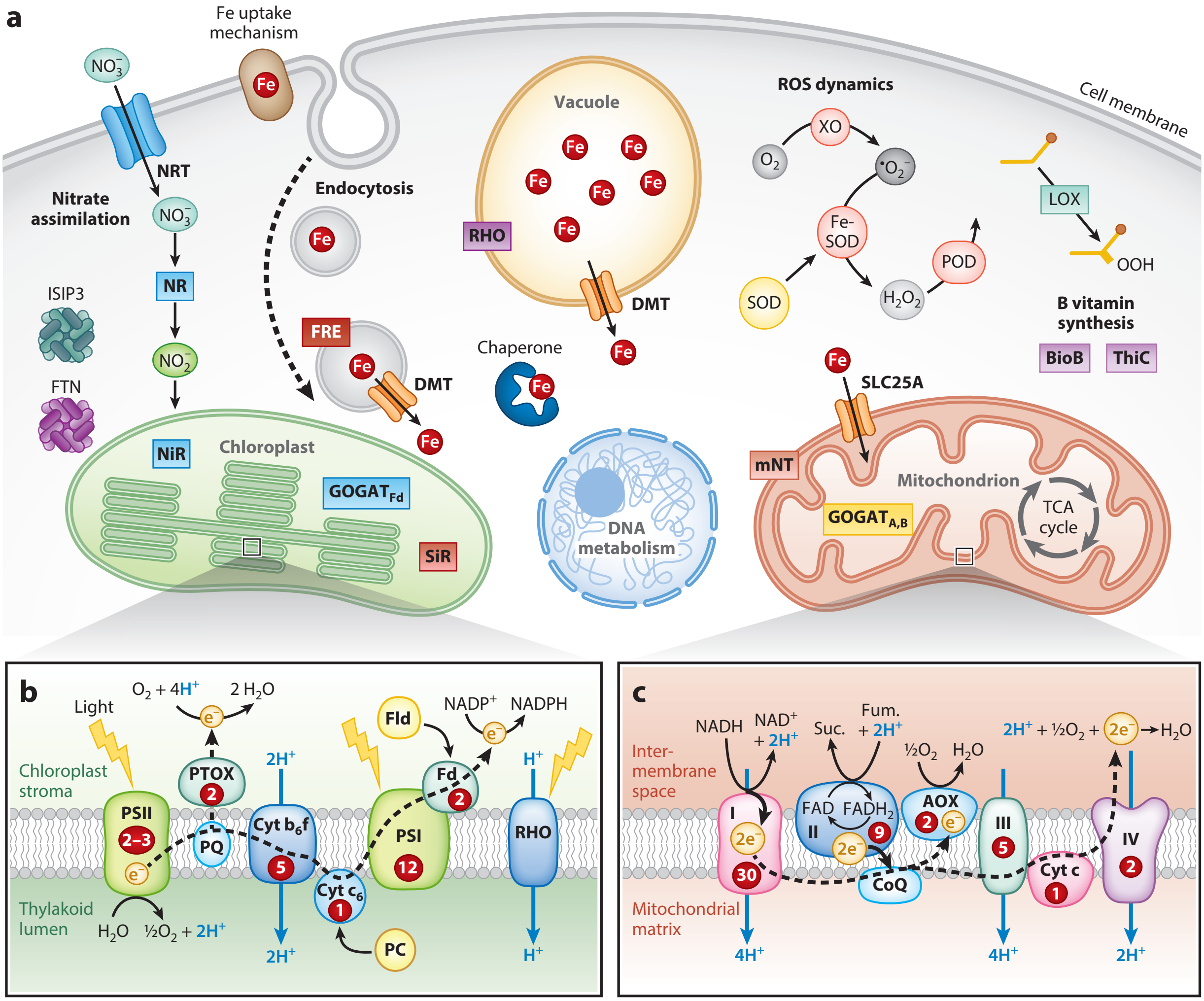

Figure 2

(*a*) Intracellular view of iron transport and storage as well as enzymes associated with iron demand. (*b*) Iron requirements for photosynthetic electron transport. (*c*) Iron requirements for mitochondrial electron transport. Abbreviations: AOX, alternative oxidase; BioB, biotin synthase; cyt, cytochrome; DMT, divalent metal transporter; FAD, flavin adenine dinucleotide; Fd, ferredoxin; Fld, flavodoxin; FRE, ferric reductase; FTN, ferritin; fum., fumarate; GOGAT, glutamate synthase; ISIP3, iron starvation-induced protein 3; LOX, lipoxygenase; mNT, mitoNEET; NiR, nitrite reductase; NR, nitrate reductase; NRT, nitrate transporter; PC, plastocyanin; POD, peroxidase; PQ, plastoquinone pool; PS, photosystem; PTOX, plastid terminal oxidase; RHO, xanthorhodopsin; ROS, reactive oxygen species; SiR, sulfite reductase; SLC25A, solute carrier family 25; SOD, superoxide dismutase; suc., succinate; TCA, tricarboxylic acid; ThiC, phosphomethylpyrimidine synthase; XO, xanthine oxidase. Figure adapted from images created with BioRender.com.

2.2. Organic Iron Uptake

Diverse eukaryotic phytoplankton isolates and natural populations also have the ability to take up iron complexed to organic ligands (70, 92, 99, 141). These include a variety of structurally different compounds such as polysaccharides, proteins, porphyrins (heme), humic acids, and siderophores. Collectively, these ligands increase the solubility of iron and form iron-ligand complexes that normally represent a majority of the dissolved iron pool (55).

Dozens of structurally distinct siderophores have been observed and quantified in seawater; however, the chemical structures of many ligands remain unknown (114). Rather, organic speciation of dissolved iron in seawater is usually characterized in bulk terms by concentrations and conditional stability constants that are assigned to ligand classes: L_1 for strong ligands or L_2 for weaker ligands (55). Stability constants, however, are poor indicators of bioavailability, and the disassociation of iron from organic ligands to Fe′ is strongly influenced by light, further complicating their bioavailability (141) (**Figure 1**). Furthermore, microbial production of iron-binding ligands in seawater is highly heterogeneous (114). As a result, it is unlikely that there is a single uptake strategy that phytoplankton can rely upon in all situations, and selective pressure exists for multiple uptake mechanisms for organically complexed iron in addition to those for inorganic iron uptake.

The mechanisms for uptake of iron complexed with polysaccharides, proteins, and humic acids remain unknown. In the case of heme uptake, SLC49-family transporters have been proposed to serve this role as in metazoans (79). Alternatively, iron may be released at the cell surface by decycling heme oxygenases (1); however, these processes remain to be experimentally validated.

In contrast, uptake of siderophore-bound iron is better characterized and appears to be common among eukaryotic phytoplankton even though no marine eukaryote is known to produce them. As siderophore production is primarily attributed to bacteria for their own uptake mechanisms (101), siderophore uptake by eukaryotic phytoplankton represents another example of phytoplankton–bacterial interactions. The diatom *Phaeodactylum tricornutum* can take up the hydroxamate siderophores ferrioxamine B (FOB) and ferrioxamine E (FOE) (148) while *Thalassiosira oceanica* can only use FOB (98). Many other diatoms have also demonstrated FOB use (153), as well as the dinoflagellate *Amphidinium carterae* (100) and the haptophytes *Gephyrocapsa huxleyi* (formerly *Emiliania huxleyi*) and *Phaeocystis antarctica* (110, 140, 153).

As previously described, early studies hypothesized that eukaryotic phytoplankton relied on a yeast-like reductive iron uptake system for both inorganic and organically complexed iron (see Section 2.1) (142). Under this model, membrane-bound ferric reductase proteins liberate iron from extracellular siderophores and other ligands to increase the Fe′ concentration available for uptake at the cell surface (97) (**Figure 1**). In addition to possessing genes that are similar to those of the yeast-like system (6), many phytoplankton species are known to exhibit extracellular ferric reductase activity that increases alongside uptake rates at low iron concentrations (142). Furthermore, Fe(II)-specific ligands, e.g., ferrozine, inhibit iron uptake, presumably by trapping reduced iron as it is produced at the cell surface. However, as this system primarily operates with micromolar-level iron concentrations (88), it remains unclear whether it is viable for organically complexed iron at the subnanomolar concentrations that are typical of the marine environment. Moreover, some marine phytoplankton lack extracellular ferric reductases, including the prasinophytes *Micromonas pusilla* and *O. tauri*, the alveolate *Chromera velia*, and *G. huxleyi*, which is still capable of FOB uptake (157, 159).

On the other hand, nonreductive siderophore uptake employing siderophore receptors occurs at lower concentrations (87). Rather than employing extracellular reduction, studies with *P. tricornutum* revealed that uptake of hydroxamate siderophores, including FOB and ferrichrome, relies on siderophore binding at the cell surface followed by endocytosis (**Figure 1**). This uptake strategy was shown to involve the proteins ISIP1 (73), FBP1, and FRE2 (33). The precise role of ISIP1 remains unclear, but it appears to predominantly be a diatom-specific protein (73). FBP1 is a siderophore receptor that was acquired via horizontal gene transfer from bacteria, while FRE2 is a ferric reductase of eukaryotic ancestry (33). Orthologs of *FBP1* are found in species known to utilize FOB, including diatoms, haptophytes, dinoflagellates, and prasinophytes.

This uptake system allows phytoplankton to access iron bound to certain hydroxamate siderophores, but not catecholates or iron bound to weaker ligands such as humic substances (33). Moreover, the *FBP1* gene has diversified and duplicated within genomes; some diatom species encode up to five paralogs that potentially bind different substrates. The FRE2 protein is one of five encoded in the *P. tricornutum* genome, yet none of the others provide functional redundancy. FRE2 also does not contribute significantly to extracellular iron reduction, indicating that this function is performed by other ferric reductases that remain to be characterized. Thus, siderophore assimilation by marine eukaryotes is likely achieved through specific receptor-mediated uptake, followed by endocytosis, reduction, and dissociation the Fe-ligand complex within the cell (**Figures 1** and **2**). As pTF-mediated iron uptake also depends on endocytosis, these independent pathways likely converge intracellularly to deliver iron to the chloroplast where cellular iron demand is likely highest (167) (**Figures 1** and **2**).

3. IRON-CONTAINING PROTEINS AND STORAGE MECHANISMS

3.1. Iron as a Cofactor

The unique electrochemical properties of iron make it an ideal enzyme cofactor for electron transfer and catalysis (8). As such, it primarily exists as iron-sulfur (Fe-S) clusters, heme, and di-iron or mononuclear iron in a variety of proteins relating to diverse metabolic processes (**Figure 2**).

Most notably, iron is heavily used in the photosynthetic electron transport chain (**Figure 2*b***). Within microalgae, theoretical estimations and biochemical data in iron-limited diatoms suggest that photosynthesis may account for greater than 50% of cellular iron (131, 152). In linear (noncyclic) electron flow, electrons are transferred from PSII (2–3 Fe) to the cytochrome b_6f complex (Cyt b_6f, 5 Fe) via plastoquinol (PQH_2), to PSI (12 Fe) via cytochrome c_6 (also known as cytochrome b_{553}, 1 Fe), and lastly to a mobile ferredoxin (Fd, 2 Fe), totaling 22–23 iron atoms per linear electron transport chain (11, 133). Phytoplankton also possess the heme-requiring protein cytochrome c_{550} encoded by the *psbV* gene, which acts as an extrinsic subunit of PSII (136).

Similarly, iron is used in the mitochondrial electron transport chain (**Figure 2*c***). There are 47 iron atoms in each: Complex I (NADH:ubiquinone oxidoreductase) has 30 Fe, Complex II (succinate dehydrogenase) has 9 Fe, Complex III (cytochrome bc_1) has 5 Fe, cytochrome c has 1 Fe, and Complex IV (cytochrome c oxidase) has 2 Fe, further contributing to cellular iron demand, although to a lesser extent than photosynthesis (131, 132). The mitochondrial alternative oxidase (AOX) is also localized to the inner mitochondrial membrane and interrupts electron transport to Complex III to mitigate stress (118); it contains 2 Fe atoms (13). Other iron-requiring mitochondrial proteins include the tricarboxylic acid (TCA) cycle protein aconitase that isomerizes citrate to isocitrate (134) and mitoNEET, which, in metazoans, resides in the mitochondrial outer membrane to regulate mitochondrial iron homeostasis (79, 85) (**Figure 2**).

In addition to electron transport chains, nitrogen assimilation requires iron and likely contributes to a large proportion of cellular iron demand (130) (**Figure 2**). In particular, the reduction of nitrate depends on the iron-containing enzymes nitrate reductase and nitrite reductase. Furthermore, nitrite reductase and the plastid-localized glutamate synthase depend on ferredoxin for electron transfer (126, 146). Phytoplankton also possess a mitochondrial NADPH-dependent glutamate synthase, and diatoms possess a NADPH-dependent nitrite reductase in addition to the ferredoxin-dependent gene; however, both of these enzymes also require iron (24, 146, 169). Besides photosynthetic electron transport and nitrogen assimilation, ferredoxins are also employed in diverse other processes, including sulfite reduction via sulfite reductase (126).

Iron is also required for the synthesis of certain organic compounds (**Figure 2**). Among the final steps of heme synthesis are coproporphyrinogen oxidase that possesses an iron-sulfur cluster and ferrochelatase that catalyzes the insertion of iron into protoporphyrin IX yielding heme

(47, 84, 122). Cytochrome P450s are a diverse family of heme-containing enzymes that are found across the tree of life and catalyze a wide range of reactions (54, 165); of particular note are specific carotenoid hydroxylases in the cytochrome P450 family that are involved in the synthesis of certain accessory pigments, such as fucoxanthin and other photoprotective xanthophylls in phytoplankton (40). The synthesis of both vitamin B_1 (thiamine) and vitamin B_7 (biotin) also requires iron via the proteins phosphomethylpyrimidine synthase (ThiC) and biotin synthase (BioB), respectively (32, 35, 39, 109). Lastly, the synthesis of the chromophore retinal for microbial rhodopsins (see Section 4) includes a β-carotene cleavage enzyme (β-carotene 15,15′-dioxygenase) that is likely an iron-containing enzyme (91, 149).

Luxury uptake: the process in which organisms take up more of a nutrient than what is required for maximum growth

Some of the proteins involved in both the production and removal of reactive oxygen species (ROS) require iron as well. Xanthine oxidase is one of several oxidoreductases that produce ROS in peroxisomes (43, 119). Detoxification of ROS is catalyzed by superoxide dismutases (SODs), which produce hydrogen peroxide (49), and one type of SOD among others that phytoplankton possess requires iron (59). Catalases or heme peroxidases, which also require iron, then dispose of the hydrogen peroxide produced SODs (50).

Other iron-requiring proteins include a variety of DNA metabolism enzymes (128) and lipoxygenases (LOXs) that are responsible for the oxidation of polyunsaturated fatty acids (44) (**Figure 2**). Furthermore, there are likely additional iron-requiring metalloenzymes and processes that remain to be uncovered. In diatoms for example, iron is incorporated into their silica cell walls, yet this process is not well understood (45, 71).

3.2. Iron Detoxification and Storage

Free iron is toxic as it produces ROS via the Fenton reaction (62); therefore, organisms require mechanisms to safely mobilize or sequester it within a cell. For intracellular trafficking and short-term storage, phytoplankton may use phytochelatins and metallothioneins as metallochaperones, both of which are low-molecular-weight proteins rich in cysteine enabling high metal-binding capacities (18, 86, 147). In the chlorarachniophyte *Bigelowiella natans*, an iron-responsive CobW domain-containing protein may serve this role (76).

The ability to take up more iron than needed to sustain maximum growth, or luxury uptake, can provide a competitive advantage to phytoplankton. In iron-limiting regions of the ocean where iron inputs are episodic, luxury uptake coupled to long-term storage may support continued growth and allow phytoplankton to subsist, particularly for certain diatoms (81, 168). Two long-term iron storage mechanisms in phytoplankton have been described: vacuoles and the protein ferritin (**Figure 2**).

Highly localized intracellular concentrations of iron in the diatom *Thalassiosira weissflogii* and green alga *D. salina* are indicative of a vacuolar storage mechanism (120, 123). In *D. salina*, these were further identified to be acidic vacuoles and may be analogous to those in other organisms where polyphosphate provides high iron-binding capacities. This hypothesis is further supported by the presence of the acidic vacuole-associated protein H^+-pyrophosphatase in *D. salina* (123), which was also found to be upregulated under iron stress in *O. tauri* (86).

Divalent metal transporters localized to the vacuole may serve to export iron to the cytoplasm. Specially, ZIP-family and NRAMP proteins are hypothesized to serve this role in diatoms (81), and in *T. pseudonana*, one ZIP-family protein showed vacuolar localization (144) (**Figure 2**). In *Ostreococcus*, high expression of *Ccc1/VIT1*, which is homologous to a vacuolar iron transporter in yeast and plants, suggests that this gene may serve this role in green algae (86).

Ferritins are ubiquitous proteins that assemble into nanocages capable of storing relatively high amounts of Fe(III) atoms (104). Diatom ferritins are generally distinct from other eukaryotic ferritins and more similar to cyanobacterial ferritins where a role in long-term storage has been shown (59, 145); however, this role is not ubiquitous. Coupled to their unusually high iron storage capacity, the diatom genus *Pseudo-nitzschia* thus far appears to uniquely express ferritin in response to high iron availability, and some diatoms, such as *T. pseudonana*, lack the gene completely (37, 81). In other diatoms, ferritin likely supports iron recycling over diel cycles, as shown in the green alga *Ostreococcus* (19); however, diel expression of ferritin has not yet been observed in diatoms (147).

The protein ISIP3 is another potentially related storage mechanism as it has a conserved domain belonging to the ferritin superfamily (DUF305) (10). It has been found across a range of phytoplankton lineages (10) and is strongly upregulated under iron stress in diatoms (1, 30), *P. calceolata* (61), and the haptophytes *G. huxleyi* and *P. antarctica* (12, 80), indicating widespread use among phytoplankton taxa. However, as high expression in low-iron conditions is inconsistent with a typical storage function, ISIP3 is hypothesized to have a role in iron reallocation and trafficking under low-iron conditions.

4. CELLULAR ADAPTATIONS TO COPE WITH IRON STRESS

In response to iron stress, phytoplankton simultaneously reduce their cellular iron requirements and improve their nutrient uptake kinetics with strategies such as downregulating iron-containing proteins and upregulating iron transporters (103). Thus, the cellular costs associated with iron-containing proteins and membrane space available for iron uptake form the basis for iron limitation in phytoplankton (111). Upregulation of iron transporters and downregulation of iron-containing proteins such as those involved in photosynthesis and nitrate assimilation can be observed in the transcriptomes and proteomes of phytoplankton in both laboratory (1, 36, 80, 90, 121) and field environments (35, 72, 105, 173). Reducing cellular iron requirements can be a temporary response to low iron availability or permanent adaptation for phytoplankton existing within chronically low iron areas, as demonstrated by chronically iron-limited oceanic phytoplankton having lower iron quotas and higher iron use efficiencies compared with coastal phytoplankton (103, 105).

In conjunction with the high iron requirement of photosynthetic proteins, a prominent manifestation of iron stress is remodeling of the photosynthetic apparatus. As the iron requirements of PSI and Cyt b_6f are higher than that of PSII (**Figure 2*b***), iron-limited oceanic phytoplankton have generally reduced their PSI and Cyt b_6f, resulting in higher PSII:PSI ratios (152), but this ratio may differ among species (151). Furthermore, coastal species may also preferentially downregulate PSI and Cyt b_6f under iron-limited conditions (152). A reduction in PSI relative to PSII may increase a cell's reliance on the plastoquinol oxidase (PTOX) that diverts electrons following PSII (11) (**Figure 2*b***). This pathway may allow ATP production to continue as a proton gradient is created by PSII proton release during water splitting, with lower iron costs than linear electron transport as PTOX only requires 2 iron atoms. Overall, phytoplankton become chlorotic under iron stress—that is, pigment inventories and chlorophyll decrease (11, 51). However, phytoplankton also increase photoprotective xanthophyll pigments and associated light-harvesting complex (LHC) proteins, such as those in the Lhcx and Lhcz families (51, 75, 147). As a consequence of this remodeling, iron-limited phytoplankton have reduced PSII photochemical efficiencies, commonly measured as F_v/F_m (11).

Another strategy to reduce iron requirements is by using functionally equivalent proteins that do not rely on iron as cofactors. In the photosynthetic electron transport chain, plastocyanin (PC) substitutes for cytochrome c_6 as the electron transfer agent between the cytochrome b_6f complex and PSII (**Figure 2*b***) (124) and may be the sole protein serving this functional role (139), constitutively expressed (105), or upregulated in response to iron availability (34). As previously described, ferredoxin is used in the photosynthetic electron transport chain and nitrogen assimilation.

Under iron limitation, ferredoxin can be substituted with flavodoxin, which is less efficient but uses flavin mononucleotide rather than iron as a cofactor (78) (**Figure 2*b***). While the ratio of expression between the ferredoxin and flavodoxin correlates well with iron in many phytoplankton, it does not in diatoms (29). This difference is explained by the possession of two distinct flavodoxins by diatoms and certain dinoflagellates with plastids of diatom origin, or dinotoms (58). Clade II flavodoxins are iron-responsive and substitute for ferredoxin, but Clade I flavodoxins are not iron-responsive and appear to mitigate oxidate stress. As another substitution, phytoplankton may exchange the iron-using SOD for other types of SODs that may be functionally equivalent and use different metal cofactors: Mn, Cu-Zn, and Ni (59) (**Figure 2**).

To circumvent chlorophyll-based photosynthesis altogether, iron-limited phytoplankton may use an alternative light-harvesting protein, xanthorhodopsin (149). As a microbial (type 1) rhodopsin, xanthorhodopsins absorb light via the chromophore retinal and may transport protons in the plastid. This proposed function would create a proton gradient driving chloroplast-localized ATP synthase and increase cellular fitness under low-iron conditions (**Figure 2*b***). Alternatively, xanthorhodopsin was localized to vacuolar membranes in the polar diatom *Pseudo-nitzschia subcurvata*, suggesting that it pumps protons to support vacuolar-type ATPases (4, 156).

With altered photosynthetic activity under iron stress, light-independent Calvin–Benson cycle genes at times are upregulated (1, 11). Perhaps most consistently, phytoplankton upregulate class I fructose 1,6-bisphosphate aldolase (FBA) (32). Phytoplankton possess multiple FBAs that likely serve different functions, and in the case of class I FBA, may be useful in producing glyceraldehyde-3-phosphate from fructose bisphosphate to temporarily fuel glycolysis (32). Respiration is also impacted by iron stress, as shown by decreased respiration rates and downregulation of associated transcripts (1, 41).

5. IRON-RELATED SIGNALING AND REGULATION

Iron deficiency stimulates changes in the abundance of a relatively large number of transcripts and proteins, including some of the aforementioned genes related to uptake, storage, and iron-sparing measures. Additionally, iron stress has been shown to trigger programmed cell death linked to the activity of certain metacaspases (16). Therefore, eukaryotic phytoplankton likely possess a sensing mechanism and associated signaling pathways in relation to their iron status (64). As in photosynthetic organisms at large, this putative sensing mechanism remains unknown, and only a relatively small number of potential regulatory elements have been proposed.

Cis-regulatory elements related to iron have been identified via genomic analyses of the diatoms *P. tricornutum*, *T. oceanica*, and *Fragilariopsis cylindrus*. Among these diatoms, there is a conserved palindromic motif upstream of the iron-responsive genes *ISIP1*, *FLDA*, and a class I FBA (*FBA3*) (95) that is homologous to an iron-responsive *cis*-element in the model freshwater green alga *Chlamydomonas reinhardtii* (42, 174). In conjunction with another motif in *P. tricornutum*, genetic substitution disrupted activity of *FLDA* and *FBP1*, while *ISIP1* was disrupted with solely by one (174). Perhaps not coincidentally, three pairs of iron-responsive genes in *P. tricornutum* have been found to be colocated in the genome: *FRE2* and *FBP1*, *CREG1* and *ISIP2B*, and *TYR1* and *ISIP1* (1). As previously described, *FRE2* and *FBP1* functionally interact to perform hydroxamate siderophore uptake (33). The timing of expression of these genes was also similar under acclimation to low-iron conditions further suggesting that expression of these gene clusters is controlled by shared *cis*-elements (174).

CREG (cellular repressor of E1A-stimulated genes) proteins have further been found to be iron-responsive in diatoms (9, 79, 95) and the chlorarachniophyte *B. natans* (76). The related human CREG1 protein is a secreted glycoprotein that mediates endocytosis of a specific growth factor (63). As diatom CREG proteins have been found to colocalize with pTF, CREG is hypothesized to positively regulate pTF-mediated endocytosis during iron-limited conditions (167).

The increased expression of certain transcription factors (TFs) under low iron suggests that they may regulate other iron-responsive genes. In *P. tricornutum*, 15 TFs of diverse families were found to be induced by low iron (147). Two of the fifteen are sigma factors that likely are localized to the chloroplast and regulate genes in the chloroplast genome. In contrast, *T. pseudonana* and *T. oceanica* had fewer differentially expressed TFs under iron limitation (9, 56).

Post-translational regulation via protein phosphorylation, which may activate or deactivate proteins during iron stress, has also been studied in the diatom *P. tricornutum* (164). Approximately 100 proteins showed phosphorylation associated with low-iron conditions; 12 of these proteins were also found to transcriptionally increase under low iron. Of note, clade II flavodoxins were phosphorylated under low-iron conditions, suggesting phosphorylation-based activation of these proteins. pTF also displayed different phosphorylation patterns depending on time of day and iron status, suggesting that phosphorylation has a regulatory role for pTF activity.

FUTURE ISSUES

1. Laboratory and environmental omic studies continue to highlight the diverse and unique adaptations used by phytoplankton in response to iron availability; however, functional characterization of genes is still in its infancy, with a large number of proteins that are not well studied or are of unknown function, necessitating continued development or use of forward and reverse genetic systems with model phytoplankton species.
2. Eukaryotic phytoplankton certainly access diverse iron species, including iron bound to both known and unknown organic ligands, yet gaps in knowledge remain with respect to the molecular bases for uptake of both inorganic and organically complexed iron, including endocytosis.
3. The identification of endocytosis as a prominent mechanism for iron acquisition demands a reevaluation of localizations of iron transporters and reductase activity. Furthermore, there are likely trade-offs to consider between high-affinity receptor-mediated endocytosis and low-affinity transporters, such as increased susceptibility to viral infection via endocytosis.
4. Not only are future iron supplies uncertain, but the interactive effects of iron with other potential stressors that can influence iron bioavailability and demand, such as ocean acidification and warming, require further examination. Furthermore, existing colimitation scenarios continue to emerge, but the interactive effects of iron limitation with other nutrients are relatively unknown.
5. What are the cellular mechanisms for sensing and signaling iron bioavailability and stress? Furthermore, what regulatory mechanisms, such as TFs and noncoding RNAs, govern cellular responses to altered iron status?
6. Phytoplankton–bacterial interactions in the context of iron availability remain unclear. For example, is there competition for iron, or is the relationship mutualistic or commensal, particularly with respect to bacterially produced siderophores? For symbiotic relationships such as eukaryotic phytoplankton and endosymbiotic diazotrophs that require high amounts of iron for nitrogenase, are there coordinated responses to iron availability?

DISCLOSURE STATEMENT

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

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