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REVIEW

Cyanobacterial blooms, iron, and environmental pollutants

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Abstract Iron determines the abundance and diversity of life and controls primary production in numerous aqueous environments. Over the past decades, the availability of this metal in natural waters has decreased. Iron deficiency can apply a selective pressure on microbial aquatic communities. Each aquatic organism has their individual requirements for iron and pathways for metal acquisition, despite all having access to the common pool of iron. Cyanobacteria, a photosynthesizing bacterium that can accumulate and form so-called 'algal blooms', have evolved strategies to thrive in such iron-deficient aqueous environments where they can outcompete other organisms in iron acquisition in diverse microbial communities. Metabolic pathways for iron acquisition employed by cyanobacteria allow it to compete successfully for this essential nutrient. By competing more effectively for requisite iron, cyanobacteria can displace other species and grow to dominate the microbial population in a bloom. Aquatic resources are damaged by a diverse number of environmental pollutants that can further decrease metal availability and result in a functional deficiency of available iron. Pollutants can also increase iron demand. A pollutant-exposed microbe is compelled to acquire further metal critical to its survival. Even in pollutant-impacted waters, cyanobacteria enjoy a competitive advantage and cyanobacterial dominance can be the result. We propose that cyanobacteria have a distinct competitive advantage over many other aquatic microbes in polluted, iron-poor environments.

Keywords Harmful algal blooms · Iron · Siderophores · Polysaccharides · Toxins · Environmental pollution · Aqueous environments and iron

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Aqueous environments and iron

Iron is an essential micronutrient required by almost every living system (Abbaspour et al. 2014). An adjustable oxidation-reduction potential as well its relative abundance led to the evolutionary selection of this metal for a wide range of fundamental cellular biochemical processes. However, water-soluble ferrous ion (Fe^{2+}) was effectively removed following the introduction of oxygen to the atmosphere by photosynthesis. After precipitating out as oxyhydroxides, the concentrations of ferric ion (Fe^{3+}) in water approximated 10^{-18} M whereas the level of iron required for life approached 10^{-4} to 10^{-6} M (Theil and Goss 2009). Iron concentrations in aqueous environments were subsequently inadequate to meet the

requirements for life and greater quantities of metal had to be procured. Living systems most frequently met this challenge by utilizing accessory pathways to acquire essential iron including 1) a chemical reduction of Fe^{3+} to Fe^{2+} (i.e. ferrireduction) with import and 2) a complexation of Fe^{3+} by chelators coupled with their receptors and uptake of the metal. Iron-catalyzed generation of radicals presented a potential for oxidative stress to living systems (Galaris et al. 2019). As a result of a capacity to catalyze toxic reactive oxygen species, iron homeostasis in cells (import, storage, and export) had to be absolutely controlled. Cells developed strategies to regulate the procurement of adequate iron for function which precluded damage to biological macromolecules. Consequently, life exists at the interface between iron deficiency and iron sufficiency.

Iron controls primary production in numerous aqueous environments (Benner 2011; Hassler et al. 2011; Lis et al. 2015). Subsequently, the availability of iron limits the abundance and diversity of life in aqueous environments (Ryan-Keogh et al. 2023). The Iron Hypothesis proposed that this specific metal is a pivotal factor in the global carbon cycle and a crucial limiting nutrient for marine productivity (Martin et al. 1991). Microorganisms in numerous aquatic environments can be iron-limited (Lis et al. 2015). A significant multidecadal (between 1996 and 2021) trend in iron stress has been delineated with concomitant declines in primary production of aqueous environments (Ryan-Keogh et al. 2023).

Cyanobacteria and iron

Cyanobacteria, a photosynthesizing bacterium, drive nutrient cycling in both marine and freshwater environments (Qiu et al. 2018). The abundance and diversity of iron-dependent proteins, with valuable contributions to photosynthesis, respiration, tricarboxylic acid cycle, DNA biosynthesis, nitrogen fixation, and other pathways, reflect the dependence of microbes on an availability of this metal (Gonzalez et al. 2016). Accordingly, iron is required for cyanobacterial growth. Iron supply controls the replication of cyanobacteria (Wang et al. 2016). The requirement for sufficient concentrations of iron can be difficult to meet (e.g., surface oceanic waters can be picomolar to nanomolar) (Morel et al. 2008). The existence of this iron limitation has also been demonstrated with an addition of iron to waters boosting growth (Boyd et al. 2000). In contrast, iron-starvation and metal chelators can challenge the growth of cyanobacteria (Raghuvanshi et al. 2007; Wang et al. 2023). Cyanobacteria appear to be increasingly starved of iron because metal availability in aqueous environments is low (Cornwall 2023; Fu et al. 2019).

While metal concentrations ordinarily limit growth, cyanobacteria can and have adapted to these low levels (Sutak et al. 2020). To survive and grow in iron-deficient environments, cyanobacteria can reduce cell size with iron deficiency (Hudson and Morel 1993; Sunda and Huntsman 1997). The rates of metal import vary with the surface-to-volume ratio and both iron uptake and the growth of smaller cells is favored under deficient conditions. In response to iron-deficiency, cyanobacteria have also developed efficient metal acquisition systems Comparable to numerous living systems, these microbes utilize reductive iron uptake in acquiring iron (Schroder et al. 2003) (Fig. 1A). There are multiple iron reduction pathways including reduction by superoxide, reduction by cell surface enzymes, direct photochemical reduction, and thermal reduction (Shaked and Lis 2012).

Siderophore production is a particularly efficient iron acquisition system observed in many microbials including cyanobacterial species grown in a wide variety of environments (Arstol and Hohmann-Marriott 2019; Enzingmuller-Bleyl et al. 2022) (Fig. 1B). These high-affinity iron chelators are low molecular weight, secondary metabolites that bind metal (Fe^{3+}) from the environment and deliver it to the cell via specific receptors. The siderophores include hydroxamates, catecholates, and carboxylates which form hexadentate octahedral complexes with Fe^{3+} (Saha et al. 2016) After chelation of the metal, the complex binds a cell receptor and the Fe^{3+} is reduced to Fe^{2+}. The ferrous complex has a lower affinity for the siderophore with dissociation of the metal resulting. Many cyanobacteria produce a siderophore or multiple siderophores (Arstol and Hohmann-Marriott 2019; Rezanka et al. 2018). Xenosiderophores, siderophores used by an organism other than that or those it produces, can also participate in metal uptake by cyanobacteria. Siderophores can impact a microbiota modifying interactions between one microbe and another (Kramer et al. 2020). Using siderophores and xenosiderophores, cyanobacteria and other microbes can

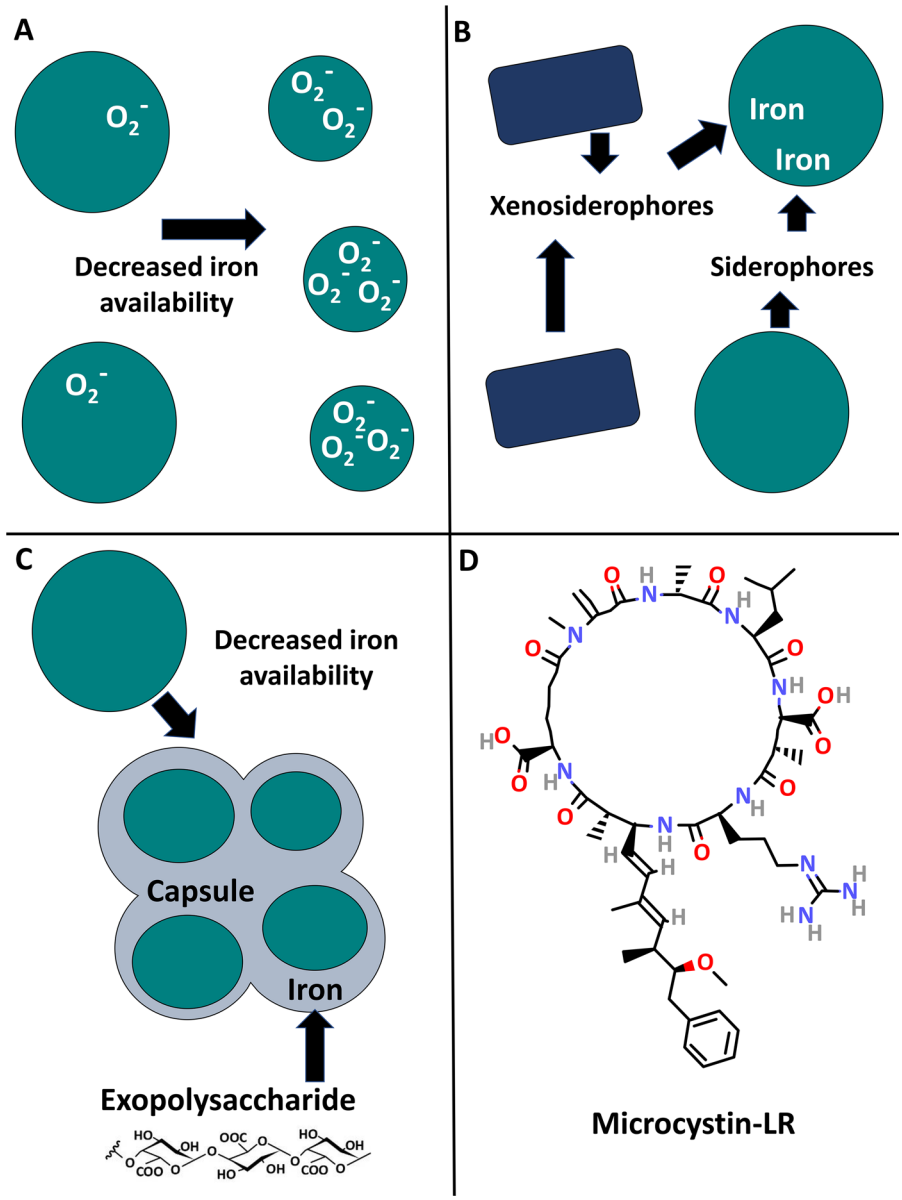

Fig. 1 Iron acquisition systems and cyanobacteria. With iron deficiency, cyanobacteria can demonstrate increased generation of superoxide which can function to reduce Fe^{3+} to Fe^{2+} (**A**). Following such ferrireduction, ferrous ion can be transported across a. Decreased availability of iron also impacts pathways for utilization of siderophores/receptors (e.g., synechobactin and anachelin) and xenosiderophores/receptors (e.g. aerobactin and desferrioxamine) (**B**). Similarly, metal deficiency will impact an increased production of polysaccharide with both release of exopolysaccharides and encapsulation which increase availability of iron (**C**). Finally, there is an augmented production of cyanotoxins with metal stress which facilitates accumulation of iron. The molecular formulas of these toxins contain numerous functional groups with a capacity to complex iron (e.g. carboxylates and amides) (**D**). A round, blue-green circle in the figure designates a cyanobacterium while any other shape designates a microbe other than a cyanobacterium

import iron from a variety of sources. The creation and maintenance of an iron-siderophore diffusion gradient bringing iron back to the host cell is an essential feature of this strategy (Shaked and Lis 2012). Therefore, cyanobacteria residing in densely populated, low turbulence environments (e.g., colony-consortiums) will favor siderophore-based iron acquisition.

The utilization of iron by cyanobacteria can also be dependent on ligands which complex or chelate the metal with a lower affinity. Nearly all of the dissolved iron in marine waters is bound to such natural, organic ligands (Hunter and Boyd 2007; Vraspir and Butler 2009). Complex formation with these ligands maintains iron solubility and increases its availability to impact microbial growth. Highly bioavailable metal associated with organic ligands stimulate growth of iron-limited cyanobacteria (Blanco-Ameijeiras et al. 2020). Prominent among these organic ligands are polysaccharides which are polyfunctional compounds with relatively low affinities for cationic metals (Fig. 1C). Polysaccharides, coupled with their cognate receptors, enhance iron utilization

by numerous microbes (Hassler et al. 2011). Cyanobacteria synthesize polysaccharides and 1) secrete them as exopolysaccharides and 2) incorporate them into a capsule. The competitive ligand exchange of iron from one ligand to another depends on the stability constant and its concentration. A weak ligand can also alter iron speciation and availability if it is present at a concentration great enough to induce the exchange from the strong ligands (Gledhill and Beck, 2012). Polysaccharides occur in much higher concentrations relative to siderophores representing up to 50% of organic matter in some aqueous environments. These low affinity ligands induce a ligand exchange for bound iron at micromolar to nanomolar concentrations, outcompete other compounds (including siderophores at picomolar concentration) for metal, and confer a potential to increase iron availability to microbes. This metal bound to polysaccharides can demonstrate a greater availability relative to that bound to siderophores.

In aqueous environments, some cyanobacteria form colonies of cells held together or defined by capsular polysaccharides. This mucilage (slimy, viscous or gelatinous materials) binds cells together forming visible colonies (Li et al. 2016). In the capsule, these same polysaccharides function as ligands to complex iron (Hassler et al. 2011; Li et al. 2016). Binding of the metal occurs specifically via carbonyl, carboxyl, hydroxyl, and sulfate functional groups (Tease and Walker 1987). Prominent among the capsular polysaccharides are the uronic acids which utilize carboxyl groups in complexation (De Philippis et al. 1998). These substances participate in metal transport and uptake (Hassler et al. 2011; Li et al. 2016). Cyanobacteria with capsular polysaccharides have larger numbers of metal ion-binding sites relative to the non-capsulated (De Philippis et al. 1998). Those cyanobacteria with a colonial morphology contain a greater number of capsular polysaccharides relative to the unicellular forms. Higher metal concentrations are attached to the colonial cyanobacteria capsular polysaccharides under decreasing iron conditions as compared to unicellular cultures (Li et al. 2016). This cell surface pathway, related to large amounts of capsular polysaccharides, for iron acquisition provides an advantage in metal procurement (Li et al. 2016). In this favorable change of morphology, the polysaccharides participate in increasing iron availability to the algae.

Toxin production can be an additional mechanism employed by cyanobacteria to survive in iron-limited conditions (Fig. 1D). Cyanobacterial toxins (cyanotoxins including hepatotoxins, neurotoxins, dermatotoxins and cytotoxins) are compounds with diverse molecular structures. The synthesis of these secondary metabolites is controlled by intracellular concentrations of iron and are synthesized in response to iron starvation (Wang et al. 2016). Accordingly, levels of toxins in an environment are significantly higher under iron-limiting conditions (Yeung et al. 2016). During iron depletion, strains of cyanobacteria which produce toxins demonstrate a higher rate of metal uptake relative to the nontoxic strains (Utkilen and Gjolme 1995; Lyck et al. 1996). In a similar manner, increased iron availability modulates the production of numerous other toxins (e.g., the genotoxin colibactin in pathogenic *Escherichia coli*) (Tronnet et al. 2016). The cyanotoxin microcystin binds iron (with stoichiometry of the interaction reported to be 1:1) as well as other metals (Ceballos-Laita et al. 2017). Structural similarities between microcystin and siderophores support a role as an iron-chelating agent. A participation of the toxin in iron transport may be limited to an intracellular site. The toxin, present in the cell, has the capacity to capture metal from the environment, concentrate it, and deliver the Fe^{3+} to the microbe. Regardless of whether it has a capacity for intracellular and/or extracellular chelation/complexation, toxin produced by cyanobacteria serves to transport iron (Klein et al 2013). Accordingly, toxin production can afford algae a selective advantage over other microbes. The cyanobacteria with the ability to express toxin can overcome iron deficiency without serious influence on its growth while microbes without such a pathway are affected with reduced growth (Alexova et al. 2011).

Cyanobacterial blooms and iron

Under specific environmental conditions, cyanobacteria proliferate to form so-called ‘algal blooms’ consisting of significant biomass and covering large areas in marine and fresh waters (Li et al. 2016). Intensive algal blooms in surface waters are a problem in many countries and are global threats to economies (Li et al. 2016; Majsterek et al. 2004). Nutrient over-enrichment (i.e., eutrophication) of aqueous ecosystems is

associated with rapid growth of cyanobacteria (Paerl et al. 2001). Phosphorus and nitrogen are proposed as the key nutrients with their overabundance initiating cyanobacteria biomass.

We propose that an alternative interpretation of an algal bloom is that iron deficiency selects cyanobacteria to grow. Algal blooms occur in iron deficient aqueous environments and the concentrations of metal decrease during such episodes (Kuwabara et al. 2009). Pathways for iron acquisition employed by cyanobacteria can be cooperative contributing to the formation of stable microbe communities. In this development, the struggle for iron leads to dependencies and symbiosis. However, the pathways can also lend themselves to competition (Kramer et al. 2020; Murugappan et al. 2012). While microbes may all have access to a pool of metal, disparities in their capacity for metal acquisition can provide cyanobacteria a competitive advantage in environments in which iron is a limited resource. Competition between the microbes plays a role in stimulating pathways for iron acquisition (e.g., secondary metabolite biosynthesis such as siderophores and toxins) (Lee et al. 2020). The iron-deficient environment applies a selective pressure to microbial communities. Cyanobacteria excel in the capacity to survive and grow in the iron-depleted environment. By competing more effectively for requisite iron, cyanobacteria displace other species and dominate the microbial population in the algal bloom (Fig. 2).

The biochemical changes in a cyanobacteria bloom can reflect elevated levels of superoxide (O_2^-) (Canini et al. 2001). The increased O_2^- functions as a ferri-reductant frequently required in the transport of iron including its import (Wang et al. 2006). In the bloom, unicellular and colonial forms of cyanobacteria show decreased cell size although the cell size of the colonial form decreased much less than that of the unicellular culture. The generation and maintenance of an iron-siderophore diffusion gradient brings iron back to the cell (Shaked and Lis 2012). This siderophore production is most effective for iron acquisition in densely populated, low turbulence environment such as a cyanobacteria bloom. Cyanobacteria equipped with these strategies would be able to acquire and import iron from a variety of sources, endowing the microbe with an obvious competitive advantage in iron acquisition.

While they can grow in a unicellular morphology, cyanobacterial blooms are characterized by colonial morphology with growth in large collections of cells and aggregations of single cells (Cao et al. 2005; Li et al. 2016). Polysaccharides in the algal blooms bind cells together forming huge (visible) colonies. The

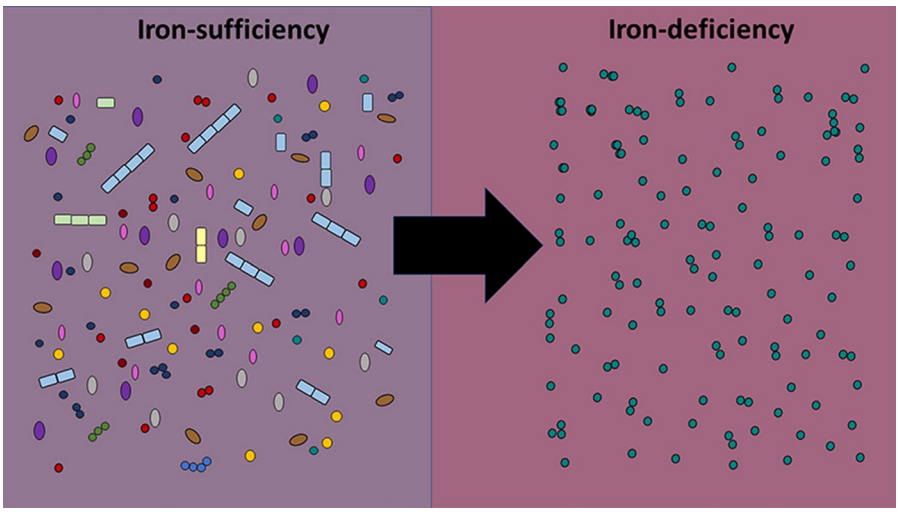

Fig. 2 Microbial population in an aqueous environment before and after iron deficiency associated with an exposure to an environmental pollutant. The pollutant complexes iron decreasing concentrations of the metal available to microbes. After exposure to an environmental pollutant, cyanobacteria are selected by the low metal concentrations to proliferate. Diminished biodiversity and a dominance of the algae result. Round, blue-green circles in the figure designate cyanobacteria while all other shapes and colored circles designate microbes other than cyanobacteria

polysaccharides in the capsule function as an iron reservoir for the cyanobacteria. Colonial cyanobacteria, with polysaccharides included in the capsule, also secrete greater concentrations of polysaccharides into the aqueous environment relative to the unicellular form (Li et al. 2009; Zhang et al. 2011). During bloom events dominated by cyanobacteria, polysaccharides can be secreted in high concentrations. These soluble exopolysaccharides bind to iron and increase the concentration of the metal available to the algae in the aqueous environment (Chen et al. 2004; Tapia et al. 2011). The colonial form, with an abundance of polysaccharides, accordingly, has an advantage in an iron-deficient environment over the unicellular form due to the large amounts of capsular polysaccharides.

Finally, cyanobacteria blooms can be characterized by increased concentrations of cyanotoxins. During blooms, cyanotoxins provide a survival advantage to the cyanobacteria over other microbes or deter predation by higher trophic levels (Berry et al. 2008; Jang et al. 2007; Vepritskii et al. 1991). Cyanotoxins inhibit the growth of other microbes leading to changes in community structure and composition. Similar to an elevated reductive capacity, decreased cell size, siderophore production, encapsulation, and exopolysaccharides, toxins provide an increased capacity for metal uptake allowing cyanobacteria to duplicate and overwhelm other microbes in an aqueous environment.

Environmental pollutants, iron, and algal blooms

An association between exposure to pollutants and algal blooms has been observed (Dansie et al. 2022). Pollutants in aqueous environments frequently include plastics (e.g., beverage bottles, straws, cups, plates), paper products (e.g., bags, cigarette butts), chemicals (e.g., PFAS), petroleum products, metals, ash, fertilizers, sewage, and insecticides (e.g., DDT). Further, a disruption of iron homeostasis has been associated with exposures to environmental pollutants (Fiorito et al. 2013; Manis and Kim 1979; Sachan et al. 2023; Santamaria et al. 2011; Wahba et al. 1988). Many of these pollutants have a chemical structure which includes electronegative functional groups with oxygen, nitrogen, or sulfur atoms capable of sharing electrons and are recognized to exhibit a direct capacity for iron complexation (e.g., phenols) (Chobot and Hadacek 2010; Perron and Brumaghim 2009). In aqueous environments, these pollutants demonstrate a capacity to complex and chelate iron (Guo et al. 2015; Schreinemachers and Ghio 2016). Alternatively, pollutants can be catabolized to iron-binding compounds (e.g., naphthoquinones and dioxins which are metabolized to phenolic compounds as well as benzene which is metabolized to catechol) (Ahmad and Rao 1999; Gillis et al. 2007; Sakaki et al. 2013; Honey et al. 2000; Kolachana et al. 1993; Melikian et al. 1999). This capacity to disrupt normal homeostasis of iron can reflect an original purpose of the compound or substance (e.g., some portion of the effectiveness of a pesticide can be explained by its capacity to complex iron and diminish its availability thus killing the pest).

Various metals can be complexed or chelated by the same compounds and substances. Other metals have demonstrated a capacity to interact with iron incorporated in proteins including its displacement. These other metals (e.g., vanadium, zinc, copper, aluminum, gallium, cadmium, and arsenic) disrupt iron homeostasis (Ghio et al. 2020). A functional iron deficiency is impacted with the cell response including an increased iron import (Ghio et al. 2015). Therefore, exposure to these metals can also impact iron deficiency predisposing to algal bloom formation.

Anthropogenic activities subsequently will impact iron availability in aquatic systems and perturbation of iron homeostasis is one mechanistic pathway favoring cyanobacteria following water pollution (Fu et al. 2019 Environmental pollutants, or their catabolic products, demonstrate a capability to complex iron through electronegative functional groups containing oxygen, nitrogen, or sulfur. Cell exposure to the chemical or its metabolite can impact a loss of requisite functional iron from intracellular sites and is subsequently associated with a functional deficiency of iron. The exposed cell is compelled to acquire further metal critical to its survival.Relative to other microbes, the cyanobacteria are anticipated to have an advantage in establishing a new equilibrium following such exposure. This is the result of numerous pathways to alter metal homeostasis including the expression of both high- and low-affinity iron chelating agents (e.g., siderophores and polysaccharides) as well as assumption of a colonial morphology and expression of toxins. In support of this, colonial

morphology is associated with greater resistance to pollutants compared to unicellular cyanobacteria (Juneau et al. 2001; Li et al. 2016).

Treatment of blooms and iron

Cyanobacteria blooms follow decreased iron availability in natural waters and anthropogenic activities (Gonzalez et al. 2018). Cyanobacteria have developed pathways of metal acquisition which allow them to successfully overcome the deprivation and compete favorably against other microbes for the iron. A cyanobacterial bloom can be the result of this successful competition with other microbes. Consequent to this dependence on iron deficiency, is it possible that the provision of additional concentrations could reduce cyanobacterial abundance during a bloom? Iron exerted significant dose-dependent negative effects on the biomass of phytoplankton (Orihel et al. 2016). The provision of iron to an aqueous environment also reduced the dominance of cyanobacteria (Orihel et al. 2016). Finally, Orihel et al. (2016) reported that iron reduced the toxicity of cyanobacterial blooms, as measured by concentrations of microcystins, at doses of 2–225 g iron/m^2 sediment. In the remediation of a cyanobacteria-dominated bloom, the provision of additional iron to an aqueous environment can be considered.

Conclusions

Iron deficiency applies a selective pressure on microbial communities. Cyanobacteria outcompete other microbes to survive and grow in iron depleted aqueous environments resulting in algal blooms. Exposure to environmental pollutants is followed by a functional deficiency of iron which predisposes to cyanobacterial blooms.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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