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How manganese empowered life with dioxygen (and vice versa)

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ABSTRACT

Throughout the history of life on Earth, abiotic components of the environment have shaped the evolution of life, and in turn life has shaped the environment. The element manganese embodies a special aspect of this collaboration; its history is closely entwined with those of photosynthesis and O_2—two reigning features that characterize the biosphere today. Manganese chemistry was central to the environmental context and evolutionary innovations that enabled the origin of oxygenic photosynthesis and the ensuing rise of O_2. It was also manganese chemistry that provided an early, fortuitous antioxidant system that was instrumental in how life came to cope with oxidative stress and ultimately thrive in an aerobic world. Subsequently, the presence of O_2 transformed the biogeochemical dynamics of the manganese cycle, enabling a rich suite of environmental and biological processes involving high-valent manganese and manganese redox cycling. Here, we describe insights from chemistry, biology, and geology, to examine manganese dynamics in the environment, and its unique role in the history of life.

1. Introduction

The rise of dioxygen, O_2, ~2.35 billion years ago (Ga) registers as the single biggest influence of life on the environment [1]. This defining moment in Earth history, widely attributed to the invention of oxygenic photosynthesis in the ancestors of modern Cyanobacteria, transformed the environmental redox landscape dramatically and irreversibly, impacted all global biogeochemical cycles, and was fundamental to the course of evolution to life as we know it today [2]. Harnessing the ability to pull electrons from water released early autotrophs from the limitations of available geochemical electron donors, e.g., Fe(II), H_2, and H_2S, allowing for a huge increase in primary production [3]. The buildup of significant amounts of O_2 in the atmosphere led to the evolution of aerobic biochemistries, and opened the door to new degrees of oxidative stress [4–6].

The element manganese is central to the production of O_2 because it plays a critical role at the active site of photosystem II (PSII) [7], which is comprised of a Mn_4CaO_5 cluster, sometimes referred to as the water-oxidizing complex (WOC) [8,9]. The WOC is one of the key features that set PSII apart from all other anoxygenic phototrophic reaction centers and is the catalyst that enables PSII to use water as an electron donor for oxygenic photosynthesis. The manganese atoms in the WOC cycle through multiple oxidation states, allowing it to couple the one-electron process of photochemical charge separation with the four-electron process of splitting water to make O_2. Emerging geological, biochemical, and comparative biological data support the hypothesis that, prior to the origin of oxygenic photosynthesis, Mn^{2+}, rather than water, served as an electron donor to the ancestor of PSII in a manganese-based version of anoxygenic phototrophy, which led to the evolution of the WOC [10–13]; this evidence is summarized further below.

Manganese also plays an important role in cellular protections against oxidative stress. Manganese ions are found as cofactors in some of the key enzymes involved in the detoxification of the reactive oxygen species (ROS) superoxide and hydrogen peroxide, i.e., manganese superoxide dismutase (MnSOD) and manganese catalase. Low molecular weight coordination complexes of manganese ions can also react catalytically with superoxide and hydrogen peroxide, and such species represent an important non-enzymatic antioxidant system in many organisms [14–18]. Furthermore, manganese can replace iron in metalloenzymes, retaining catalytic activity, while conferring resistance to oxidative damage [19]. Taken together, these antioxidant properties along with the importance of manganese in the evolution of photosynthesis reveal that manganese played a central role in both the production of O_2 and the strategies by which the first life to encounter O_2 survived the severe oxidative stress induced by its presence [4].

In Earth surface environments today, O_2 enables a diverse suite of processes that involve manganese redox chemistry. The standard reduction potentials of manganese redox couples are higher than those of most other common environmental species, which means that the oxidized forms of manganese are among the strongest oxidants found in the environment [20]. O_2 and species derived from it, such as peroxides and hydroxyl radicals, are the only oxidants able to oxidize Mn^{2+} under environmentally relevant conditions. Accordingly, the biogeochemistry of manganese is uniquely sensitive to the presence or absence of these

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species. The introduction of O_2 provided a way to unlock the rich redox chemistry of manganese, allowing it to participate in numerous important biochemical and ecological processes as a powerful oxidant.

Biology and geology provide two different yet complementary perspectives on the ever-present cross talk between the evolution of life and its environment. Examining extant organisms can provide detailed mechanistic insight into biological processes as well as a way to develop hypotheses about the evolutionary relationships between different taxa and what traits can be considered ancestral [21–23]. However, inferences gleaned from comparative biology can only place evolutionary processes in the framework of relative time, and using extant life to understand the ancient biosphere is hampered by the omnipresent effects of extinction—even for microbes [24]. On the other hand, observations of physical and chemical fingerprints preserved in sedimentary rocks can provide a direct, albeit coarse, record of the life and environments that at one time existed. In this work, we incorporated both of these approaches to examine the intimately connected histories of manganese and O_2 and their interactions with the evolving biosphere.

2. Manganese speciation and reactivity in the modern environment

The biogeochemical dynamics of manganese are defined by its unique redox chemistry. Elemental Mn is a first-row transition metal with the outer-shell electronic configuration $3d^5 4s^2$. There are seven valence electrons, two electrons completely filling the 4s orbital and one each in the five 3d orbitals, half filling the 3d level. This electron configuration makes it possible for manganese to have formal oxidation states ranging from −3 to +7, providing the largest number of accessible oxidation states of any 3d transition metal [25]. In biological and environmental systems, however, the main oxidation states are limited to Mn(II), Mn(III), and Mn(IV) [26]. Other oxidation states may exist transiently as reactive intermediates, e.g., Mn(V) just prior to O—O bond formation during photosynthetic water-splitting [27], but they never accumulate in natural systems. The fate of manganese in the environment, from its sources in weathering rocks to its sinks in sedimentation and subduction, is characterized by redox transformations.

Mn(II) is abundant in the Earth's crust (0.1 wt% MnO [28]) as a common minor constituent substituting for Fe(II) in igneous minerals [29]. In sedimentary and supergene (ore produced from oxidative weathering of Mn(II)-bearing rocks) deposits, manganese can be found in much higher concentrations, largely as Mn(II) in carbonate salts and Mn(III)/Mn(IV) in oxides [30]. These geological sources are mobilized by various processes of erosion or weathering (hydrolysis and dissolution) and transported as windborne dust particles and suspended or dissolved species in rivers [26]. In natural waters, soils, and sediments, both abiotic and biologically-mediated processes can contribute to manganese redox cycling. Table 1 contains an overview of manganese species found in the environment, and Fig. 1 summarizes the major sources, sinks and conversions in the modern manganese cycle.

The geochemistry of manganese is often compared and contrasted with that of iron [31]. Both are redox active in Earth surface environments today. Both of their reduced cations, i.e., Mn^{2+} and Fe^{2+}, are divalent and soluble in water; and both form insoluble oxide and oxyhydroxide minerals under redox conditions that favor their oxidation. Unlike manganese, Fe(II) and Fe(III) are the only biologically and environmentally stable oxidation states of iron, whereas Fe(IV) may exist transiently but does not accumulate in the environment. The dramatic difference in the relative stabilities of the trivalent and tetravalent oxidation states of manganese and iron, respectively, is a consequence of the differences in their outer-shell d-electron configurations and the extra degree of stabilization that is predicted by quantum mechanics and observed experimentally for electronic configurations in which each of the five 3d orbitals contains one electron, i.e., $3d^5$. While elemental manganese has the outer-shell electron configuration $3d^5 4s^2$, elemental iron has an additional d-electron, i.e., $3d^6 4s^2$. Thus the divalent ions have the outer-shell configurations $3d^5$ for Mn(II) and $3d^6$ for Fe(II). The result is that it is relatively easy to oxidize Fe(II), $3d^6$, to Fe(III), $3d^5$, but relatively difficult to oxidize Mn(II), $3d^5$, to Mn(III), $3d^4$. Indeed, unless Mn(III) is stabilized by its ligand environment in a coordination complex or in an ionic solid, it takes less energy to remove two electrons from a single Mn(II) species to form a Mn(IV) species than to remove two electrons from two Mn(II) species to form two Mn(III) species (Fig. 2A). Consequently, Mn(III) species generated in an environment lacking sufficient ligand stabilization will react rapidly with themselves in a bimolecular reaction by disproportionation, i.e., 2Mn(III) → Mn(II) + Mn(IV) [32,33]. Due to this relative instability of Mn(III), for many years the classical paradigm for manganese speciation in the environment was a dichotomy of soluble Mn(II) species and insoluble Mn(III)- and Mn(IV)-containing oxide minerals.

Breaking with this classical view, we now know that Mn(III) species can persist in solution when coordinated by suitable stabilizing ligands. Mn^{3+} and Fe^{3+} show similar ligand preferences due to their high positive charge and small ionic radii. Anions are preferred over neutral ligands (e.g., HO^- versus H_2O), and chelating anionic ligands with oxygen donor atoms are particularly favored. In the case of Mn^{3+}, the large degree of stabilization provided by chelating ligands can stabilize that relatively unstable oxidation state with respect to its disproportionation reaction, allowing Mn(III) species to persist in solution and participate in other reactions. Ligand stabilization can also significantly change the standard reduction potential of manganese redox couples, thereby changing the energetics of electron transfer reactions (Fig. 2B).

The exact identities of the ligands that stabilize Mn(III) in natural systems are often unknown. Nevertheless, the properties of these species can be predicted, to an extent, based on studies of known Mn(III) complexes that have been chemically characterized in aqueous

Table 1
Major manganese species and minerals found in the environment.

	Mn(II)	Mn(III)	Mn(IV)
Aqueous species	$[Mn^{II}(H_2O)_6]^{2+}$ $[Mn^{II}(OH^-)]^+$ Mn(II)-L[a]	Mn(III)-L[a] Mn(III) oxide nanoparticles	Mn(IV) oxide nanoparticles
Mineral species	Mn^{2+} as a trace constituent in igneous minerals kutnohorite/manganoan calcite $(Mn^{2+},Ca^{2+})(CO_3^{2-})$ rhodochrosite $Mn^{2+}(CO_3^{2-})$ rhodonite $Mn^{2+}(SiO_3^{2-})$	bixbyite $(Mn^{3+},Fe^{3+})_2(O^{2-})_3$ braunite $Mn^{2+}Mn_6^{3+}(SiO_4^{4-})(O^{2-})_8$ hausmanite $Mn^{2+}Mn_2^{3+}(O^{2-})_4$	Mn(IV) oxide $Mn^{4+}(O^{2-})_2$ Common polymorphs include pyrolusite, todorokite, hollandite, cryptomelane and birnessite[b]

[a] Known ligands that form aqueous manganese complexes include pyrophosphate, (bi)carbonate, citrate, tartrate, and humic acids. In general, the diversity and distribution of Mn-L species in the environment remains poorly constrained.
[b] Can include some Mn(III).

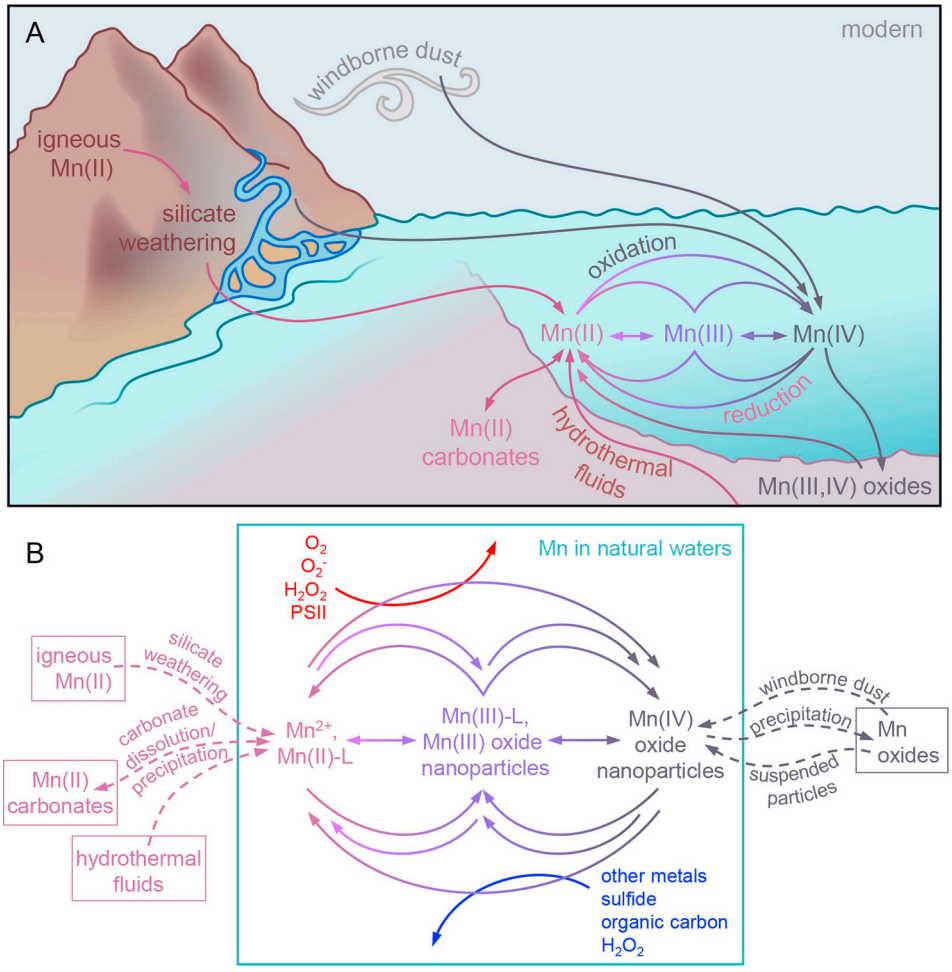

Fig. 1. Manganese cycling in modern environments. Geological sources of manganese include manganese as a minor constituent of igneous rocks, and sedimentary deposits of Mn(II) in carbonates and Mn(III)/(IV) in oxides. These geological sources are liberated by processes of weathering and erosion, including by rivers and wind. In natural waters, manganese cycles between the Mn(II), Mn(III), and Mn(IV) oxidation states—biology plays a range of important roles in this cycling.

solution. Some particularly instructive examples of such Mn(III) complexes were described by Klewicki and Morgan for the Mn(III) complexes of pyrophosphate, EDTA, and citrate [34]. When these Mn(III) complexes decompose, it is not solely due to Mn(III) disproportionation, but also due to instabilities of the metal-bound ligands. In the case of pyrophosphate, complexation to Mn(III) is expected to enhance the reactivity of the bound pyrophosphate ligand with water resulting in the disappearance of the pyrophosphate by hydrolysis to give two phosphate ions [34,35]. In the case of EDTA and citrate, the Mn(III) complexes decompose due to internal (i.e., intramolecular) electron transfer from the ligands to Mn(III), thus producing Mn(II) and products that result from ligand oxidation. Another instructive example is the Mn(III) complex of desferrioxamine B (DFOB), studied by Duckworth and Sposito [36]. At pH < 7, Mn(III)DFOB^{+} decomposes slowly by internal electron transfer to give Mn(II) and the oxidized ligand, similar to the Mn(III) complexes of EDTA and citrate. The reactivity of Mn(III) complexes is an important branch of manganese biogeochemistry, participating in major ecosystem processes including the oxidative breakdown of recalcitrant organic matter like lignocellulose—the most abundant organic compound on Earth [37].

The occurrence of significant amounts of high-valent manganese has been documented in the soluble fractions in many environmental systems and attributed to the presence of soluble, ligand-bound Mn(III) complexes [38–41]. However, it is important to note here that environmental studies typically define “dissolved species” operationally based on filtration (e.g., anything that passes through a 0.2 µm or 0.45 µm filter). Colloidal or nanoparticulate matter can include insoluble manganese oxide minerals and will typically be present in the environmental fractions classified as operationally soluble. The abundance of colloidal or nanoparticulate manganese in the environment is largely unknown, however the few studies that have measured it revealed that it can be substantial. For instance, one study found that in parts of the San Francisco Bay, up to 20% of operationally dissolved manganese fell within a colloidal fraction (defined as any particles $>$ 10 kDa and $<$ 0.2 µm) [42]. Another study on the Loire River Watershed found 80% of operationally dissolved manganese to be colloidal (defined as particles $>$ 0.01 µm and $<$ 0.45 µm) [43]. A better understanding of the distribution, diversity, and reactivity of both Mn(III)-ligand complexes and oxide mineral nanoparticles is required to improve our understanding of manganese redox dynamics in natural waters, soils, and sediments.

In minerals, the coordination of the higher oxidation states Mn^{3+}, Mn^{4+}, and Fe^{3+} is dominated by oxide ligands. Water molecules become extremely acidic when coordinated to these highly charged cations and dissociation of protons to give HO^{-} and/or O^{2-} can be suppressed only at very low pH. These hydroxo and oxo ligands are excellent bridging ligands and polymerization via M-O(H)-M or M-O-M bridging leads to the precipitation of insoluble metal oxides, which can take on a wide array of crystalline forms [44]. The relative stabilities of the higher oxidation states of the metal ions in either manganese- or iron-containing minerals are hugely variable, depending on crystal form, degree of crystallinity, and particle size, in addition to pH and

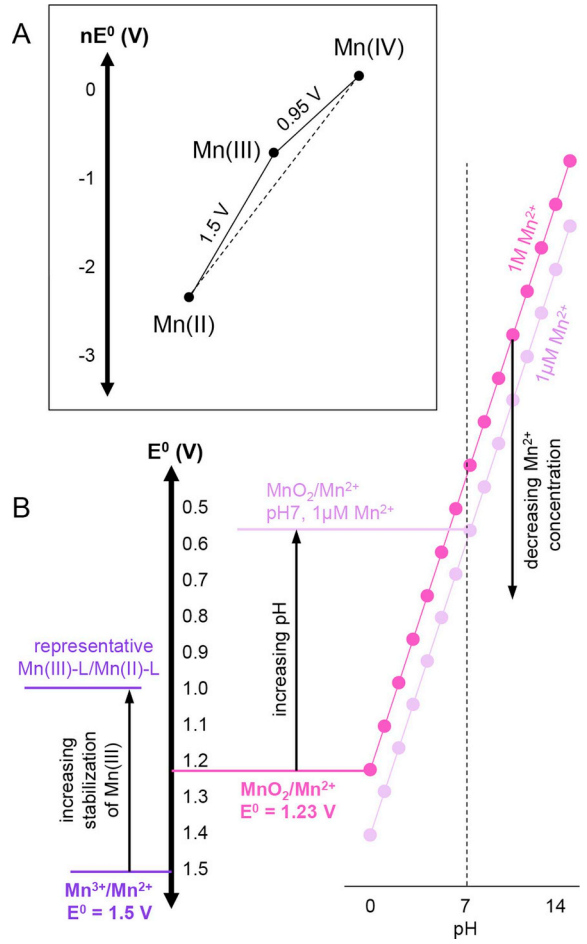

Fig. 2. Breadth of manganese redox chemistry. ***A.*** Frost diagram of manganese in acidic solution [129]. The slope of the line connecting two points represents the reduction potential for that redox couple. A state that is offset from the line connecting the states above and below it, i.e., Mn(III), is unstable with respect to disproportionation. ***B.*** Redox tower showing reduction potentials for different manganese species. The standard electrode potentials (E^0) vs. SHE for the Mn(III)/Mn(II) and Mn(IV)/Mn(II) couples are very high [130–132]. However, pH, concentration, and coordination environment can affect the reduction potentials considerably, and therefore these are critical factors in determining the energetics of manganese redox transformations in the environment. For instance, the MnO_2/Mn^{2+} redox couple decreases by 0.82 V when adjusted to pH 7 and increases by 0.18 V when adjusted to 1 μM Mn^{2+}. E^0 was converted to redox potentials under environmentally relevant conditions using the Nernst equation.

$$Eh = E^0 + \frac{RT}{nf}\ln Q = E^0 + \frac{0.059}{n}\log_{10} Q$$

For a reaction $xA_{ox} + yH^+ \rightleftharpoons zA_{red} + H_2O$; $Q = \frac{[A_{ox}]^x[H^+]^y}{[A_{red}]^z}$

total metal concentration [45].

Oxidations of either Fe^{2+} or Mn^{2+} by O_2 to give oxides of Fe^{3+} or Mn^{4+} are thermodynamically favorable for either metal [26], but the reactions of Fe^{2+} with O_2 tend to be fast in most cases whereas the reactions of Mn^{2+} with O_2 can be prohibitively slow in the absence of a suitable catalyst (typically more than four orders of magnitude slower than Fe for homogeneous oxidation by O_2) [46]. The kinetic barrier for the oxidation of aqueous Mn^{2+} with O_2 arises from the instability of the Mn(III) oxidation state in a homogeneous environment where water molecules are the only ligands. However, this kinetic barrier can be overcome with the presence of Mn(III) stabilizing ligands such as hydroxide, pyrophosphate, or citrate, or with the presence of a variety of metal oxide surfaces like iron, manganese, or aluminum oxides [47–49]. The binding of the Mn^{2+} ion to the metal oxide surface also allows stabilization of the Mn(III) oxidation state, similar to the coordination of chelating ligands. The ability of manganese oxides to catalyze the oxidation of Mn^{2+} to manganese oxides means that, upon generating sufficient product, the reaction becomes autocatalytic.

In natural waters at circumneutral pH, the abiotic oxidation of Mn^{2+} with O_2 has been considered of relatively minor importance, due to the kinetic limitations of the homogeneous reaction. However, the presence of colloidal or nanoparticulate metal oxides in the water column may significantly promote heterogeneous oxidation. Furthermore, nanoparticles have also been shown to exhibit different surface atomic structures than their larger-scale bulk counterparts—this leads to exotic chemistries with important implications, including the ability to catalyze Mn^{2+} oxidation at much faster rates [50]. Thus, in certain settings, abiotic oxidations of Mn^{2+} with O_2 may hold a more significant role in environmental manganese cycling than previously appreciated.

The reaction of Mn^{2+} with superoxide, O_2^-, has been given considerable attention, and once again the outcome is dependent upon the presence or absence of stabilizing ligands [16,20,51]. Superoxide reacts with Mn^{2+} to form a transient MnO_2^+ intermediate, which can dissociate to give Mn^{3+} and H_2O_2. This reaction is readily reversible, and the transient MnO_2^+ intermediate can also be observed in the reaction of Mn^{3+} with H_2O_2, which results in manganese reduction back to Mn^{2+} [16]. This equilibrium (Reaction 1) can be pulled to the right toward accumulation of the Mn(III) product by removal of the H_2O_2 product, thus preventing its back-reaction with Mn^{3+}. For example, the enzyme catalase, which catalyzes the degradation of H_2O_2, has been implicated in Mn^{2+} oxidation by superoxide, a phenomenon discussed further below [52,53]. The presence of chelating anionic ligands that significantly stabilize Mn(III), for example, pyrophosphate or citrate, can also limit the extent of the back-reaction with H_2O_2, resulting in the accumulation of Mn(III)-ligand complexes. However, in the presence of monodentate anionic ligands like carbonate or phosphate, the MnO_2^+ intermediate is sufficiently stabilized to enable a new bimolecular reaction that ultimately results in the catalysis of the disproportionation of two O_2^- to give H_2O_2 and O_2, regenerating Mn^{2+} in the process (Reaction 2) [16,51]. This catalytic removal of O_2^-, with no net Mn^{2+} oxidation, has been proposed to be the basis for the antioxidant activity of the Mn(II)-small molecule complexes [4].

$$Mn^{2+} + O_2^- + 2H^+ \rightleftarrows MnO_2^+ + 2H^+ \rightleftarrows Mn^{3+} + H_2O_2 \quad (1)$$

$$MnO_2^+ + MnO_2^+ + 2H^+ \rightarrow 2Mn^{2+} + H_2O_2 + O_2 \quad (2)$$

Hydrogen peroxide, H_2O_2, can serve as both an oxidant for Mn(II), and a reductant for Mn(III) or Mn(IV). The rates of these reactions are also ligand dependent. Similar to the phenomenon discussed above for O_2^-, the disproportionation of H_2O_2 can also be effectively catalyzed by Mn^{2+} [54]. For this reason, the enzymes MnSOD and manganese catalase are unusual relative to other metalloenzymes in that the metal ion alone, in this case Mn^{2+}, in the absence of any protein, is an effective catalyst of the same reactions catalyzed by the metalloenzymes [16,55].

3. Manganese and modern biology

In modern environments, manganese redox chemistry interfaces with biology in a myriad of ways. Manganese is an essential trace element with numerous biochemical roles within cells [26], and geochemical redox cycling affects the bioavailability of manganese, thereby controlling the biological processes dependent upon it—including photosynthesis [56]. Conversely, manganese redox transformations in the environment, both oxidation and reduction, are often microbially-mediated [20]. These microbial manganese transformations can be either direct enzymatic reactions or indirect reactions occurring via the biological production of a chemical species that reacts with manganese, and/or impact on local solution chemistry in a way that accelerates abiotic oxidation (like autotrophs taking up CO_2 and

thereby raising pH). Biological catalysis can greatly increase the fluxes and decrease the timescales that are relevant for these reactions, adding to their ecological significance [56]. In the case of manganese oxidation, the kinetic limitations of the abiotic reaction have led to the widely held premise that the dominant processes of manganese oxidation in the environment are biological [57]. While this assumption may not accurately account for the extent of oxide nanoparticles and their role in heterogeneous abiotic manganese oxidation, there are many known bacteria and fungi (although no known archaea) that do oxidize Mn(II), and account for significant fluxes of oxidized manganese species in the environment. Notably, no organisms have been discovered to date with a metabolism based solely on manganese oxidation, although such chemolithotrophic or photolithotrophic metabolisms are thermodynamically plausible based on the redox potentials of certain high-valent manganese species (Figs. 2B and 4A).

Among the bacteria, two enzyme families have been identified with members that carry out direct Mn(II) oxidation coupled to O_2 reduction: the multicopper oxidases, and the peroxidase cyclooxygenases. These enzymes are typically extracellular or outer membrane proteins, and the manganese oxidation reactions they catalyze are not thought to be involved directly in energy-conservation. The multicopper oxidases have been identified in a diverse set of manganese-oxidizing bacteria, including *Bacillus* sp. SG-1 [58–61], *Pseudomonas putida* GB-1 [62,63], *Leptothrix discophora* SS-1 [64,65], and *Pedomicrobium* sp. ACM 3067 [66]. The peroxidase cyclooxygenases (formerly animal heme peroxidases [67]) have been identified in *Erythrobacter* sp SD21 [68], *Aurantimonas manganoxydans* SI85-9A1 [69], and *Pseudomonas putida* GB-1 [70]. Both of these enzymes oxidize Mn^{2+} via single electron transfer steps to form a Mn(III) intermediate, which is then further oxidized or disproportionates to form Mn(IV) [60,71,72].

A third flavor of bacterial manganese oxidation was described in *Roseobacter* sp. AxwK-3b. In this system, an NADH oxidoreductase has been hypothesized to produce superoxide. The superoxide then oxidizes Mn(II), while another enzyme with sequence similarity to MopA, the peroxidase cyclooxygenase in *Erythrobacter*, acts as a catalase to disproportionate the hydrogen peroxide produced by superoxide reduction [52,53]. The catalase activity draws down the concentration of hydrogen peroxide, thereby pulling the equilibrium discussed earlier (Reaction 1) towards the accumulation of oxidized manganese product, minimizing the back-reaction of manganese reduction by hydrogen peroxide. Like the other modes of bacterial manganese oxidation discussed here, manganese oxidation in *Roseobacter* is an extracellular phenomenon, with no role in energy conservation.

Fungi are also known to oxidize manganese by both direct and indirect mechanisms. Similar to the *Roseobacter* system, fungi have been shown to oxidize manganese indirectly using superoxide that is produced by NADPH oxidoreductase (e.g. Nox family) enzymes as a signaling molecule during cell differentiation [73]. Fungi also have mechanisms of direct enzymatic manganese oxidation—conducted by manganese peroxidase, a heme peroxidase found in a wide range of fungi involved in plant litter decomposition [74]. Manganese peroxidase catalyzes successive single-electron oxidations of two Mn(II) to produce two Mn(III), coupled to the reduction of hydrogen peroxide or an organic peroxide. The Mn(III) product is stabilized by ligands—predominantly oxalate—to create a diffusible oxidant which plays a critical ecological role in environmental lignin degradation [37].

The only known mode of manganese oxidation where the electrons definitively go into the electron transport chain involved in an organism's energy metabolism is during the assembly of the WOC of PSII in Cyanobacteria and the plastids of algae and plants. The WOC is synthesized biologically via a process known as photoassembly, which involves the direct photochemical oxidation of Mn^{2+} by PSII [75]. During photoassembly, four Mn(II) atoms are oxidized over five light-induced charge separation events to $Mn(III)_3Mn(IV)$ to generate the S_0 baseline oxidation state of the WOC. During the catalytic cycle, the cluster is further oxidized over four more light induced charge separation events to a hypothesized $Mn(IV)_3Mn(V)$ state and then regenerated to the S_0 state with the four-electron oxidation of H_2O to O_2. Notably, this is the only known mechanism of biological manganese oxidation that does not use O_2 or other reactive oxygen species as an oxidant.

Unlike manganese oxidation, manganese reduction has been well documented as a form of microbial metabolism that conserves energy—namely as the final electron acceptor for anaerobic respiration. In extant organisms, manganese reduction is not known to be an obligate metabolism; generally organisms capable of respiring manganese are also capable of using other electron acceptors such as other metal oxides, dioxygen, nitrate, organic compounds, or sulfur compounds [76]. In anaerobic environments with abundant manganese oxides, manganese reduction can theoretically yield more energy than other forms of respiration and represents an important pathway of organic carbon remineralization [20]. The best studied organisms that respire manganese oxides are *Shewanella oneidensis* MR-1 [77], and *Geobacter sulfurreducens* [78], both of which employ extensive networks of multiheme cytochromes that transport electrons from the periplasmic membrane to extracellular electron acceptors, via either direct outer membrane electron transfer enzymes or small molecule electron shuttles like humics, flavins, or phenazines [79]. Incubations done with environmental samples also suggest that manganese reduction may be syntrophically coupled to other microbial metabolisms such as the anaerobic oxidation of methane [80].

Intracellularly, manganese is found as both high molecular weight species bound to proteins and low molecular weight species bound to small molecules, including ortho- and polyphosphates, carbonates, and organics [14]. In proteins, manganese is used both as a structural element and catalytically, both as a Lewis acid and as a redox cofactor [32,81]. Beyond O_2 production (PSII) and reactive oxygen species detoxification (MnSOD and manganese catalase), enzymes that contain manganese perform a diverse suite of functions, ranging from DNA synthesis to carbohydrate metabolism. In addition to magnesium, manganese exhibits the highest diversity of enzyme functional requirements spanning all six enzyme commission class designations and representing over 125 unique manganese enzymes (as listed in the protein database ExPASy) [82]. These enzymes utilize manganese at mono-, bi-, and tetranuclear sites [83]. No known trinuclear manganese proteins exist, although the tetramanganese cluster of the WOC is comprised of a trimanganese distorted cubane structure bound to the fourth, so-called 'dangler' manganese by an oxo-bridge [8,11,84]. Table 2 presents a representative list of known manganese enzymes, with a focus on those that are redox-active (for a more complete list see Ref. [85]).

Some enzymes have absolute requirements for manganese (e.g., PSII), while others are cambialistic and allow Mn^{2+} to substitute for other divalent cations like Zn^{2+}, Cu^{2+}, Fe^{2+}, Ni^{2+}, Co^{2+}, Mg^{2+}, and Ca^{2+} and yield a functioning enzyme (e.g., cytochrome *c* oxidase, xylose isomerase) [86]. The most common of these substitutions is between Mn^{2+} and Mg^{2+} due to similarities in ionic radii and ionization potential, despite the fact that manganese typically has four orders of magnitude lower cellular concentration (10^{-7} M manganese versus 10^{-3} M magnesium [81], though manganese concentrations can vary significantly between organisms, and reach as high as 10^{-3} M [17,87]). For example, cytochrome *c* oxidase (i.e. complex IV, heme-copper O_2 reductase), which pumps protons across the mitochondrial membrane and catalyzes the reduction of dioxygen to water, contains a number of redox active iron-copper centers as well as two non-redox active divalent metal centers typically composed of Zn^{2+} and Mg^{2+} [85]. However, in some bacteria (e.g., the alphaproteobacterium *Paracoccus denitrificans*) up to 20% of the Mg^{2+} is replaced by Mn^{2+} [85,88]. It is currently unknown if this substitution plays a catalytic role or if the divalent metal only serves a structural role, although some evidence shows that the Mg/Mn site may be responsible for transport of the product waters and advected protons [89]. Another intriguing example

Table 2
Selection of known manganese-bearing metalloproteins, including redox-active and nonredox-active enzymes that require manganese for catalytic functioning, and also enzymes known to perform manganese oxidation but that do not use manganese as a cofactor. **No. of Mn** shows the number of manganese atoms required for protein function; **Redox-active Mn** defines whether or not the manganese cofactor (or substrate in the case of MnxG and MopA) undergoes a redox state change during the course of the reaction; **Mn valence** indicates the valence state manganese will exist or transition through during the reaction cycle; **EC no.** indicates the enzyme commission number. One can infer that the redox-active proteins that oxidize or reduce manganese either as innate metal center(s) or a substrate all evolved after the rise of O_2, and that manganese-bearing metalloproteins prior to the rise of oxygen were likely limited to performing simpler chemistry, e.g. laboring as hydrolases or isomerases.

Enzyme	No. of Mn	Redox active Mn	Mn valence	EC no.	Enzyme class/function	Overall reaction	Distribution
PSII	4	Y	II/III/IV/(V)	1.10.3.9	Oxidoreductase; Catalyzes oxidation of water to release dioxygen	$2\ H_2O + 2$ plastoquinone $+ 4$ light $\rightarrow O_2 +$ 2 plastoquinol	Cyanobacteria, chloroplasts
Mn catalase	2	Y	II/III	1.11.1.6	Oxidoreductase; Catalyzes the disproportionation of hydrogen peroxide to water and dioxygen	$2H_2O_2 \rightarrow 2H_2O + O_2$	Bacteria
Mn superoxide dismutase (MnSOD)	1	Y	III	1.15.1.1	Oxidoreductase; Redox enzyme; acts on superoxide radical	$2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$	Mitochondria, chloroplasts, bacteria
Oxalate oxidase	1	Y	II/III	1.2.3.4	Oxidoreductase; Aids in carbohydrate metabolism by catalyzing conversion of oxalate and dioxygen to hydrogen peroxide and carbon dioxide	$(COOH)_2 + O_2 \rightarrow H_2O_2 + 2CO_2$	Plants, bacteria
Oxalate decarboxylase	1	Y	II/III	4.1.1.2	Lyase; Aids in carbohydrate metabolism by catalyzing cleavage of oxalate into formate and carbon dioxide	$(COOH)_2 + H^+ \rightarrow HCOO^- + CO_2$	Bacteria
Arginase	2	N	II	3.5.3.1	Hydrolase; Catalyzes the final step in the Urea Cycle	L-arginine $+ H_2O \rightarrow$ L-ornithine + urea	Yeast, bacteria, mammals
Xylose isomerase	1 or 2	N	II	5.3.1.5	Isomerase: Catalyzes the interconversion of aldose and ketose sugars with broad substrate specificity	D-xylopyranose → D-xylulose	Bacteria
Mn dioxygenase	1 or 2	Y/N[a]	II/possibly III [139]	1.13.11.39	Oxidoreductase; Catalyzes the degradation of catechol through incorporation of O_2	Biphenyl-2,3-diol $+ O_2 \rightarrow$ 2-hydroxy-6-oxo-6-phenylhexa-2,4-dienoate	Bacteria
Type Ib ribonucleotide reductase (RNR)	2	N[b]	III	1.17.4.1	Oxidoreductase; Catalyzes the reduction of ribonucleotide diphosphates to corresponding deoxyribonucleotides via reductive elimination of 2-hydroxyl	2′-deoxyribonucleoside diphosphate + thioredoxin disulfide $+ H_2O \rightarrow$ ribonucleoside diphosphate + thioredoxin	Bacteria
Mn peroxidase (MnP)[c]	-	Y	II/III	1.11.1.13	Peroxidase; Redox enzyme, degrades lignin	$2Mn^{2+} + 2H^+ + H_2O_2 \rightarrow 2Mn^{3+} + 2\ H_2O$	Fungi
Mn-oxidizing multicopper oxidase (MnxG)[c]	-	Y	II/III	1.16.3.3	Oxidoreductase; Oxidizes soluble Mn^{2+} to insoluble manganese oxides; typically located on the outer surface of the cell resulting in encrustation of the cells by the oxides.	$4\ Mn^{2+} + 2\ O_2 + 4\ H_2O \rightarrow 4\ MnO_2^+ + 8\ H^+$	Bacteria
Mn-oxidizing protein (MopA)[c]	-	Y	II/III	Unknown	Oxidoreductase; Extracellularly oxidizes soluble Mn^{2+} to Mn^{3+} via single electron transfer, which then accumulates as a soluble species (ligand unknown) or disproportionates to form Mn^{4+}	Exact reaction pathway currently unknown[d]	Bacteria

[a] Some studies have shown that extradiol dioxygenases that require Mn^{2+} or Fe^{2+} may not go through a redox change while undergoing oxygen activation [140].

[b] While the Mn in Type Ib RNR is not known to be redox active in the reduction of RNA to DNA, the biosynthesis of the protein does require oxidation of the $2Mn^{2+}$ into the final active cofactor $Mn^{III}Mn^{III}$-tyrosyl radical. Two proposed protein assembly schemes for the active cofactor are: (1) $2Mn^{2+}$ + Tyrosine $+ 2H_2O_2 + e^- + H^+ \rightarrow Mn^{III}Mn^{III}$ + Tyrosyl radical $+ 2H_2O$/(2) $2Mn^{2+}$ + Tyrosine $+ O_2^- + H^+ \rightarrow Mn^{III}Mn^{III}$ + Tyrosyl radical [141].

[c] MnP, MnxG and MopA are proteins that perform manganese oxidation and do not require or use Mn as a cofactor in the enzyme.

[d] Based on sequence similarity the protein is known to fall in the peroxicin subfamily of the peroxidase cyclooxygenase superfamily [68]. O_2 is required for the reaction to proceed and therefore is postulated to be the likely terminal electron acceptor to form Mn(III) as the product.

of a metal site sometimes occupied by Mg^{2+} and sometimes by Mn^{2+} is found in ribulose-1,5-biphosphate carboxylase/oxygenase (or RuBisCO)—the premier carbon fixation enzyme in the Calvin Cycle and most abundant protein on Earth. While the role of this substitution is also currently unknown, hypotheses have been proposed that it could regulate the notorious oxygenase activity of RuBisCO [90].

All of the known enzymes that use manganese in a redox capacity touch O_2 in some way, either as a direct product of the reactions they catalyze (e.g., PSII, catalase) or as an oxidant used to generate a catalytic Mn(III) or Mn(IV) center or product (e.g., oxalate decarboxylase, manganese peroxidase, multicopper oxidase MnxG). Thus O_2 enables manganese redox activity, greatly expanding the diversity of uses for manganese by biology. While the evolutionary history of specific proteins can be difficult to assess when they are subject to horizontal gene transfer and rapid evolutionary rates, we infer that all of these proteins that interface with manganese redox chemistry postdate the rise of O_2—with the single, salient exception of PSII (discussed further below).

4. Manganese in the history of earth and life

O_2 was not present on the early Earth in any meaningful amounts prior to the Great Oxygenation Event that occurred at ~2.35 Ga, following the origin of oxygenic photosynthesis. Multiple proxies in the geological record constrain earlier O_2 levels to exceedingly low. For example, the presence of weathered detrital grains of redox-sensitive minerals like pyrite and uraninite deposited in river sediments constrains O_2 levels to $< 10^{-5}$ atm [4,91], and a mass-independent fractionation signal in the sulfur isotopic composition of sedimentary rocks caused by SO_2 photochemistry (enhanced by absence of an ozone layer) constrains O_2 levels to $< 10^{-10}$ atm [92–94]. Both of these proxies are widespread in strata deposited prior to the rise of O_2, and completely absent in younger strata. Thus, both the advantages and disadvantages provided by O_2 were not available to ancient biochemistry.

Manganese was abundant in natural waters on the early Earth. Mn(II) hosted in igneous rocks was easily released by silicate weathering, which, combined with hydrothermal sources of Mn(II), led to an accumulation of Mn^{2+} in the oceans (Fig. 3A). Because Mn(II) does not readily form sulfide or disulfide minerals as Fe(II) does, the only significant manganese-bearing phases that formed were carbonate salts. Thus, before the rise of O_2, the primary sink of Mn^{2+} was as a minor constituent of carbonate salts (aragonite, calcite, and dolomite) precipitated from seawater, where Mn^{2+} can substitute for Ca^{2+} [4,95]. Archean age (> 2.5 Ga) marine calcite cements contain substantial amounts of Mn(II), in contrast to their modern equivalents, which reflects the high abundance of dissolved Mn^{2+} prior to the onset of manganese redox cycling and oxidative removal of manganese from the water column [95–101]. An equilibrium partition coefficient provides a means of estimating the amount of Mn^{2+} that was present in the ancient ocean from observations of the Mn:Ca ratio in well-preserved marine herringbone calcite cements—a rock type/texture that grew slowly and provides a meaningful proxy for aspects of ancient seawater chemistry [102] (Fig. 3C). The Mn:Ca ratio in these rocks is many orders of magnitude greater than occurs in younger rocks (Fig. 3D), and suggests Mn^{2+} concentrations of up to 120 μM characterized seawater prior to the rise of O_2 [4,103]; this is in stark contrast to the nanomolar concentrations typical of modern open oceans [26]. This Mn^{2+} was a prospective resource for the early anaerobic biosphere—the biochemical challenge was figuring out how to access it.

In spite of the high manganese concentrations in natural waters, all available evidence suggests that if Archean biology used manganese at all it was as a divalent cation with no redox activity. From a geological perspective, no Archean age rocks display robust evidence of the presence of oxidized manganese mineral phases. Evidence for meaningful manganese redox cycling first appears in the geologic record in Paleoproterozoic strata (~2.4 Ga) shortly before the rise of O_2 [10]. And from a biological perspective, enzymes that use manganese that could have been present in Archean organisms employ Mn(II) in roles that do not solicit its redox chemistry. Without the high potential oxidants supplied by O_2 or PSII, none of the known biological mechanisms for manganese redox chemistry would have been accessible.

The onset of manganese redox cycling was accompanied by a tremendous change in the style of sedimentary manganese deposition, as the precipitation of insoluble manganese oxides is the only mechanism that can generate highly concentrated manganese ores [95,104]. Primary minerals deposited in poorly consolidated sediments commonly undergo a suite of post-depositional alteration processes as the sediment is lithified into rock; this means that the primary mineral phases are often lost, and instead a complex mixture of secondary and tertiary mineral products end up preserved in the geologic record. Accordingly, understanding the diagenetic history and petrogenesis of manganese deposits has been a valuable source of data to reconstruct past processes of manganese redox cycling at different times in Earth history. The manganese-bearing minerals preserved in sedimentary deposits appear to follow a similar pattern, where primary Mn(IV) oxide minerals like birnessite accumulate in shallow sediments, but then during burial these are reduced by organic carbon in sedimentary porewaters—a process likely catalyzed by manganese-reducing microbes [105], to form secondary phases of mixed valence Mn(III)-bearing minerals like braunite or Mn(II)-bearing carbonates like kutnohorite (Table 1), which can be further recrystallized and metamorphosed to form tertiary phases like rhodochrosite and rhodonite [95]. Therefore, high concentrations of Mn(II)-bearing minerals in sedimentary rocks can provide evidence for the initial deposition of insoluble Mn(IV) resulting from oxidative processes in the overlying water column or locally at the seabed.

For most of geologic time, the history of manganese oxide deposition reflects the history of O_2, as O_2 and other species derived from it are the only meaningful oxidants for Mn^{2+}. However, the earliest authigenic manganese deposit is found in the Koegas Formation, a package of sedimentary rocks in the Transvaal Supergroup in South Africa, which was deposited at ~2.4 Ga [106]. Careful comparison of the onset of manganese deposition with independent proxies that constrain the amount of O_2 demonstrated that these manganese deposits predate the rise of O_2 [10]. Evidence from other coeval Paleoproterozoic sedimentary basins preserved in Australia and Canada support a similar history of manganese deposition [11,95,107,108]. These observations suggest a novel mechanism of manganese oxidation occurring just before the invention of oxygenic photosynthesis and fluxes of dioxygen in surface environments.

Oxygenic photosynthesis evolved from anoxygenic phototrophy, simpler versions of light-driven metabolism that use electron donors other than water. Both geological observations and constraints from comparative biochemistry indicate that anoxygenic phototrophy evolved very early in Earth history—likely sometime prior to 3.4 Ga, predating oxygenic photosynthesis substantially [13,109]. To convert light energy to chemical energy that fuels electron transport chains, modern anoxygenic phototrophs use biochemical machinery (reaction centers) that share distant homology to the photosystems of oxygenic photosynthesis, indicating a common evolutionary history [13,110,111]. Today, organisms conducting these metabolisms exist in niche environments where high concentrations of their electron donors are available; these environments are often anaerobic, and the microorganisms that live there are adapted to extreme temperature or chemical conditions where they have less ecological competition. However, prior to the origin of oxygenic phototrophy, anoxygenic phototrophs were likely more prevalent in ancient surface environments [109,112–114].

All known forms of anoxygenic phototrophy use electron donors that are accessible to reaction center electron acceptors with moderately high reduction potentials, ~250–500 mV; this is much lower than the reduction potential needed to access the H_2O/O_2 couple, which is accomplished by PSII with substantial overpotentials estimated at

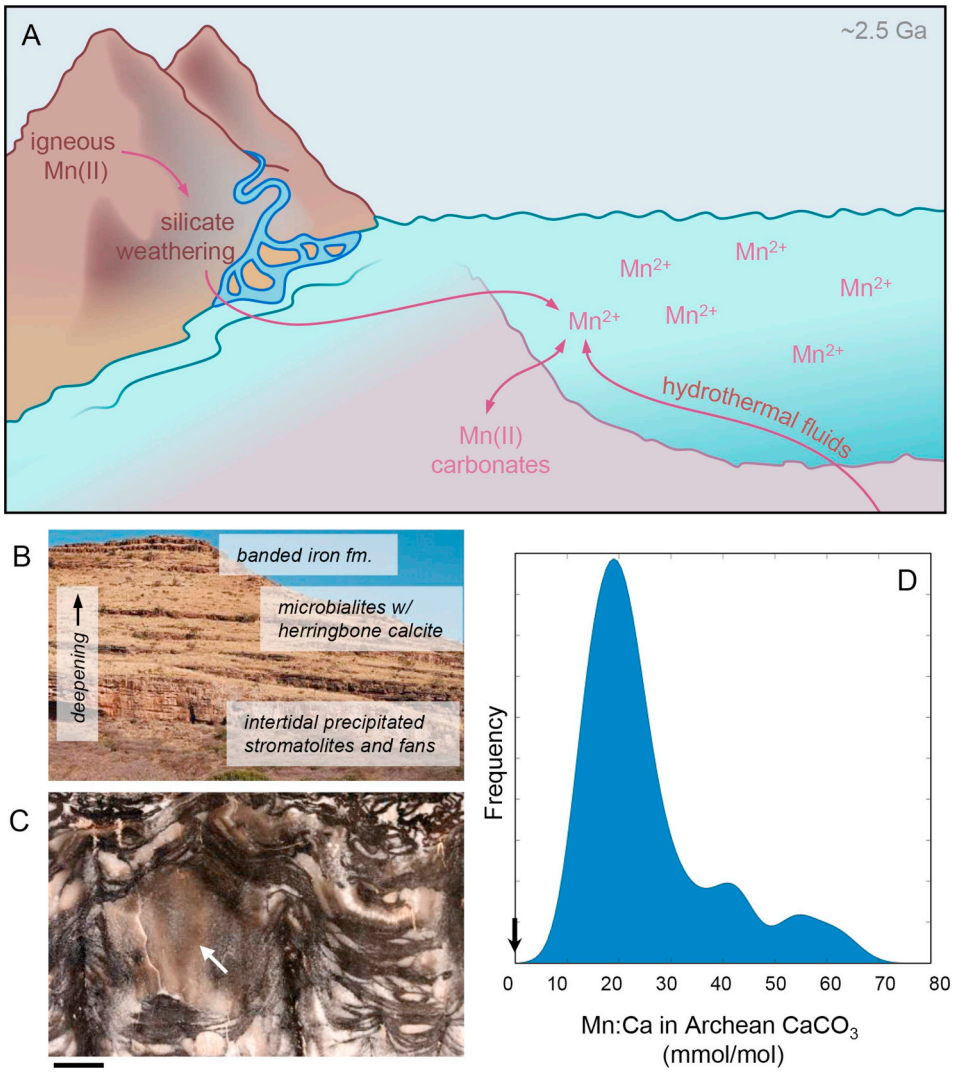

Fig. 3. A simple manganese cycle on the early Earth—prior to the rise of O_2. ***A.*** Manganese is present in the crust exclusively as Mn(II) where it substitutes for Fe(II) in a range of igneous minerals. Both low temperature and high temperature (hydrothermal) silicate weathering sources dissolved Mn^{2+} to surface waters where it ultimately accumulates to substantial levels in the oceans, with the only meaningful sink as a minor constituent of marine calcium carbonate salts. ***B.*** Geological strata of a 2.5 Ga carbonate platform, deposited at a time prior to the appearance of any dioxygen in the atmosphere or oceans [96,113,133]. These strata contain abundant marine calcite ($CaCO_3$) cements—including a specific texture termed 'herringbone calcite' that precipitated from subtidal seawater [134]. ***C.*** Close up view of herringbone calcite (white arrow) deposited on ancient microbialites. These $CaCO_3$ cements contain substantial concentrations of Mn(II) [4]. ***D.*** Kernel density estimate of 90 measurements of the Mn:Ca ratio in Archean carbonates show very high Mn(II) contents. These are many orders of magnitude higher than seen in carbonates after the rise of oxygen (typical modern value shown by the black arrow) and reflect very high concentrations of Mn^{2+} in seawater at this time—levels that would have naturally provided some oxidative stress resistance in marine environments [14,16,96].

~1250 mV. The extremely high potential of PSII must have evolved prior to the origin of oxygenic photosynthesis, as it is required to oxidize water. This implies an evolutionary missing link: a high-potential version of anoxygenic phototrophy bridging the canonical versions of lower-potential anoxygenic phototrophy with oxygenic phototrophy. Indeed, comparative biology of the D1 and D2 proteins of PSII with the analogous L and M subunits of the closest related anoxygenic reaction centers indicated that an ancestral version of PSII used a high potential electron donor (which must have been a small molecule, and not the single electron protein carriers employed by typical reaction center donors of cytochrome *c*, cupredoxin, or high-potential iron-sulfur protein) for anoxygenic phototrophy before the evolution of the WOC [13]. Mn^{2+} is the only plausible electron donor to this ancestral version of PSII [13].

The hypothesis that Mn^{2+} served as an electron donor to ancestral PSII leading up to the evolution of oxygenic photosynthesis provides a natural explanation for the onset of manganese oxidation observed in the geologic record shortly before the rise of O_2 [10]. Capturing light energy to generate a strong biochemical electron acceptor is the only known mechanism for manganese oxidation in the absence of a chemical electron acceptor, i.e., O_2, and therefore the most conceivable mechanism for that earliest manganese oxidation. Furthermore, using Mn^{2+} as an electron donor is exactly what modern PSII does during the assembly of the WOC [75]. Thus, all biological water oxidation first requires phototrophic manganese oxidation, and as such, phototrophic manganese oxidation must have preceded the ability to oxidize water [11].

The high concentrations of dissolved Mn^{2+} in the ancient oceans provided an enticing ecological opportunity. Prior to gaining the ability to use the abundant resource of water as an electron donor, rates of primary productivity by the biosphere were not nutrient limited as they are today, but rather they were electron limited, with the most abundant sources of electrons coming from a geological trickle of rock-weathering derived electron donors like H_2, sulfur compounds, and Fe (II) [3,11]. While Fe(II) represents the largest available geochemical electron source, iron appears to have had already developed a redox cycle and empirical observations show that Fe^{2+} was largely depleted from Late Archean surface waters [98,113]. At the same time, surface waters were rich in Mn^{2+}, water, and light. Therefore, Mn^{2+} represented a valuable untapped electron reservoir, providing a tangible incentive to evolve a much higher-potential reaction center capable of manganese oxidation—an evolutionary trajectory that would ultimately pave the way to oxygenic photosynthesis.

With the origin of oxygenic photosynthesis came the first appearance of meaningful sources of O_2. For biology, O_2 is a double-edged sword—it enabled the development of aerobic respiration, the most energy-rich form of metabolism, but it also brought the risk of devastating oxidative stress. Thus the appearance of O_2 in the environment imparted strong new selection pressures on life. Today, effective systems for combating oxidative stress are thoroughly integrated in biochemistry, but prior to the introduction of O_2 there would have been little use for such systems, and therefore little reason for them to have already evolved. As such, the

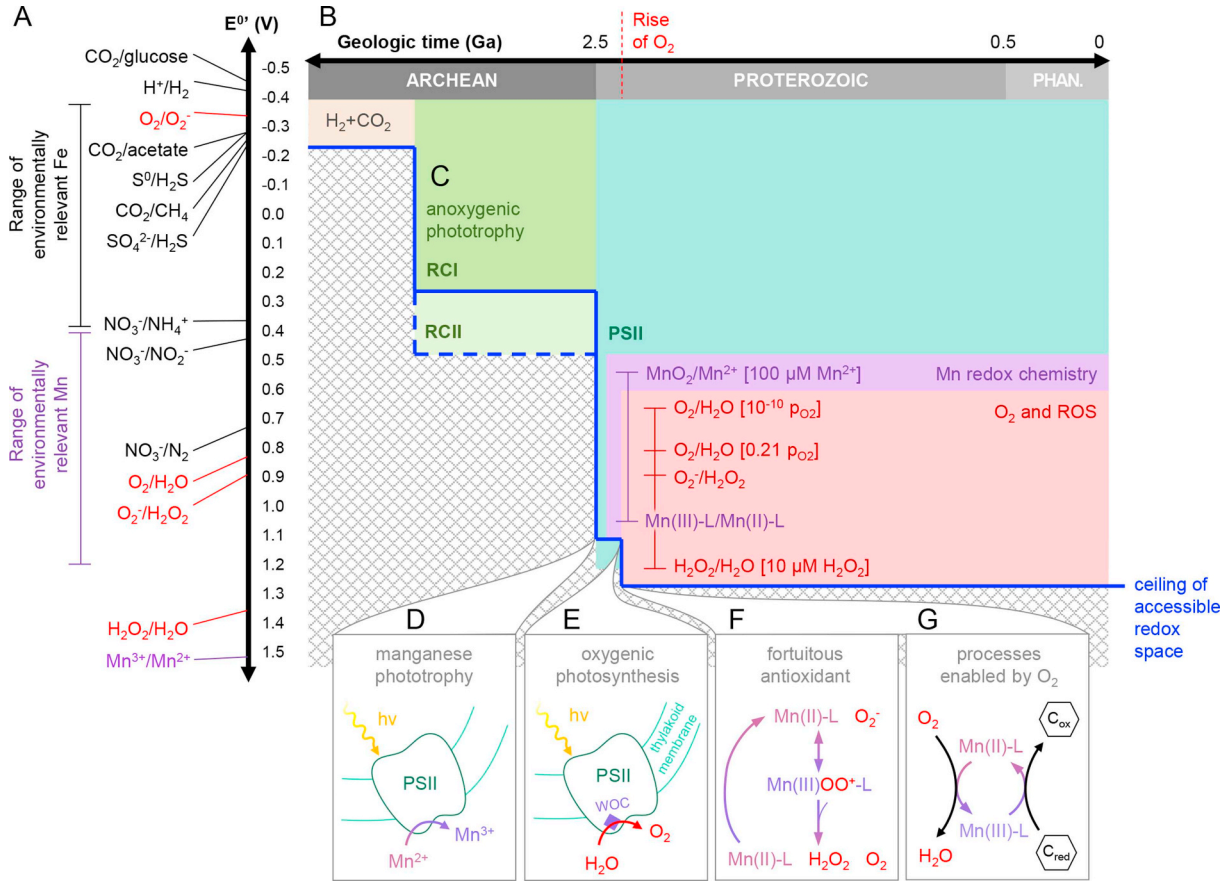

Fig. 4. The breadth of redox chemistry exploited by the biosphere through time ***A.*** Redox tower showing midpoint reduction potentials at pH 7 ($E^{0'}$) for a selection of biologically and geochemically relevant species [26,130–132,135–138]. Manganese redox couples occupy a range of redox space that is typically higher on the tower than most other environmentally and biologically relevant species—a range that overlaps with O_2 and other reactive oxygen species. ***B.*** Geologic timeline, illustrating how manganese expanded the high-potential limit of accessible redox chemistry. The earliest redox chemistry exploited by life depended on pre-existing thermodynamic disequilibria in the environment, allowing microbial metabolisms like H_2-CO_2 methanogenesis and acetogenesis [3]. ***C.*** Phototrophy, the ability to capture and transduce the energy in visible light to create strong biochemical oxidants and reductants, enabled redox chemistry that was previously inaccessible; anoxygenic phototrophy was one of the most important early developments in high-potential metabolism (e.g. energy conservation around complex III). ***D.*** The evolution of a version of phototrophy with a high enough potential to oxidize Mn(II) introduced a source of high-valent manganese to the environment, and provided a stepping stone for the evolution of oxygenic photosynthesis [10,11]. ***E.*** The evolution of the WOC endowed the biosphere with the ability for photosynthetic water-splitting, and the rise of O_2 ensued. ***F.*** The introduction of O_2 and ROS further raised the ceiling of accessible redox space, defining the redox landscape in aerobic cells and environments today. Today the antioxidant properties of manganese are a critical feature of cellular protections against oxidative stress; the high Mn(II) concentrations in early environments and within cells would have been available as fortuitous (non-enzymatic) antioxidant systems that allowed life to cope and thrive with the rise of O_2. ***G.*** In the modern, aerobic world, manganese redox chemistry is involved in numerous biogeochemical processes. Enzymes with diverse functions incorporate redox-active manganese cofactors, and manganese redox cycling plays a key role in ecological processes, such as the oxidative degradation of recalcitrant organic matter.

first organisms to encounter oxidative stress had to rely on the antioxidant properties of molecules that served other functions intracellularly or pre-existed in the environment. The ability of Mn^{2+} complexes to catalytically quench reactive oxygen species [16,54], along with the ability of Mn^{2+} to confer resistance to oxidative damage by replacing Fe^{2+} in metalloenzymes [19], makes manganese a key example of such a fortuitous antioxidant system. The concentrations of Mn^{2+} in ancient seawater were sufficiently high that manganese antioxidant chemistry could be considered naturally built-in to the environment. That O_2 production evolved in organisms that were already conducting a manganese-based version of phototrophy, and therefore already inclined to accumulate manganese intracellularly, means that those cells were readily poised to co-opt this manganese-based antioxidant system. Genomic analyses demonstrate that aerobic respiration evolved subsequent to oxygenic photosynthesis in the ancestors of Cyanobacteria [115]. Early antioxidant systems would have been a critical ingredient that allowed these cells that had just learned how to produce O_2 to survive, and eventually evolve more complex strategies of coping with, and ultimately exploiting the energy available in O_2.

5. Manganese and humans

The manganese chemistry unlocked by O_2 enabled a suite of novel processes that have proven valuable in the uses of manganese materials by humans. Humans have been present for only a tiny fraction (< 0.5 Ma) of the ~4 Ga history of life on this planet, but we are another species that left a disproportionate impact on the environment [116–118], like the Cyanobacteria that changed the atmosphere forever with the introduction of O_2—albeit in our case through societal and technological innovations rather than biochemical ones. As such, it seems appropriate to briefly discuss the role of manganese in human society in this history of manganese in the co-evolution of life and the environment.

Hominids have interacted with manganese for at least tens of millennia, as archaeological evidence for the use of manganese oxides has been found at numerous Middle Paleolithic sites. A common interpretation is that these materials were used as pigments, for both cave art and body decoration. However, the unique redox chemistry of high-valent manganese minerals may have provided another, more specific,

use. Heyes et al. showed that manganese oxides can promote fire ignition under conditions where it otherwise would not ignite; gases derived from wood pyrolysis are oxidized by MnO_2, causing the reductive decomposition of the MnO_2, which releases O_2, lowering the ignition temperature of the wood. Taken together with archeological evidence of MnO_2 associated with fire places, this data suggests that Neanderthals used MnO_2 to ease fire-making, an innovation that may have been critical during the glacial periods of the Paleolithic [119].

Today, human activities contribute substantially to the redistribution of manganese in the environment, with 50,000,000 metric tons of manganese ore produced every year [120], and anthropogenic emissions accounting for a significant flux of manganese to natural waters and the atmosphere [121,122]. The biggest industrial use of manganese is in steel production [44]. Manganese is requisite in modern steel making, both as a refining additive and also as an essential alloy [123]. It lends unique properties to the steel, such as a considerable increase in tensile strength. There is no known satisfactory substitute for manganese in metallurgy, and as such it is considered a critical mineral commodity [124]. Beyond steel, manganese is used in a staggeringly diverse array of other applications [125,126]. It is used as a pigment in glass, ceramics and paints. It is used as an oxidizing agent in the chemical synthesis of a wide range of products, from dyes and fragrances to yellow-cake uranium. It is used as a scavenger in water treatment, and as an octane booster/anti-knock agent in unleaded gasoline. Manganese was used as an electron acceptor in the earliest Leclanché type primary cell batteries, and continues to be used to this day in zinc/manganese primary and secondary cell batteries [127]. Thus, this strange and wonderful element[1] has been repurposed by the biosphere once again—this time via the evolution of human creativity.

6. Conclusion

In the ancient, anaerobic world, manganese redox chemistry was not accessible until after the evolution of a phototrophic reaction center with a high enough reduction potential to oxidize manganese—this was the direct ancestor to PSII. Unlocking manganese redox chemistry shattered the previous ceiling of redox space available to biology and was a crucial evolutionary bridge that led to the origin of oxygenic photosynthesis and the rise of environmental O_2 (Fig. 4). The fact that the production of O_2 evolved in organisms with a keen interest in manganese meant that the first organisms to encounter significant fluxes of O_2 had a built-in fortuitous antioxidant system, thanks to the ability of manganese complexes to catalytically quench dangerous reactive oxygen species like superoxide and hydrogen peroxide (Fig. 4F). The antioxidant properties of Mn^{2+} along with its high concentrations in ancient oceans may have been the key to life surviving and ultimately thriving in an aerobic world.

As life discovered O_2 through manganese—and manganese continues to be the requisite catalyst for O_2 production—by reciprocity O_2 opened a doorway into a world of rich redox chemistry, enabling a diverse suite of processes that use high-valent manganese. O_2 provided chemical species with even higher reduction potentials than manganese, further raising the ceiling of redox space available to biology and enabling energetically-favorable manganese oxidation without the input of light energy. Manganese redox chemistry was harnessed by enzymes with a wide range of functions (Table 2); some of these allow cells to cope with reactive oxygen species (e.g. catalase), while others enable important ecological processes like lignin degradation (Mn peroxidase). All manganese redox-active proteins interact with O_2 or species derived thereby, and appear to have only evolved in the wake of the rise of O_2. With its redox cycle, manganese would come to play an essential role in the function of biogeochemical cycles and participate in numerous redox and sorption processes affecting the availability and distribution of other key elements. Diverse components of the modern biosphere, from niche microbes to human industry, still exploit these relationships between O_2 and the biogeochemical dynamics of manganese.

[1] The etymology of manganese comes from the Greek root *mangania*, or magic [128].

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