The Role of Microbial Electron Transfer in the Coevolution of the Biosphere and Geosphere

Benjamin I. Jelen,[1] Donato Giovannelli,[1,2,3,4] and Paul G. Falkowski[1,5]

[1]Environmental Biophysics and Molecular Ecology Program, Institute of Earth, Ocean and Atmospheric Sciences, Rutgers University, New Brunswick, New Jersey 08901; email: ben.jelen@rutgers.edu, giovannelli@marine.rutgers.edu, falko@marine.rutgers.edu

[2]Institute of Marine Science, National Research Council, 60125 Ancona, Italy

[3]Program in Interdisciplinary Studies, Institute for Advanced Studies, Princeton, New Jersey 08540

[4]Earth-Life Science Institute, Tokyo Institute of Technology, Tokyo, Japan 152-8550

[5]Department of Earth and Planetary Sciences, Rutgers University, New Brunswick, New Jersey 08854

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Abstract

All life on Earth is dependent on biologically mediated electron transfer (i.e., redox) reactions that are far from thermodynamic equilibrium. Biological redox reactions originally evolved in prokaryotes and ultimately, over the first ~2.5 billion years of Earth's history, formed a global electronic circuit. To maintain the circuit on a global scale requires that oxidants and reductants be transported; the two major planetary wires that connect global metabolism are geophysical fluids—the atmosphere and the oceans. Because all organisms exchange gases with the environment, the evolution of redox reactions has been a major force in modifying the chemistry at Earth's surface. Here we briefly review the discovery and consequences of redox reactions in microbes with a specific focus on the coevolution of life and geochemical phenomena.

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DISCOVERY OF BIOLOGICAL ELECTRON TRANSFER REACTIONS

In 1863, four years after the publication of *The Origin of Species*, George G. Stokes, Lucasian Professor of Mathematics at Cambridge University, published a paper "On the Reduction and Oxidation of the Colouring Matter of the Blood" (120). Inspired by descriptions of remarkable spectra created by sunlight shining through dilute blood (56), Stokes envisioned a way to test his supposition that the characteristic color change from bright red (arterial) to deep purple (venous) blood was accomplished by reduction of the coloring pigment, now known to be hemoglobin (120). Using blood of sheep or oxen supplied by his butcher, Stokes carefully chose reducing agents (e.g., ferrous sulfate) compatible with an alkaline solution (acidic solutions decomposed the pigment) and recreated the reversible spectral changes in a tube using chemical oxidation and reduction.

Of course, before the discovery of the electron, the terms oxidation and reduction had a more literal meaning than the electron-transfer formalizations of today. In its earliest descriptions by Antoine Lavoisier, reduction was the loss of molecular oxygen, whereas oxidation was its addition (76). By Stokes's time, electricity had been discovered and the thermodynamic relationship between electricity and chemistry would soon be precisely defined (96). Concomitantly, biochemical transformations at the microbiological level were being studied in such labs as those of Robert Koch and Louis Pasteur. Their pioneering research, which recognized the importance of oxidation-reduction reactions, was largely limited to isolated cultures and carbon-based transformations (e.g., fermentation). The recognition that oxidation-reduction reactions are critical in changing environmental chemistry came about largely through the insight of Sergei Winogradsky (31). Early in his career, Winogradsky was intent on understanding the role of the large sulfur granules accumulated by *Beggiatoa* in natural environments. His experiments culminated in describing an organism able to derive energy solely from sulfur compounds, an entirely new type of metabolism that is now called chemolithotrophy. Subsequently, Winogradsky isolated nitrifying bacteria, taking microbiology a further leap forward by confirming the biological ability to fix inorganic carbon using energy from the redox transformations of inorganic (nitrogen) compounds (133). The knowledge that nonphotosynthetic microbes could obtain energy and carbon not only from organic compounds (e.g., carbohydrates) but also from inorganic molecules (e.g., hydrogen sulfide, ammonia, ferrous iron, carbon dioxide) effectively was the beginning of a new field of science—microbial ecology. Indeed, Winogradsky was the first to isolate a free-living diazotroph (nitrogen-fixing organism), thereby proving that microbes can not only oxidize ammonium but also reduce dinitrogen gas from the atmosphere. His work led to the notion that biological electron transfer reactions involving carbon, nitrogen, and sulfur form a network of interdependent elemental cycles mediated solely by microbial metabolism (116, 117).

Fundamentally, however, the microbiologists of the time failed to appreciate that microbial metabolism can change Earth's chemistry on a global scale. By the end of the nineteenth century, the Russian-Ukrainian geochemist Vladimir Vernadsky was formulating a broad theory of Earth history, with the fundamental hypothesis that life itself was a geological force that had shaped the planet. His book *The Biosphere* was published in Russian in 1926, but the full English translation was not published until 1997 (103, 126). Consequently, Vernadsky's ideas were largely isolated from European and American scientists. Vernadsky understood that neither individual cycles nor biology and geology operate independently; rather, they are constantly interacting, the planetary steady state being balanced by positive and negative feedback. In the latter part of the twentieth century, Vernadsky's ideas were echoed and eloquently elaborated upon by James Lovelock and Lynn Margulis (who formulated the "Gaia hypothesis"; 81).

Ferredoxin: low molecular weight iron-sulfur protein that acts as a multifunctional electron carrier in biological redox reactions

Like most geologists at the time, Vernadsky believed that Earth had always been in a steady state, and he never considered explicitly the origin and evolution of biogeochemical cycles. We now understand (albeit still incompletely) that biogeochemical cycles largely result from an interaction between biological electron transfer reactions (with or without protons) that, over geological timescales, can profoundly change the chemistry of Earth's surface. The emergent network of elemental cycles is far from thermodynamic equilibrium, and the primary source of external energy is solar radiation. This charged, electron-transfer network can be thought of as a global electrical circuit board, driven by solar power that is transduced by enzymes able to catalyze electron flow. At this scale, the connections between the biological transistors are the atmosphere and oceans, which act as global wires, ferrying oxidants and reductants across the planet (34, 88).

OXIDOREDUCTASES: CORE STRUCTURES AND COFACTORS

The enzymes responsible for electron transfer are called oxidoreductases (Enzyme Commission Class 1; i.e., EC1; 122). These proteins, composing the core machinery of metabolism, are ubiquitous across the tree of life (**Figure 1**). Structural analysis of EC1 proteins reveals a relatively small subset of key folds, many of which contain transition metals at their active sites (50, 105, 119). Indeed, the entire network of contemporary global electron transfer reactions (34) employs fewer than 400 homologous genes, all of which evolved in prokaryotes in Precambrian time (**Figure 2**; **Supplemental Table 1**; follow the **Supplemental Materials link** from the Annual Reviews home page at **http://www.annualreviews.org**). Analysis of the metal-containing oxidoreductases reveals that approximately 60% contain iron in the active site. Of iron-containing oxidoreductases, more than half use iron-sulfur clusters, whereas the remaining members mostly employ hemes (51).

Supplemental Material

The role of iron-sulfur minerals in catalyzing prebiotic reactions has long been recognized as a potential pathway leading to the formation of simple organic molecules and chemical bond energy required for the origin of life (114, 128, 129, 132). Available during the early Archean Eon (52), these mineral motifs appear to have been appropriated into short peptide folds very early in the origin of metabolism (26). In a prebiotic world, short peptides, condensed from amino acids, could have sequestered iron-sulfur clusters from the environment to form protoferredoxins (44, 113). Indeed, the Fe_4S_4 cluster in the active site of ferredoxins is bound to a very highly conserved protein fold consisting of a CxxCxxC. . .C peptide sequence (65, 91). Notably, early in the evolution of iron-sulfur-containing proteins, there appears to have been very strong selective pressure for specific folds. Iron-sulfur clusters themselves are achiral. However, an analysis of 3D structures of iron-sulfur-containing oxidoreductases in the Protein Data Bank (**http://www.rcsb.org**) reveals that all folds around the metal centers are right-handed. Given life's early selection of L amino acids in all structural proteins, right-handed protein folds are favored over left-handed folds around

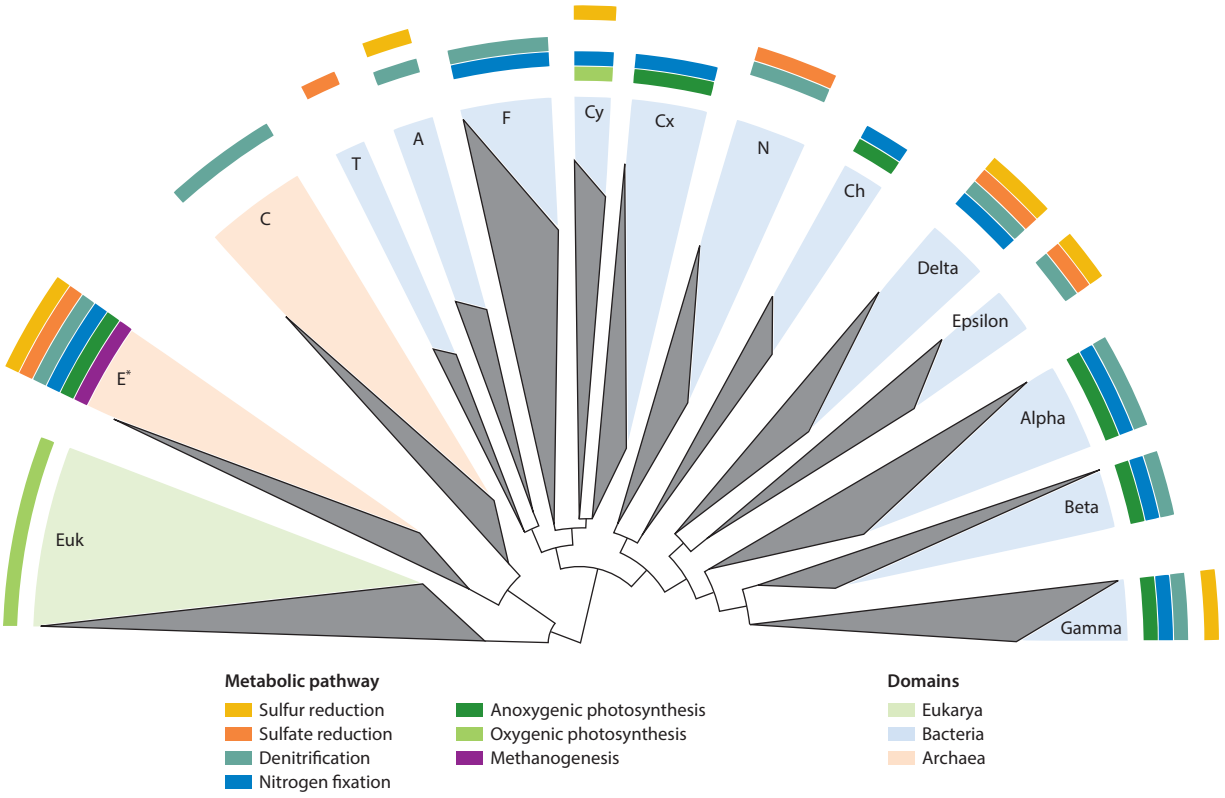


Figure 1

Distribution of selected metabolic pathways on the 16S rRNA tree of life. The tree (constructed with ARB; 104) was edited for clarity and shows selected bacterial and archaeal taxa. The area of each branch is proportional to the total number of 16S rRNA sequences present in the database. Metabolic pathways were assigned based on physiological data (**Supplemental Table 2**). Sulfate reduction includes sulfite and thiosulfate reduction pathways. **Euryarcheata* are capable of bacteriorhodpsin-based photosynthesis only. Abbreviations: A, *Aquificae*; Alpha, *Alphaproteobacteria*; Beta, *Betaproteobacteria*; C, *Crenarchaeota*; Ch, *Chlorobi*; Cx, *Chloroflexi*; Cy, *Cyanobacteria*; Delta, *Deltaproteobacteria*; E, *Euryarchaeota*; Epsilon, *Epsilonproteobacteria*; Euk, *Eukarya*; F, *Firmicutes*; Gamma, *Gammaproteobacteria*; N, *Nitrospirae*; T, *Thermodesulfobacteria*.

Supplemental Material

iron-sulfur centers owing to an increased number of hydrogen bonds stabilizing the cluster's entatic state (65, 125). The ubiquitous right-handed fold around iron-sulfur centers across the tree of life emphasizes how mineral availability, mineral electronic structure (54), and contingency during selection of chiral amino acids played critical roles in shaping oxidoreductases. Ferredoxins and other iron-sulfur-containing proteins are found throughout life, both alone and as domains of larger enzymes (73, 101). The ferredoxin fold underwent gene duplication and variation leading to a wide set of iron-sulfur-containing oxidoreductases (108), such as iron hydrogenase, the evolution of which allowed microbes access to free hydrogen as a source of reductant (66).

Entatic state: a specific electronic state of an atom or group, defined by the surrounding protein environment

The ability to synthesize organic molecules from inorganic precursors was a critical invention in the early stages of the evolution of life and ultimately required redox reactions. Six pathways of carbon fixation are known (43). Although the Calvin-Benson-Bassam cycle is the most prominent in the extant biosphere (58), other pathways have long been studied because, among other things, they provide clues to understanding how carbon metabolism evolved (38). The last universal common ancestor may have used a combination of parts from different extant pathways (12), though it is possible the original pathway for carbon fixation no longer exists (98). The reductive

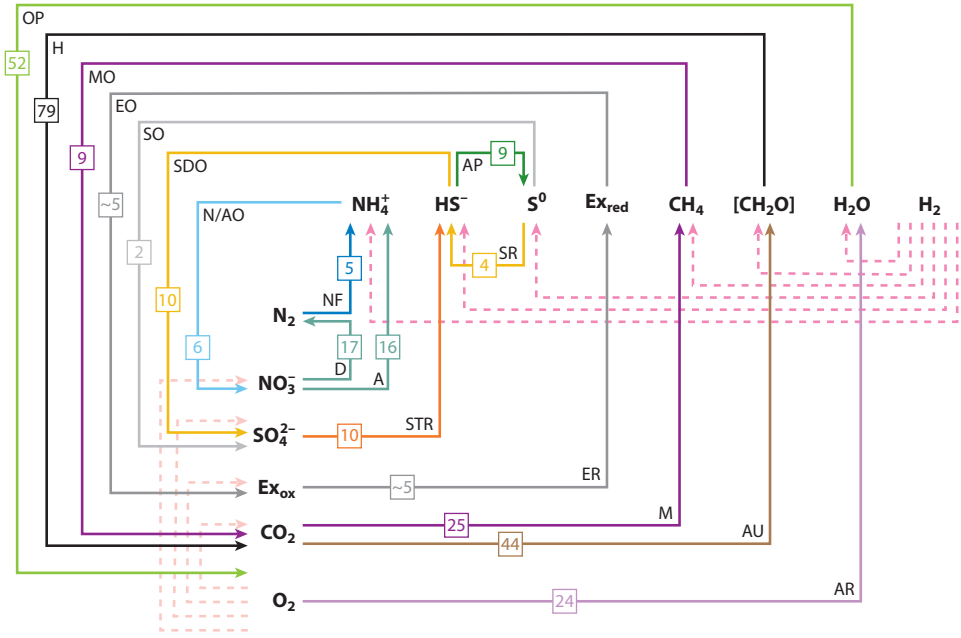


Figure 2

Earth's electron marketplace. Figure redrawn and adapted from Reference 34. The number in each box represents the number of EC1 homologs responsible for the redox reactions within the metabolism. Intracellular energy transduction EC1 homologs are omitted. The complete list of the 392 identified homologs is available in **Supplemental Table 1**. Arrows in the upper-left portion of the figure represent oxidative reactions, and arrows in the lower-right corner represent reductive reactions. Solid lines connect redox couples, as presented in **Figure 3*b***. Dashed lines represent participation of O_2 or H_2 (H^+) in the reaction. Abbreviations: A, ammonification; AP, anoxygenic photosynthesis; AR, aerobic respiration; AU, autotrophy; D, denitrification; Ex_{ox}, other elements oxidation; Ex_{red}, other elements reduction; H, heterotrophy; M, methanogenesis; MO, methane oxidation/methanotrophy; N/AO, nitrification/ammonia oxidation; NF, nitrogen fixation; OP, oxygenic photosynthesis; SDO, sulfide oxidation; SO, sulfur oxidation; SR, sulfur reduction; STR, sulfate reduction.

Supplemental Material

acetyl-CoA pathway [also known as the Wood-Ljungdahl (WL) pathway] (80, 106) is found in life's most deeply branching lineages, such as methanogens (43). Given its small energy requirements and its capacity to incorporate different one-carbon compounds and carbon monoxide of geothermal origin, this linear pathway potentially served as a primordial carbon fixation and energy metabolism pathway. The EC1 enzyme central to the WL pathway, the bifunctional carbon monoxide dehydrogenase/acetyl CoA synthase, and early nickel- or iron-containing hydrogenases all have active sites with structures bearing resemblance to the ready-made metal centers of minerals such as greigite, mackinawite, and millerite (114). As with ferredoxins, it is possible that in a prebiotic world, short peptides condensed from amino acids appropriated existing mineralogical (Fe,Ni)S catalytic activity to kick-start autotrophic pathways (127).

Bioinformatic network analyses suggest that ferredoxin-like Fe_2S_2 and Fe_4S_4 domains share great evolutionary connectivity to those binding hemes (most often containing an iron atom bound within a porphyrin ring) (50, 79). Hemes are used across the tree of life in the transfer of single electrons without undergoing protonation. Heme-containing molecules such as cytochromes are often interspersed between electron carriers that also undergo protonation, such as quinones. This results in a hopscotch-type pattern in which protons are ferried on one carrier and then ejected into a confined space while the electrons continue to be carried through the membrane to an

oxidant (i.e., the Q cycle) (124). By conserving energy derived from a vectoral flow of protons, life evolved to access energy released from the oxidation and reduction of a large variety of electron donor-acceptor pairs (110). The result is that virtually identical molecular motors transducing energy throughout the tree of life are flexibly fueled.

Moreover, in the course of early evolution, life became increasingly dependent on a more reliable source of energy—light. As hemes evolved, several sets of porphyrin derivatives emerged with large effective photon absorption cross sections. Among these are bacteriochlorophylls, phycobilins, and chlorophylls (46). Bacteriochlorophylls, in association with carotenoids, allowed for efficient collection of dilute solar energy and its conversion to chemical bond energy under anaerobic conditions. These molecules are distributed solely within the bacterial domain, where they are coupled to the reduction of inorganic carbon using a variety of electron donors, including hydrogen, hydrogen sulfide, organic matter, and ferrous iron. (Bacterio)chlorophylls themselves are modified tetrapyrroles with an extra ring (chlorins) and contain a covalently bound magnesium atom (86). Despite their structural complexity, bacteriochlorophylls are more deeply rooted than chlorophylls (135). In both iron-containing and magnesium-containing porphyrins and chlorins, photon-induced oxidation-reduction reactions do not lead to displacement of the metal center, meaning that they are not sacrificial but reversible and catalytic. The evolution of chlorophyll-protein complexes ultimately allowed access to water as a virtually limitless electron source, leading to formation of free oxygen gas as a waste product. Oxygenic photosynthesis, which evolved in a single bacterial clade, the *Cyanobacteria* (**Figure 1**), would ultimately result in almost complete oxidation of Earth's surface and profoundly transform the very mineral chemistry from which it evolved.

How life originally converted light to chemical energy is not known, but the solar excitation of certain minerals can drive electron transfer reactions far from thermodynamic equilibrium even without life (13, 15, 61, 87, 136). Photogeochemical, abiotic formation of high-energy chemical products is sacrificial rather than catalytic; however, these reactions potentially provided prebiotic substrates for the subsequent evolution of biological catalysis. For example, siderite ($FeCO_3$) was likely an abundant sedimentary mineral in shallow waters of the early Archean Eon, when soluble ferrous iron was available, oxygen concentrations were extremely low, and carbon dioxide concentrations were presumably very high. Exposure of siderite to ultraviolet radiation under anoxic conditions leads to the irreversible, photochemical oxidation of iron and the reduction of protons to form molecular hydrogen (67). The effective cross sections for the photochemical oxidation of siderite by ultraviolet radiation potentially supplied electrons for life in the Archean oceans at fluxes comparable to if not exceeding that from hydrothermal vents (67, 121). Significant steps in the reductive tricarboxylic acid cycle (one of the six extant carbon fixation pathways) have been carried out abiotically with photo-driven zinc sulfide catalysis (48, 136). These and other photogeochemical reactions involving minerals almost certainly played a significant role in fueling the earliest life-forms on Earth as well as foreshadowing the emergence of photosynthesis (92, 118).

The abilities to harvest chemical energy, to reduce inorganic carbon, and to access the continuous flux of solar energy reaching the planetary surface can be considered key tipping points in altering Earth's redox state and pushing the planet even further from thermodynamic equilibrium. Currently, microbes are still the major players in Earth's elemental cycling.

BIOGEOCHEMICAL CYCLES: MICROBIALLY MEDIATED REDOX REACTIONS AND THE GEOSPHERE

Although more than 25 elements can be found in biomolecules, 6 elements are most common (24, 117). These are carbon, hydrogen, nitrogen, oxygen, phosphorus, and sulfur, the so-called CHNOPS set of elements. Among these, phosphorus is the only element that exists primarily in

a single oxidation state under most biological conditions (102, 111). (The discovery that anaerobic microbes can produce reduced phosphorous as phosphine gas, and that phosphine is a global constituent of Earth's atmosphere, is prompting reconsideration of phosphorous biogeochemistry.) Considering biological redox reactions as a means of decoupling protons from electrons to generate the proton motive force necessary for energy transduction (i.e., generating ATP), all elements can be divided into two categories: carriers of both electrons and protons (hydrogen molecules) and carriers of only electrons. Of the major elements, carbon, nitrogen, oxygen, and sulfur (CNOS) are hydrogen carriers, with carbon and nitrogen higher in hydrogen density (i.e., methane and ammonia, respectively). In this context, all other redox elements of biological significance, such as selenium, arsenic, iron, and manganese, are electron carriers only and are minor players in the contemporary global electron marketplace (82, 94). Using redox chemistry, biology sequesters CNOS into reduced oxidation states for construction of organic macromolecules (70).

Whereas multicellular eukaryotes contribute to a small number of elemental cycles (e.g., organic carbon mineralization, photosynthesis), biogeochemical cycling of all other elements is largely under prokaryotic control (34, 99, 112, 126, 130, 131). The extremely high abundance of microorganisms on Earth (most recent estimates suggest a total of between 9 and 31×10^{29} cells) (62) highlights their quantitative importance in influencing the biogeochemical cycling of elements. Microbes (including eukaryotic algae) are responsible for up to 45% of carbon fixation [and, hence, oxygen inputs to the atmosphere (40)] and about 95% of its consumption during the remineralization of organic matter (68). They are also responsible for approximately (68) 50% of nitrous oxide (42, 85) and between 26 and 30% of methane (71) emissions.

A detailed overview of single biogeochemical cycles is beyond the scope of this review (see 19, 33, 43, 47, 58, 71); however, a better understanding of the emergence and function of the electron marketplace as a whole is required to understand the direction and magnitude of ongoing changes (4, 28). Although single cycles are often described in separate models, microorganisms have evolved to couple specific cycles of CHNOS within their energy transduction schemes (**Figure 2**). For example, the oxidation of reduced sulfur species (e.g., sulfide, thiosulfate, elemental sulfur) is often coupled with the respiration (reduction) of oxygen or nitrate. The resulting energy obtained from these reactions is used to fix carbon dioxide within the same organism. The coupling of different CHNOS half-cells within an organism effectively interconnects the major biogeochemical cycles across time and space. This intimate connection between separate cycles can also be seen at the ecosystem level, with processes like denitrification able to limit the carbon cycle on large scales (35, 45, 49). The individual species responsible for these reactions are largely irrelevant—as long as the metabolic processes are transferred across geologic time (34).

As discussed, a set of bacteriochlorophylls, phycobilins, and chlorophylls evolved from hemes, allowing life to access the Sun as a practically unlimited energy source. The first phototrophs were anoxygenic, similar to those found in today's anaerobic photic zones. Anoxygenic phototrophs transfer electrons from ferrous iron, hydrogen, or hydrogen sulfide to either type I (iron-sulfur center) or type II (pheophytin/quinone complexes) reaction centers (e.g., green sulfur bacteria or purple bacteria, respectively) (8). The requirement for exhaustible electron donors, however, sets a metabolic limit on these autotrophs and their ability to fix carbon. The emergence of oxygenic photosynthesis, lifting limits on electron supply, is incompletely understood (9), but the ability to access a surfeit of electrons from unlimited water greatly boosted the energy available to phototrophs. The active site responsible for oxidizing water and releasing oxygen, the so-called water-oxidizing complex, is composed of a unique tetramanganese complex, held in a specific orientation by the D1 protein of photosystem II. Phylogenies of cyanobacterial D1 sequences suggest that the water-oxidizing complex evolved from an anoxygenic type II photosystem (21). The only extant prokaryotic phylum capable of oxygenic photosynthesis (**Figure 1**), the *Cyanobacteria*,

express both type I and type II reaction centers. There are two major competing hypotheses for how both types of reaction centers were acquired by *Cyanobacteria*: (*a*) they evolved independently and subsequently were incorporated into one organism via horizontal gene transfer (HGT); or (*b*) they evolved in parallel in one organism via gene duplication followed by mutation and selection (8). All photosynthetic eukaryotes share a common cyanobacterial ancestor acquired by endosymbiotic engulfment that resulted in the formation of plastids (7, 9). The evolution of oxygenic photosynthesis and the transfer of its molecular machinery to eukaryotes massively enhanced the primary productivity of the planet (20).

Great Oxidation Event (GOE): the first significant rise of atmospheric oxygen, resulting from cyanobacterial splitting of water and burial of organic carbon; about 2.4 Ga

Craton: a large, stable block of Earth's crust forming the nucleus of a continent

LIFE'S COEVOLUTION WITH ENVIRONMENTAL REDOX STATE

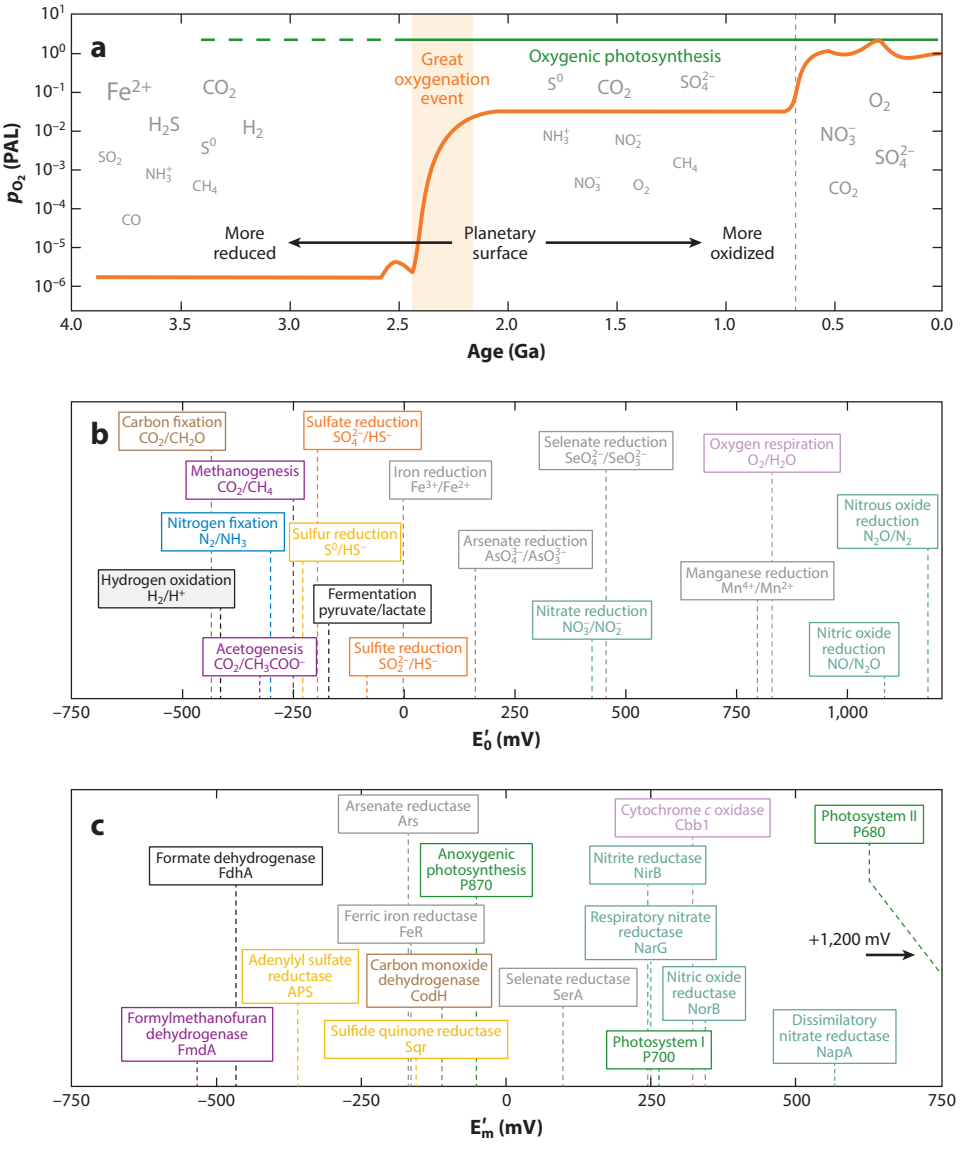
The intimate connection between the biosphere and geosphere can be inferred from geochemical proxies and physical fossils over the history of Earth (27) (**Figure 3*a***). The most intensively studied change occurred between 2.3 and 2.4 Ga and is called (somewhat euphemistically) the Great Oxidation Event (GOE) (17, 39, 55, 83). The oxidation of Earth's atmosphere is itself a consequence of the coordination of biologic and geologic processes (18, 36). Oxygenic photosynthesis appears to have evolved only once in prokaryotes (**Figure 1**) and led to the formation of molecular oxygen as a waste product. This process was necessary but not sufficient to lead to net accumulation of oxygen in Earth's atmosphere. On geologic time scales, net accumulation of oxygen in the atmosphere and ocean can only be achieved by the burial of organic matter (i.e., the global half-cell reductant) in the lithosphere and its sequestration by tectonic activity, either on cratons or deep into the mantle by subduction (where it is not reachable by heterotrophs) (18, 36, 84).

Life occupies a large range of environmental redox states, reflected in the >1.6-V range in midpoint potentials of the oxidoreductases (**Figure 3*c***). A Winogradsky column classically demonstrates how metabolisms can be coupled in a relatively small spatial scale across this range in potentials. The anaerobic organisms at the bottom of the column derive energy from the redox pairs available to fix carbon chemoautotrophically. To accomplish this, their enzyme cofactors possess appropriately low midpoint potentials to oxidize hydrogen and reduce low-potential substrates such as SO_4^{2-}. The facultative or aerobic organisms living above the anaerobes in the column occupy an increasingly oxidized environment. The cofactors at active sites of their redox

Figure 3

Coevolution of geosphere and biosphere through time as depicted by change in planetary redox state, availability of redox couples, and midpoint potential of EC1 enzymes. (*a*) Rise of Earth's oceanic oxygen, throughout Earth's history. Modified from Reference 83. The two main oxygenation events are presented together with the availability of relevant electron donors and acceptors (size proportional to the inferred availability; 1). (*b*) Standard reduction potential at pH 7 (E'_0) of biologically relevant redox pairs. Redox half-reactions represent the reductive side (i.e., terminal electron acceptor) of given pathways. Hydrogen oxidation represents the only exception given as reference. (*c*) Midpoint potential (E'_m) of key EC1 enzymes involved in selected energy metabolism pathways presented in panel *b*. The midpoint potential of the catalytic redox center is reported. The initial accumulation of oxygen following the Great Oxidation Event appears to have been relatively modest, perhaps leading to only 1% of the atmospheric volume or less (panel *a*), but it was sufficient to oxidize many transition metals on the surface of the planet (2, 132). A second, larger rise of oxygen that occurred circa 750 Mya (18, 37, 109) attributed to the rise to ecological prominence of eukaryotic algae (72), which are larger and sink faster than cyanobacteria. The subsequent burial of carbon fixed by eukaryotic algae brought oxygen closer to its present atmospheric level (77, 83), facilitating creation of further oxidized mineral species. As a consequence, approximately 2,800 new mineral species were formed, making biological processes responsible for a majority of the 5,000 mineral species estimated on the planet today (53) (**http://rruff.info/ima**).

enzymes show increasingly higher midpoint potentials, necessary to reduce, for example, NO_3^- (**Figure 3*c***). At these active sites, enzymes rely on bound transition metals (i.e., Fe, Ni, Mn, Co, Mo, W, Cu, V) or other cofactors like NAD or FAD that can readily switch between oxidation states at physiological pH ranges. The electrons are guided through protein structures via cofactors by outer-sphere electron transfer (24). Cofactors have been selected for based on, among other things, their redox properties. Iron, for example, provides access to low reduction potentials, with examples in the iron-binding active sites of hydrogenases, the enzymes oxidizing one of the strongest environmental reductants, H_2. Hemes, owing in part to their delocalized π-bonds, can reach higher potentials. Finally, Cu gives access to relatively high midpoint potentials, like



that in cytochrome *c* oxidase, reducing one of the strongest biologically accessible environmental oxidants, oxygen (22, 78).

E′m: standard midpoint potential (group is half reduced, half oxidized) at pH 7.0

α helix, β sheet, and loops: elements of protein secondary structure; local repetitive conformations of peptide chains

An electron transfer pathway is most efficient with cofactors in the pathway ordered by redox potential (24), with centers approximately 14 Å apart (100)—both highly conserved structural features of EC1 enzymes. Cofactors generally coordinate with specific ligands, allowing a fine-tuning of their native redox potentials (57). The redox tuning is strongly related to the protein environment (23) and is generally accomplished by one of three broad mechanisms. The first is by controlling degree of solvent exposure; burying a redox center into a hydrophobic protein center will increase its reduction potential. The second is by adjusting the electrostatic environment of the center. For example, the addition or removal of nearby polar or charged amino acids can vary potentials by 100 to 200 mV (78). Lastly, the hydrogen bonding networks around metal center ligands can also affect the redox potential and have been shown to be primarily responsible for the differences in ferredoxin, rubredoxin, and HiPIP (high potential iron proteins) reduction potentials.

Midpoint potentials (E′m) for Fe bound by different proteins range from −500 to +400 mV (89), providing a large range in redox functionality (41). A recent analysis of the secondary structure directly surrounding metal centers in EC1 structures (i.e., their tuning environment) illustrated an evolutionary transition from centers with high loop character (implying higher rates of evolution and low catalytic specificity) to centers with either distinct α-helix or distinct β-sheet character, bestowing high catalytic efficiency (high substrate specificity) at the expense of evolvability and locking these enzymes into their current form (14, 66). Nitrogenases, sulfite, and nitrite reductases exemplify relatively promiscuous enzymes in terms of substrate specificity, implicating them as more evolvable and ancient. Perhaps paradoxically, phylogenetic analysis suggests the molybdenum-containing form of nitrogenase appears to be ancestral to the iron or vanadium versions, despite the presumed relatively low availability of molybdenum in the Archean ocean (11). It is worth noting that tungsten may have substituted for molybdenum in ancestral enzymes, and cambialistic molybdenum/tungsten enzymes are found in contemporary hyperthermophiles. A pre-GOE nitrogenase may well have been driven by an early nitrogen limitation, exemplifying the intimate evolutionary relationships between the geosphere and biosphere (45). An illustration of the relationship between oceanic redox state, availability of redox couples, and the progression of metal center midpoint potentials is given in **Figure 3**.

The oxidation state of the oceans has had profound effects on transition metal availability. Transition metals containing minerals come in two main "flavors" at Earth's surface: sulfides and oxides. Under mildly reducing conditions, iron, for example, primarily occurs as soluble ferrous iron. It is estimated that in the oceans of the Archean Eon, soluble, ferrous iron ion concentrations were several micromoles per liter (1). Following the GOE, ferrous iron became oxidized to insoluble ferric iron and precipitated as virtual ferric hydroxides (rust). Similarly, manganese was extremely soluble as a divalent ion (Mn^{2+}) under reducing conditions and precipitated as manganese oxides following the GOE (115). In contrast, copper and molybdenum were relatively insoluble under reducing conditions and would have been found as sulfide mineral deposits in marine sediments. Upon oxidation of the ocean, these two would become mobilized as soluble ions, and the metals would become increasingly available for biological reactions. For example, in the contemporary ocean, vertical profiles of molybdenum are virtually invariant with depth, and this element does not limit any known biological reaction in the modern oceans. The change in the oxidation state of the oceans contributed to a change in the selection of metals incorporated into the active sites of oxidoreductases. Thus, the second most abundant metal found in EC1 proteins is copper. Proteins containing copper generally have high midpoint potentials (78) and often are involved in electron transfers with molecular oxygen.

Proteome analyses have revealed a fundamental evolutionary constant, that the number of metal-binding proteins within a proteome scales with proteome size (30). Given a relatively constant proteome size across the tree of life (within an order of magnitude), the selection of a different metal often leads to tradeoff of an existing metal. This evolutionary selection system has allowed each superkingdom's use of Fe, Mn, Zn, and Co to evolve and corresponds to the metals' bioavailabilities in the chemical environments at the time of their origin (30). When manganese and copper became available as a result of increased oxidative weathering, folds evolved to bind these elements, driven by availability as well as selective pressure from an increasingly oxidizing environment. As organisms evolved in increasingly higher redox potential environments, folds that incorporated the Cu-binding domain of cytochrome *c* oxidase emerged, with the more reducing folds, once required by the reducing Archean environment, lost from the sequences encoded in their genomes. It is becoming increasingly compelling to geochemists and microbial biologists not only that biology has caused global redox trends (18, 34) and expanded mineral evolution (53), but also that the evolution of microbial genomes has responded to these trends through changes in the number and identity of metal-binding folds (30).

Proteome: the entire set of proteins expressed by a genome at a particular time

Gene homologs: genes with a common ancestor

During the GOE, change was brought to much of the planet's anaerobic life in the form of oxygen, poisonous to metal centers, especially iron, in many anaerobic enzymes. Branches of life unable to evolve were forced to retreat into anoxic environments, in deep sediments and near ocean vents (60). Although some of the evidence and specific mechanisms leading to the GOE are still debated (3, 16, 29, 63), sequestration of reduced carbon into the lithosphere uncoupled oxidative and reductive pathways, resulting in accumulation of oxidants (primarily oxygen, nitrate, and sulfate) at the planetary surface (**Figure 3*b***), prompting the emergence of still higher midpoint potentials for catalytic centers like nitrate reductase and cytochrome *c* reductase (**Figure 3*c***) (22). These molecules, accessing high-energy reactions made possible by free oxygen, significantly altered the landscape of biological metabolism (107).

OXIDOREDUCTASES AND THE TREE OF LIFE: A DIVERSIFIED INVESTMENT

The molecular machines that capture energy from the Sun, from redox gradients, or from consuming organic matter (phototrophy, chemotrophy, and heterotrophy) all share homologous components, using electron transfer chains built from appropriately poised redox enzymes (66). The energy for life is transduced exclusively from electron flow (74), catalyzed by a small set of EC1 proteins operating far from thermodynamic equilibrium, ultimately creating a vectoral flux of protons coupled to the formation of ATP (38). (A proton flux is not required for the generation of ATP during substrate-level phosphorylation reactions in fermentative pathways, but ultimately these pathways depend on previously fixed organic carbon.) In every organism, electrons stripped from the geosphere at a high energy (or excited to a higher energy by light), are used to power intracellular processes and then either deposited back to the geosphere or incorporated into organic molecules (75, 123).

Contemporary oxidoreductases have had billions of years to evolve and radiate across multiple lineages, often via HGT. The age and mode of evolution often obscure the origin of individual proteins. However, even distantly related genes have been required to conserve aspects of protein structure and function through geological time (59, 119). Considering only genes encoding EC1 proteins, it becomes clear that a small number of highly conserved geometries and cofactors have been selected as life's redox catalysts. We estimate that only about 400 gene homologs are part of complexes directly participating in electron transfer for energy metabolism (**Figure 2**; **Supplemental Table 1**). Despite the extraordinary diversity of life, the core machines responsible for

Supplemental Material

energy metabolism are of a strikingly small set. One reason for this parsimony was described by Dayhoff & Eck (26) decades ago in a paper discussing the evolution of the structure of ferredoxin: "We explain the persistence of living relics of this primordial structure by invoking a conservative principle in evolutionary biochemistry: The process of natural selection severely inhibits any change in a well-adapted system on which several other components depend." Owing to the interaction of other enzymes with ferredoxin, iron-sulfur clusters are central to biology, irreplaceable even if iron is often a limiting nutrient (41). (There are some organisms that do not require iron, such as the causative agent of Lyme disease, *Borrelia burgdorferi*, and certain strains of *Lactobacillus*.)

Once evolved, genes for an entire metabolic pathway can spread readily, even between the domains *Bacteria* and *Archaea* (95). Acquisition between lineages is primarily via HGT (5), with genome analyses pointing to prolific early gene sharing (25). For example, genes for sulfite reduction are well distributed through *Bacteria* and *Archaea*, while there is strong support for their monophyletic origin (69). The core genes for Earth's redox network are spread across multiple microbial lineages (**Figure 1**), revealing life's investment in oxidoreductases as highly diversified. Individual organisms certainly die, and branches on the tree of life go extinct. However, even during the worst of environmental collapse, instructions for catalyzing proton-coupled electron flow between diverse substrates are robustly conserved, ready to reexpand as conditions allow. There are interesting exceptions to this pattern, with some pathways for energy metabolism more evenly distributed than others. For example, whereas glycolysis can be found in all three domains of life, nitrification and nitrogen fixation (11) are not found in eukaryotes. Methanogenesis is so far confined to the *Euryarchaeota*, a phylum of *Archaea* (although recent environmental genome reconstructions suggest the potential for methanogenesis in other uncultured archaeal groups; 32). The reasons for these limitations are not well understood. It may be that complex metabolic pathways built on a large number of genes are difficult to transfer in bulk unless via endosymbiosis (10). Eukaryotic life, the most morphologically diverse and complex, is built upon redundant biochemistry (heterotrophy and oxygenic phototrophy) completely inherited from prokaryotes. Owing to this very limited metabolic capability, eukaryotes are ultimately dependent on the prokaryotic metabolic pathways for (among other things) key nutrients and recycling of wastes.

CONCLUSIONS

The progressive oxidation of Earth's surface is analogous to the ordered layers of metabolism in a Winogradsky column. In effect, the latter is a spatially organized structure that represents the sequential evolution of microbial metabolism and, in effect, recapitulates geochemical oxidation states over Earth's history. The layered properties of a Winogradsky column are emergent; that is, the microbes self-organize along a redox gradient that they create, the metabolism of each group of organisms coupled within the column via gas exchange, based on the gases of CHNOS. Whereas this coupling occurs on a local scale over months in a Winogradsky column, it also occurs on a global scale over geologic time. In both cases, the reactions are far from thermodynamic equilibrium and are ultimately powered by solar energy.

The presence in every organism of a half-cell redox reaction as part of this balanced, yet decoupled scheme (**Figure 2**) (34) has ultimately pushed and effectively sustained Earth far from thermodynamic equilibrium. The function-bearing 3D structures responsible for catalyzing redox reactions have evolved to transduce energy from the Sun (as well as geothermal sources) and, via a highly replicative biological framework, now cover practically the entire surface of Earth, the only planet that we know of with an atmosphere so far from thermodynamic equilibrium. Microbes, generating gases such as methane, nitrous oxide, nitric oxide, and oxygen, have had a significant impact on atmospheric composition, setting the scene for complex multicellular evolution. Many

of these gases have infrared absorption spectra that make them potential targets for remotely sensing the potential of life on extrasolar planets (6). Better separation of contingency's role in development of Earth's redox network from the inevitable outcomes based on appropriate conditions will factor into the statistics and stages of life existing elsewhere (64, 90, 93, 97, 134).

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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