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The Elements of Life: A Biocentric Tour of the Periodic Table

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Abstract

Living systems are built from a small subset of the atomic elements, including the bulk macronutrients (C,H,N,O,P,S) and ions (Mg,K,Na,Ca) together with a small but variable set of trace elements (micronutrients). Here, we provide a global survey of how chemical elements contribute to life. We define five classes of elements: those that are (i) essential for all life, (ii) essential for many organisms in all three domains of life, (iii) essential or beneficial for many organisms in at least one domain, (iv) beneficial to at least some species, and (v) of no known beneficial use. The ability of cells to sustain life when individual elements are absent or limiting relies on complex physiological and evolutionary mechanisms (elemental economy). This survey of elemental use across the tree of life is encapsulated in a web-based, interactive periodic table that summarizes the roles chemical elements in biology and highlights corresponding mechanisms of elemental economy.

Keywords

elements; macronutrients; micronutrients; metallomics; periodic table

1. Elemental Requirements for Life

Life requires only a selected subset of the atomic elements. The major macromolecules of the cell account for the bulk of life's mass and are composed almost entirely of six elements (C,H,N,O,P, and S; abbreviated as CHNOPS). These macromolecules include the DNA genome, RNA as genetic messenger (mRNA) and for protein synthesis (rRNA, tRNA) and regulation, and proteins. Polysaccharides function in carbon storage (e.g. glycogen), in cell surface structures, in exoskeletons (e.g. chitin), and as the major structural constituent in woody plants (cellulose). The cell is defined by a lipid membrane, commonly a phospholipid bilayer, that is studded with essential transport and signaling proteins. Within the cell, life processes are a manifestation of carefully constrained chemistry. Enzymes play the key role as catalysts by degrading nutrients to provide energy (catabolism) and in assembly of cell constituents (anabolism). Globally, enzymes mediate the most important reactions in the biogeochemical cycling of elements, including the life-sustaining processes of carbon fixation through photosynthesis and nitrogen fixation from atmospheric dinitrogen gas.

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While CHNOPS provide the foundation for life, these six elements are by no means sufficient; other elements are required to provide cofactors for catalysis and an appropriate chemical environment for cell function.

We here present a current perspective on the biological roles, if any, of each chemical element. We consider elements from the lightest (hydrogen, $_{1}$H) to the heaviest (uranium, $_{92}$U) that occur naturally on Earth, with a focus on those with either essential or beneficial roles. Elements will be referenced by symbols, with a subscript to indicate atomic number when first introduced (for simplicity, oxidation states are specified only when necessary). A current summary of the biological utility of each element can be mapped onto the periodic table <Figure 1>. We assign each element into one of five classes: (i) essential for all life, (ii) essential for many organisms in all three domains of life, (iii) essential or beneficial for many organisms in at least one domain, (iv) beneficial (and rarely, essential) to at least some species, and (v) of no known beneficial use. A summary of the key roles of each element in biology, as well as notable mechanisms of elemental sparing, is presented in a supplemental web resource (https://elementaleconomics.wixsite.com/website, see section 10.5).

Our element-by-element tour through the periodic table begins with the major macronutrients (CHNOPS) and then proceeds (from left to right) from group 1 (alkali metals) through 17 (halogens). Within each group, elements are considered in order of increasing atomic number rather than biological importance. The group 18 elements (noble gases) are non-reactive and not biologically important.

We conclude with efforts to define a common core of essential elements (required for all life). Even complex life forms such as animals and plants have a modest number of essential elements, with best estimates of 20 for humans and 17 for plants. Microbes get by with even fewer. This overview is by necessity superficial and seeks to emphasize those advances that have occurred in recent years. Foundational ideas can be found in the important monograph *The biological chemistry of the elements: the inorganic chemistry of life* (Fraústo da Silva & Williams, 2001). We also build on concepts of elemental economy, the ability of organisms to adapt to limitation for one element by re-routing metabolism through alternative pathways or enzymes, as reviewed previously in this series (Merchant & Helmann, 2012). This is a vast topic and touches on areas as diverse as microbiology, cell biology, biochemistry, biogeochemistry, marine sciences, agriculture, plant sciences, astrobiology, and human nutrition.

1.1 Macronutrients, Micronutrients, and Trace Elements

Life relies on a variable subset of chemical elements, and the roles of many elements (if any) are still unknown. As educators (and parents) will appreciate, the simplest questions often are the hardest to answer. Of note, we are not yet able to confidently answer the question: *What is the minimum set of elements essential to sustain life?* An important corollary is: *Which elements have a beneficial role in biology, and which are either ignored, only adventitiously accumulated, or consistently deleterious*? We approach these questions with a broad purview that embraces all three domains of life: Bacteria, Archaea, and Eukarya. The elements required to sustain microbial life will of course vary depending on the nutrients available in the environment. For organisms that harbor symbionts or

commensal partners, the elemental requirements for growth may be considered also at the level of the host together with its microbial partners (the holobiont) (Postler & Ghosh, 2017; Vandenkoornhuyse et al., 2015). Finally, the elemental requirements for a healthy ecosystem will encompass the needs of diverse organisms at different trophic levels. Here, for simplicity, we will focus on individual organisms, both microbial and multicellular.

There is consensus on the core macronutrients that are required for all known life on Earth. Six macronutrients (CHNOPS) account for >99% of all elements in the human body (Fraústo_da_Silva & Williams, 2001). Life also requires other elements, many of which function as ions. These may be relatively abundant in cells (e.g. K, Mg) or present at lower levels, leading to their designation as micronutrients or trace elements. The trace elements include several transition metals, but the actual set required for life varies. Some elements accumulate adventitiously, whereas others are actively imported, which is suggestive of a beneficial role. Importantly, even in the best studied organisms, the precise set of essential and beneficial elements is still debated.

The selection of life's elements from those present on the surface of Earth has been much debated but likely reflects three main parameters. First, relative *abundance* must be considered: life evolved to take advantage of those elements that were readily available in the environment. While the elemental composition of the many habitats on Earth varies, as a proxy for overall abundance we consider typical levels found in the oceans and in Earth's continental crust <Figure 2>. The transition elements of greatest utility to life are those that are both abundant in the crust and mobilized into the aqueous phase readily, as judged by their concentration in seawater divided by that in the lithosphere (Nies, 2022a). Second, elements were selected for their *utility,* either in the formation or stabilization of complex molecular structures or their ability to promote chemical reactions. Third, elements were selected for their *compatibility* with the chemical milieu of the cytosol: those elements that interfere with biological processes were rejected by the earliest cells and are often actively exported.

1.2. The Challenge of Defining Essential Elements

We use the term *essential* for those elements that are required for growth and viability of an organism under all known conditions. In microbial systems, efforts to define essential elements benefit from an ability to grow cells in chemically defined medium. However, the ultimate criterion to exclude a biological role is to demonstrate growth with less than 1 atom per cell of any given element. This represents a formidable technical challenge that has rarely been met. Moreover, elements may be *conditionally essential*: required under some growth conditions but not others. This includes sets of elements that are redundant.

Functional redundancy is most common for micronutrients, including many metal ions, where deficiency of one element may be compensated by substitution with another (Merchant & Helmann, 2012). This is often mediated by expression of an alternative enzyme with a distinct metal cofactor preference. More rarely, enzymes may be able to function with more than one metal cofactor. As one notable example, the ancient antioxidant enzyme superoxide dismutase (SOD) may have originally functioned with either Fe or Mn as cofactor (Valenti et al., 2022). Enzymes that function with both metals (termed

cambialistic) are still present in several bacterial species, but most members of the Fe/Mn-SOD family are specific for one or the other metal (Frye et al., 2022). The ability of one element to substitute for another can result in a phenomenon ecologists term colimitation, a condition in which the addition of any of a set of nutrients can increase growth (Saito et al., 2008). Generally, defining essentiality for the chemical elements shares some of the same conceptual challenges as efforts to define the minimal genome: genes may be essential, conditionally essential, or appear dispensable despite encoding essential functions due to genetic redundancy (Reuss et al., 2016; Tarnopol et al., 2019).

The universally essential elements in class (i) are intimately tied to cell physiology. In addition, multicellular organisms may require additional elements for specific roles in organismal rather than cellular physiology (one notable example is iodine (I) in human physiology). Finally, some elements may be important at an ecosystem level in support of biogeochemical processes that sustain life on Earth, even if they are not essential for some individual species. For example, many nitrogen-fixing Bacteria (*diazotrophs*) rely on molybdenum (Mo) as an essential cofactor for nitrogenase, which is therefore important both for those specific organisms, and also for the ecosystem as whole.

1.3 General Strategies of Elemental Economy

Limitation of cells for an element may be compensated by reducing demand. For example, cells may suppress the synthesis of cellular constituents rich in the limiting element or replace one element with another. These mechanisms may be conditionally expressed in a process termed *acclimation*. For example, organisms may encode two related enzymes that differ in their required metal cofactor, with the alternative enzyme induced when the cofactor for the dominant element is absent. Alternatively, organisms may have *adaptations* that are genetically encoded to facilitate their survival in environments chronically depleted of specific elements. For example, phytoplankton from oceanic regions chronically deficient in P have replaced most of their membrane phospholipids with sulfolipids (Van Mooy et al., 2009). These mechanisms confer “elemental economy” (Merchant & Helmann, 2012).

1.4 Early Earth and cell composition

Earth has been endowed with a complete set of stable elements, as literally “written in stone” during our planet’s formation from the solar nebula (~4.6 x 10^9 years ago; 4.6 giga-annum or Ga). During the earliest geologic eon (the Hadean), Earth contained a chemically complex lithosphere (our planet’s thin, fragile, and mobile crust) and ample surface water but was devoid of life. When microbial life evolved on Earth over 3.5 Ga our planet had an atmosphere vastly different from the present day. During the Archean eon (~4 to 2.5 Ga) the atmosphere had an abundance of carbon dioxide (CO_2), methane (CH_4), and nitrogen gas (N_2) and was anoxic (lacking molecular oxygen, O_2) (Catling & Zahnle, 2020). The origins of the earliest-evolving cells are shrouded in mystery, but they likely developed a biochemistry reflective of elemental availability at that time, including the presence of FeS and other minerals with catalytic potential. Many consider contemporary Bacteria and Archaea to be the earliest evolving lineages, but alternative scenarios are also debated (Danchin; Harish et al., 2013; Mariscal & Doolittle, 2015). In the anoxic oceans of the early Archean, the level of dissolved Ni and Fe was vastly greater than in current, O_2-rich

surface waters, whereas Cu and Zn levels were significantly reduced by the precipitation of insoluble sulfide complexes (Moore et al., 2017). This, in turn, has led to different preferred metal cofactors in early evolving Bacteria and Archaea (greater use of Fe,Ni,Co) compared to many later evolving Eukarya (greater use of Cu and Zn) (Dupont et al., 2006; Moore et al., 2017).

The single greatest change in Earth's chemistry resulted from the evolution of oxygenic photosynthesis. The great oxidation event (GOE) has been dated to 2.4 Ga and led to a $>10^4$-fold increase in atmospheric O_2 from $<10^{-5}$ of present atmospheric level (PAL=21%) in the Archean atmosphere to levels near 0.1 PAL. The GOE resulted from the evolution in cyanobacteria (~ 2.7 Ga) of a novel form of photosynthesis that used electrons from water as a reductant for fixing CO_2 into organic matter (Sanchez-Baracaldo et al., 2022). Oxygenic photosynthesis releases oxygen gas (O_2) as a waste product. After a delay of at least 300 million years, excess O_2 began accumulating in the atmosphere, leading to the GOE of ~2.4 Ga. This prolonged delay is thought to be due to chemical inertia: for many millions of years O_2 was consumed as fast as it was produced. This consumption was due to in part to oxidation of dissolved ferrous Fe in ancient oceans to insoluble ferric oxides visible now in sedimentary rocks as thick banded iron deposits. In addition, O_2 released to the atmosphere was consumed by photochemical reaction with methane (Goldblatt et al., 2006). One possible driving factor that contributed to increased O_2 accumulation at the time of the GOE is a depletion of oceanic nickel (Ni), an abundant element in the Archean ocean that functions as an essential cofactor in methane-generating microorganisms (Konhauser et al., 2009). The resulting Ni famine, likely resulting from a reduction in Ni release from the mantle, may have limited methanogenesis, decreased atmospheric methane, and favored O_2 accumulation (Konhauser et al., 2009; Saito, 2009). Clearly, the GOE was not an "event" in the common understanding of the word and is instead a process that played out over many millions of years. The English language lacks good descriptors for such slow processes: even "glacial pace" suggests an unrealistic rapidity in this context!

Even after the GOE, atmospheric O_2 levels were low by contemporary standards and likely fluctuated around ~1% of current levels during much of the Proterozoic eon (2.5 to ~0.8 Ga). This low level of O_2 was sufficient to support the evolution of aerobic respiration in a subset of then extant Bacterial and Archaeal lineages (Brochier-Armanet et al., 2008; Soo et al., 2017). The Eukarya arose during this time (~1.2 and 1.8 Ga), although earlier arising (now extinct) Eukaryal lineages are possible (Cohen & Kodner, 2022; Porter, 2020). The later origin of multicellular plants and animals (~0.6 Ga) is much better understood since it is recorded in the fossil record. Aerobic respiration is a defining feature for nearly all Eukarya, including plants and animals (Fischer, 2016; Zhang et al., 2016). Geologic evidence suggests that there were repeated periods of relative anoxia during the Proterozoic (Reinhard & Planavsky, 2022): a stable, O_2-rich atmosphere similar to that present today (~21%) did not arise until after the Earth's land surfaces were widely colonized by vascular plants during the Devonian period some ~0.4 Ga (Reinhard & Planavsky, 2022).

2. Elemental Economy and Life's Macronutrients (CHNOPS)

All life requires six macronutrients (CHNOPS) as the major building blocks (class (i) elements). We begin by considering these six universally required macronutrients and some of the better understood mechanisms that allow cells to acclimate or adapt to elemental limitation. A summary of class (i) and class (ii) elements is presented in <Table 1>.

2.1 Hydrogen ($_1$H) and Oxygen ($_8$O)

Life evolved in water (H_2O), and cells are mostly water. H is the most abundant element in the universe, and O, formed in early generations of stars, is the third most abundant (a distant third, after $_2$He). Water itself is a primordial compound, and likely one of the most abundant molecules in the universe (Frenkel-Pinter et al., 2021). Water was abundant in the accretion disk that led to our solar system. Earth has a favored environment that allows water to be abundant in all three physical states: solid, liquid, and gas.

We cannot consider the role of H and O in biology without first considering water. The properties of water are unusual for a molecule of its size, with strong H-bonding that allows H_2O to maintain a liquid state over a wide-range of temperatures. These and other properties contribute to the unique role (as far as is known) of water as "an active matrix" that serves as both a solvent for and a participant in life's processes (Ball, 2017; Frenkel-Pinter et al., 2021). *Escherichia coli* (as a model for the Bacteria) and *Saccharomyces cerevisiae* (representing the Eukarya) both contain ~65-75% water by weight (Milo et al., 2010). Water is incorporated in molecules by both hydrolysis and hydration reactions and is generated as a product during dehydration-based syntheses. Studies in *E. coli* have suggested that as much as 70% of cytosolic H_2O is a product of metabolism (Kreuzer-Martin et al., 2005). Flux calculations for *E. coli* growing aerobically on glucose conclude that 15.7% of cell water derives from reduction of O_2 (Frenkel-Pinter et al., 2021). The vast majority of cell metabolism involves water as reactant or product, and the average water molecule in the cell is chemically transformed ~3 to 4 times during each cell cycle (Frenkel-Pinter et al., 2021). These calculations refute any notion of water as a largely passive solvent for life's processes. The reversible chemical consumption of water by hydration reactions is not only a feature of biological systems, but of Earth's geology. Water reacts with CO_2 to generate carbonic acid in the hydrosphere, and water bound in hydrated minerals in the lithosphere can be released by metamorphic dehydration during subduction of the continental crust (Brovarone et al., 2020). Indeed, the total amount of water inside the Earth (in the crust and mantle layers) is likely to be greater than that on the surface (Genda, 2016; Spiga et al., 2019).

Access to water is crucial for sustaining life. In environments with little available water the amount of biomass that can be sustained is very limited and growth is slow. Areas of the Earth with limited or very low water availability are classified as deserts. The Atacama Desert in Chile, in the rain shadow of the Andes mountains, is an extreme example and considered one of the most arid regions on Earth. Even here, microbial life is ubiquitous (approaching 10^6 cells per gm of soil). Desert microbiomes are often dominated by cyanobacteria and actinomycetes and are host to legions of yet to be cultivated organisms (Azua-Bustos et al., 2012; Bull et al., 2016). One adaptation to this hostile environment is for photosynthetic Bacteria to colonize spaces within rocks and to access water adsorbed

from the atmosphere, a process called deliquescence (Gómez-Silva, 2018; Wierzchos et al., 2006). Limiting access to water can also prevent food spoilage: dried foods and sugar-rich concentrates such as honey and maple syrup have low available water that impedes microbial growth (Lievens et al., 2015).

Considering the ubiquitous presence of water in living systems, cells have ready access to both H and O. Note that here we are focused on the elements; H and O also form diatomic gases that are important for many cells. For example, O_2 is required for organisms from all three domains of life that generate energy by aerobic respiration, and H_2 is important for Archaea that reduce CO_2 to methane (methanogens) (Gregory et al., 2019). Both H and O are ubiquitous constituents of the organic molecules and macromolecules of life, and these elements are often (not always) derived from water.

Although our atmosphere has not always been rich in O_2 gas, there is no shortage of O on Earth. Indeed, O is the second most abundant element (after Fe) in the overall chemical composition of our planet and at ~46% by mass is the single most abundant element in the continental crust (Figure 2) (Haynes, 2016). The continental crust is largely composed of rocks that are oxides of other elements, particularly Si and Al. Given that both H and O are ubiquitous in nature, we can confidently assign both H and O (as elements) and H_2O (as a molecule) as universally required for life as we know it. Unlike the other members of the class (i) essential elements, no mechanisms of elemental sparing are known for atomic H and O.

2.2 Carbon ($_6$C) and Nitrogen ($_7$N)

Carbon (C) is the basis of life. Most C in biology has its origins in CO_2, which comprises ~0.041% (~410 ppm) of the present-day atmosphere. Fixation of CO_2 into organic molecules, predominantly by ribulose-1,5-bisphosphate carboxylase/oxygenase (RuBisCO) in the Calvin-Benson cycle of photosynthesis, provides the bulk of C that supports life. Indeed, RuBisCO is considered the most abundant protein on Earth (Bar-On & Milo, 2019; von Caemmerer, 2020). Organisms that use this or other (rarer) pathways that allow growth on CO_2 are *autotrophs*.

Nitrogen is also universally required for life. Nitrogen gas (N_2) is the major component of the atmosphere (80%), so it is abundant in most environments. However, N_2 is not assimilated by most organisms, which rely instead on “fixed” forms of nitrogen such as ammonia, amines, or nitrate. The ability to fix N_2 into ammonia is found in a relatively small subset of Bacteria and Archaea (*diazotrophs*) that harbor the enzyme nitrogenase (Dos Santos et al., 2012). Diazotrophs therefore play a critical role in converting N_2 into a bioavailable form for use by other organisms. Some Bacteria (rhizobia) are symbionts of leguminous plants and are therefore important in agriculture (e.g. supplanting or reducing the requirement for chemically synthesized, nitrogen-rich fertilizers). In marine systems, cyanobacteria and other phytoplankton may fix N_2 as well as CO_2 and thereby provide a foundation for marine food chains (Gruber, 2019).

Given their central role in cell composition, it is no surprise that growth ceases when C or N become limiting. For both elements, mechanisms of elemental economy may be engaged

as a response to limitation. Indeed, the evolutionary pressure exerted on cells by limitation for these critical elements has left an imprint (albeit subtle) on macromolecular composition. In general, the signatures of resource conservation are most dramatic for proteins that are highly expressed under nutrient limitation (Bragg et al., 2012).

In several microbes, proteins expressed when cells are C-limited have, on average, fewer amino acids with longer (C-rich) side chains (Bragg et al., 2012). This presumably functions as an acclimation mechanism to conserve C, the limiting elemental resource. Similarly, in baker's yeast (*Saccharomycess cerevisiae*) transporters used to assimilate N-containing compounds are preferentially built from amino acids containing, on average, fewer N atoms (e.g. substitution of Asp for Asn) than proteins for sulfur assimilation (Baudouin-Cornu et al., 2001). In the model photosynthetic eukaryote, the alga *Chlamydomonas reinhardtii*, N-limitation leads to a global decrease (by ~6%) in the N content of the proteome (Schmollinger et al., 2014). Although these amino acid changes make a modest impact on the cellular atomic budget, even small savings can (over many generations) confer a significant growth advantage.

Optimization of resource allocation by fine-tuning of proteome composition is also apparent in organisms that live in relatively stable environments. In marine systems, the surface waters are more typically limited by N rather than C, whereas the converse may be true in deeper waters (Polz & Cordero, 2020). In organisms prevalent in ocean surface waters, the imprint of selection against N-rich amino acids in abundant proteins is readily apparent. Indeed, the predicted proteomes from metagenomic samples of ocean surface waters are depleted in N-rich amino acids when compared to the predicted proteomes from microbial communities in coastal waters (Dittberner et al., 2018; Grzymski & Dussaq, 2012). An additional consequence is that the genomes of organisms from N-limited surface waters tend to have a higher fraction of adenine:thymine (AT) base pairs, which require less N than a similarly-sized, GC-rich genome (Shenhav & Zeevi, 2020). *Prochloroccus*, an abundant marine cyanobacteria, also responds dynamically to N-limitation by increasing the use of internal transcription start sites, possibly to reduce the N-cost associated with mRNA and protein synthesis (Read et al., 2017). Although many examples are known of microbes adapting their proteomes and genomes to N availability, a similar signature was not apparent in marine isopods, leading to the suggestion that these adaptations may be largely limited to the microbial world (Francois et al., 2016).

In addition to optimization of the proteome and genome to efficiently utilize limiting resources, many cells recycle their nutrients. In the case of abundant macronutrients such as C, N, and P, this recycling may involve the targeted degradation of macromolecules or sub-cellular organelles, a process known as *autophagy* in Eukarya (Gross & Graef, 2020). When targeted to the ribosome, this is known as *ribophagy* <Figure 3>. Since ribosomes are abundant during rapid growth, but only needed at low levels in slow growing cells, their degradation is an efficient mechanism for elemental recycling and is seen in all three domains of life. In baker's yeast (*S. cerevisiae*) and *Escherichia coli,* ribosomes may be degraded under N-limitation and, in some conditions, during C-limitation (Kaplan & Apirion, 1975; Kraft et al., 2008). Similarly, abundant proteins are degraded in response to N-limitation in both mammals (Vabulas & Hartl, 2005) and in the alga *C. reinhardtii* (Martin

et al., 1976). As these examples illustrate, even elements as ubiquitous as C and N can be either transiently or chronically limiting, and mechanisms of elemental economy help cells to sustain growth.

2.3 Phosphorus ($_{15}$P)

Phosphorus (P), most commonly in the form of phosphate (PO_4 or P_i), is universally required for life. The utility of phosphate as a chemical linkage relies on the stability of its phosphoryl esters (Westheimer, 1987). P is a constituent of many of the signature molecules of life, including DNA, RNA, nucleotides, and phospholipids. The phosphoryl group is a key facilitator for many of the transformations in central metabolism. For example, in *E. coli* growing on glucose, the metabolite pool is ~300 mM and accounts for ~3% of cell mass (Bennett et al., 2009). On a molar basis, this pool is dominated by glutamate and other amino acids (~50%). However, the majority of the remaining molecules, including nucleotides and glycolysis intermediates, contain at least one phosphoryl group (Bennett et al., 2009). Collectively, rRNA and NTPs represent the bulk of P in rapidly growing bacterial cells (R. E. Bruna et al., 2022).

For most of its uses in physiology and metabolism, P is irreplaceable. However, one major contributor to P-demand is for phospholipids in the membrane bilayer. The demand for phospholipids can be reduced by their replacement with other types of lipids that lack phosphate. Many photosynthetic organisms synthesize abundant thylakoid membranes. In P-limited plants and algae, the chloroplast membranes may have high levels of neutral glycolipids (digalactosyldiacylglycerol) and anionic glycolipids such as sulfoquinovosyldiacylglycerol, SQDG (Holzl & Dormann, 2019). In the plant *Arabidopsis thaliana,* mutants defective in SQDG synthesis are growth defective under P-limitation (Yu et al., 2002). Marine phytoplankton, particularly those found in P-limited areas, may also substitute phospholipids with sulfolipids. For example, *Prochlorococcus*, a dominant cyanobacterium in P-limited environments, can accumulate SQDG as up to 66% of total membrane lipids (Yu et al., 2002). In some algae, betaine lipids and glucuronosyldiacylglycerol may substitute for some phospholipids (Kalisch et al., 2016). A reduction in membrane phospholipids is not limited to photosynthetic organisms; the pathogenic fungus *Crytococcus neoformans* responds to P-limitation by up-regulating the synthesis of P-free betaine lipids (Lev et al., 2019). Conservation of P by reducing the demand for phospholipids has likely evolved independently in multiple lineages.

Limitation for P may also trigger the active remodeling or recycling of other components of the cell envelope. For example, the Gram-positive bacterium *Bacillus subtilis* has a thick peptidoglycan cell wall that is covalently linked with an abundant anionic polymer, wall teichoic acid (WTA). The WTA in *B. subtilis* 168 is an alternating copolymer of glycerol and phosphate. However, under conditions of P-limitation the cell instead synthesizes a distinct, P-free anionic polymer known as teichuronic acid with the negative charge from P_i replaced by carboxylate groups (Qi & Hulett, 1998). A similar strategy is found in *E. coli* when a P-starvation inducible enzyme (WaaH) modifies cell surface lipopolysaccharide (LPS) to replace phosphate groups with negatively charged glucuronic acid moieties, presumably to liberate P_i for import into the cell (Gardner et al., 2019; Klein et al., 2013).

Starvation for P also elicits a reduction in ribosome synthesis, and existing ribosomes may be degraded to recycle P. The content of ribosomes in *E. coli* is reduced by up to 50% within 80 minutes of onset of P starvation and at slower rates in cells starved for C (Fessler et al., 2020). Turnover of ribosomes is also triggered during longer term stationary phase elicited by P limitation to replenish both P_i and NTP pools (Himeoka et al., 2022). More generally, the turnover of NTPs is a major source of P_i in growing cells. Translation, as a major NTP-dependent process in growing cells, is strongly affected by changes in both cytosolic P_i and Mg pools (Pontes & Groisman, 2018). Acclimation to P-limitation in the red yeast *Rhodosporidium toruloides* also involves active degradation of RNA and inhibition of ribosome synthesis. The TCA cycle is inhibited, while triacylglycerol biosynthesis is activated, which leads to a flux of carbon into storage lipids (Wang, Zhang, et al., 2018).

Arsenic ($_{33}$As) lies immediately below P in the periodic table and has somewhat similar chemical properties. This allows As to substitute for P in some chemical reactions. However, arsenoesters are many orders of magnitude less stable than phosphoesters, and this lability precludes their use in place of phosphate in nucleic acids and NTPs (Westheimer, 1987). Despite this, a bacterium (GFAJ-1) isolated from the As-rich waters of Mono Lake, California was proposed to substitute As for P, thereby allowing growth in the absence of P (Wolfe-Simon et al., 2011). However, the “minus-P” medium used contained biologically ample levels of P, as apparent from the authors’ own analysis, and the evidence for incorporation of As into macromolecules was technically flawed (Erb et al., 2012; Reaves et al., 2012). Subsequent work refuted the notion that this bacterium uses As in place of P (Erb et al., 2012; Reaves et al., 2012). GFAJ-1 is better considered as a P-dependent organism that can tolerate high levels of As. Indeed, it has evolved a binding protein for phosphate uptake that has an enhanced ability to discriminate against As (Elias et al., 2012). There is no broadly accepted evidence that GFAJ-1 benefits from or even uses As in its metabolism.

2.4 Sulfur ($_{16}$S)

Sulfur is universally essential for all life. It is necessary for the synthesis of proteins because it is contained in the amino acids methionine (Met) and cysteine (Cys). Sulfur is also found in low molecular weight thiols (glutathione, mycothiol, bacillithiol), coenzyme A, biotin, and lipoic acid (Francioso et al., 2020). On early Earth, reduced forms of sulfur (sulfides) were common, and similar chemistry is represented in contemporary organisms in FeS clusters, an important class of enzyme cofactor. In many aerobic environments, S is present in its oxidized state as sulfate.

Sulfur limitation has been a selective pressure in plants and microbes, so these organisms have evolved mechanisms to sustain growth even under S-limited conditions. As for many nutrients, one of the most universal responses to limitation is to increase import of sulfate and other S-containing molecules. These efforts at S-acquisition are complemented by elemental sparing responses that help optimize use of available S. One response to S limitation in microbes is to alter cellular protein composition to reduce demand for S-containing amino acids. This strategy was first revealed when it was noted that the content of Cys and Met is greatly reduced in proteins expressed under S limitation in both *E. coli* and the yeast *S. cerevisiae* (Baudouin-Cornu et al., 2001). In *S. cerevisiae*, S limitation is

triggered when cells are exposed to Cd due to the defensive synthesis of large amounts of the S-containing metabolite glutathione (Fauchon et al., 2002). The resultant depletion of S pools triggers a remodeling of the proteome in which some highly abundant enzymes from central metabolism are replaced by isozymes that are depleted of S-containing amino acids. This proteome remodeling reduces the amount of assimilated S used for protein synthesis from 80% to 20% of the total, and contributes to an estimated 30% decrease in the total S demand to support protein synthesis (Fauchon et al., 2002).

S limitation does not impact all metabolic pathways equally. Studies in yeast first revealed that media limited for S selectively reduces the levels of the 2-thiouridine (s^2U) nucleoside present in the wobble position of the anticodon loop in some tRNAs. Modification of tRNAs to incorporate S represents a significant investment; under S-replete conditions the total S in tRNAs corresponds to ~20 μM, comparable to the S concentration present in free Met pools (Laxman et al., 2013). As cells become S-limited, tRNA thiolation is reduced, and this spares the limiting S atoms to help sustain overall protein synthesis. The resulting drop in S-thiolated tRNAs serves as a cellular stress signal to reroute metabolism (Gupta & Laxman, 2020). Remarkably, studies in *B. subtilis* have revealed that diminished S-availability also affects tRNA S-thiolation. In this case, the enzymes required for tRNA modification are reduced in abundance in S-limited conditions, whereas other enzymes involved in synthesis of S-containing molecules are not. As a result, s^2U modification decreases, whereas other S-modified tRNA nucleotides and FeS enzymes are unaffected. These results further support the suggestion that s^2U in tRNA may serve as a molecular signal of cellular S status (Edwards et al., 2022).

The S-sparing response has been well characterized in the alga *C. reinhardtii*. Sulfolipids (e.g. SQDG) are a major component of the thylakoid membrane, which reduces cellular P demand. However, these same SQDG lipids represent a significant store of S and can represent 13% of total cell S (Saroussi et al., 2017). During S limitation, degradation of SQDG and mobilization of the constituent S can provide a large percentage of the S needed for ongoing protein synthesis (Sugimoto et al., 2010). The S-demand is also reduced by proteome remodeling, including production of a sulfur-depleted variant of a major light-harvesting complex protein in photosystem II (LHCBM9) (Nguyen et al., 2008). Increased expression of S-import, recycling, and redistribution pathways enables S-deprived cells to prioritize maintenance of an adequate Cys pool to support protein synthesis, while production of S-containing cofactors needed in comparatively low amounts (S-adenosylmethionine, thiamine, biotin) is down-regulated (González-Ballester et al., 2010).

The full diversity of S-sparing mechanisms is yet to be appreciated. In the cyanobacterium *Calothrix* sp. PCC7601 three different operons encode phycocyanins, one of which (*cpc3*) is induced in response to S limitation and encodes a protein selectively depleted of S-containing amino acids (Mazel & Marliere, 1989). Another strategy employed by many photosynthetic organisms under S limitation is to recycle existing cell constituents to free up S for essential tasks. For example, phycobilisome complexes, which constitute about half of the total protein in *Synechococcus*, are targeted for degradation in response to either N or S limitation (Collier & Grossman, 1992). Since phycobilisomes function in photosynthetic

energy generation and C fixation, they are in excess in cells limited for N or S. A S-sparing response is also observed in land plants. For example, in seeds of soybeans the S content of storage proteins is determined by the level of S nutrition: S-rich glycinin is the major protein if S is available, but S-depleted B-conglycinin accumulates when S is limited (Kim et al., 1999). Thus, various organisms all adapt to S limitation with mechanisms that reduce the S content of the proteome and redeploy S from reservoirs accumulated in times of plenty.

3. Monovalent Cations (group 1)

Biologically, the group 1 elements are present as highly soluble, monovalent cations. The sole element in group 1 that is essential for all organisms (class (i)) is potassium (K). Both sodium (Na) and K are essential elements for humans, but Na is not required for growth of many organisms and is here assigned as class (iii). Why early evolving cells chose K, rather than more abundant Na, as the major intracellular monovalent cation is unclear. This choice could reflect a specific chemical property of this cation in key biochemical reactions, or perhaps it is an accident of evolution (Danchin & Nikel, 2019). Although group 1 also includes lithium (Li), rubidium (Rb), cesium (Cs), and francium (Fr) as congeners (elements within a common group in the period table), none of these are thought to be essential in any organism. However, Li can replace Na to at least some level, and Rb can partially replace K. This raises the possibility that these elements might have a modest beneficial effect under specific conditions, and they can (perhaps generously) be assigned as class (iv). Many enzymes require a monovalent cation for efficient catalysis, and in some cases this activity is very sensitive to cation identity (Gohara & Di Cera, 2016; Vasak & Schnabl, 2016). For cytosolic enzymes, activity may require any of several monovalent cations (typically, Na or K) or may be specific (most often requiring K). A summary of elements with beneficial effects is provided in Table 2.

3.1 Lithium ($_3$Li)

The lightest group 1 cation is lithium (Li). At 20 ppm in the Earth's crust (Figure 2) Li is rare among the light elements and when compared to the other group 1 elements sodium (Na) and potassium (K). This scarcity, which Li shares with Be (2.8 ppm) and B (10 ppm), reflects the overall scarcity of these elements in our solar system. This is due, in turn, to the nature of nucleosynthesis during fusion reactions in stars, which bypasses these elements: they are primarily generated later in fission reactions triggered by cosmic rays interacting with heavier elements in interstellar space (cosmogenic nucleosynthesis) (Johnson, 2019).

Although Li is not known to be required for any organism, Li may partially substitute for Na in some select situations. Li had been suggested to be essential for mammals based on studies with rats and goats fed Li-deficient diets (Schrauzer, 2002). However, the effects were largely limited to decreased fecundity and were manifested over several generations. Although low levels of Li are ubiquitous in many foods and water supplies, there is little evidence for effects of deficiency in either plants or animals. The current consensus seems to indicate a mildly beneficial, although not essential, role in eukaryotes (Szklarska & Rzymski, 2019). Some of the most notable effects of Li are on mood. Li salts are used in

the treatment of manic-depressive disorders, and several studies have established an inverse correlation between dietary Li and suicide, for example (Del Matto et al., 2020).

Although there are currently no known organisms that require Li, it has the potential to be beneficial for certain Bacteria as part of a Na-sparing response. *Vibrio parahaemolyticus* is a halophilic bacterium that requires high NaCl for growth. Optimal growth occurs at 0.5 M NaCl, although this can be reduced to 0.1 M in the presence of sucrose as an osmotic stabilizing agent. The requirement for Na can be largely but not completely replaced by Li, and to some extent other monovalent cations. However, a minimum concentration of 3 mM Na was still required for growth, presumably for proper function of Na-coupled import systems (Morishita & Takada, 1976). Li can also functionally substitute for some Na in several species of *Salinispora*, a marine actinomycete, to maintain maximal growth and yield (Tsueng & Lam, 2010).

It is unclear whether Li is beneficial in natural settings. Perhaps the best candidates for organisms with a Li requirement are those that grow in extremely Li-rich environments. For example, there are extensive salars (salt flats generated by solar evaporation) with very high Li content in the Andes mountains. Two *Bacillus* spp. isolates obtained from these salars were able to grow in Li levels of 1.44 M, but also grew well in the absence of Li salts (Cubillos et al., 2019). Similarly, other Bacteria can tolerate high levels of Li salts, but without any demonstrable requirement for growth (N. Bruna et al., 2022; Kamekura & Onishi, 1982). Thus, Li is best viewed as a biologically unimportant element, but with a potential to benefit some select microbes under very specific conditions of Na limitation. The extent to which microbes benefit from Li in natural settings is not well established, but at least for humans there is epidemiological support for some beneficial effect on cognition (Szklarska & Rzymski, 2019). Thus, Li is tentatively assigned to class (iv): beneficial to at least some species.

3.2 Sodium ($_{11}$Na)

Both sodium (Na) and potassium (K) are very abundant elements (6th and 8th most abundant in the lithosphere; Figure 2) and Na ion is the second most abundant solute in marine systems (closely behind chloride). Despite its ubiquity, Na was a disfavored element during the evolution of life, and K is the dominant intracellular cation (Danchin & Nikel, 2019). Na is a required element for some animals and selected microbes, but not for most plants (Nieves-Cordones et al., 2016). Therefore, we assign Na to class (iii): essential or beneficial for many organisms in at least one domain.

Na is a required nutrient for animals, which rely on the Na^+/K^+ pump to maintain resting potential across the cell membrane. The essential nature of Na, typically consumed in the form of its common salt, NaCl, has been appreciated throughout history. Access to salt has determined the location of numerous cities and trade routes and has influenced geopolitics, including the French revolution and the campaign for Indian independence (Cirillo et al., 1994).

Although Na is most noted for its role as a major extracellular cation, Na may occasionally also serve as a cellular osmolyte. Most intracellular enzymes that require a monovalent

cation prefer K, which is likely the physiological cofactor. A specific requirement for Na in enzyme catalysis is seemingly rare and often a feature of enzymes that function extracellularly, where Na in excess of K both in multicellular organisms and in many environments.

Because of its requirement for animal but not plant life, Na availability can provide an important constraint at the ecosystem level (Kaspari, 2020). Plants vary widely in Na content, and this variance may be under selective pressure. For example, secretion of Na-rich nectars may attract pollinators and beneficial insects, whereas reduced Na levels in plants may make them less attractive to herbivores (Kaspari, 2020). K activates several enzymes in the plant cell. Na is often able to functionally substitute in activating these enzymes, though it may be less effective (Wakeel et al., 2011). K is the most common ion used to maintain osmotic pressure in the plant cell, but under K-limitation, Na, Mg, and Ca can partially replace K in sustaining the internal osmotic pressure. In the red beet, photosynthesis remains high under K limitation if there is high Na (Subbarao et al., 1999). In this plant, Na may functionally replace more than 95% of cellular K, suggestive of a beneficial function (Subbarao et al., 1999).

Na is essential for some Bacteria, including many marine organisms, for transport, pH regulation, and motility. There is a correlation between the presence of a Na pump and an obligate Na requirement in 22 of 27 marine isolates (Oh et al., 1991). In *Vibrio parahaemolyticus*, Na cannot be entirely replaced by other cations, although supplementation with Li can reduce the Na requirement from 100 mM (in isotonic medium) to 3 mM (Morishita & Takada, 1976). In marine Bacteria, a sodium motive force (SMF) generated by respiration is used to power active transport and flagellar motility. One exception is the fish pathogen *V. anguillarum*, where Na is not required for growth, although it is important for survival under nutrient-depleted conditions (Fujiwara-Nagata & Eguchi, 2004). Na is also an obligate growth requirement for many Bacteria in the rumen of herbivores and cannot be replaced by other monovalent cations (Caldwell & Hudson, 1974). In sum, Na is essential for animals and a subset of microbes.

3.3 Potassium ($_{19}$K)

Potassium (K) ion appears to be universally required for life as a major cellular osmolyte and is therefore included in class (i). K functions as a counterion to balance the negative charges of carboxylates and phosphates and as a required cofactor for enzymes (Danchin & Nikel, 2019). The concentration of K is much greater than the concentration of Na in the cell cytosol, and Na is actively extruded by most organisms. One hypothesis for the essentiality of K is that cells evolved in K-rich environments, perhaps on the surface of minerals such as biotite (Hansma, 2022). Subsequently, as life moved to more Na-rich environments like the ocean, Na efflux became critical for life (Dibrova et al., 2015).

The essential role of K may be due, in part, to its use as an enzymatic cofactor. In plants, K is thought to be a required cofactor for several key enzymes of central metabolism: pyruvate kinase, pyruvate dehydrogenase, succinyl-CoA synthetase, asparaginase, and fructose 1,6-bisphosphatase (Cui & Tcherkez, 2021). K ions are also considered essential for the proper assembly and function of the ribosomes (Rozov et al., 2019). Whether this role of K could

ever be replaced by another cation is not clear (see section 4.2). Finally, K is critical for maintenance of an ionic environment compatible with life. Given these varied and complex requirements for K, it is not surprising that there are no reported examples of organisms that are viable in the absence of K, although this is within the realm of possibility.

Bacteria have well-established requirements for K. For example, *B. subtilis* has 3 K importers (Gundlach et al., 2017). In the absence of these transporters, cell growth is K-limited and the bacterium is unable to survive unless it acquires a compensatory (suppressor) mutation. One class of suppressor mutations increases production of positively charged amino acids like ornithine, citrulline, and arginine. It is likely that these positively charged amino acids partially substitute for the functions of K in the cell, and their supplementation supports growth under K-limited conditions (Gundlach et al., 2017). In this case, cationic amino acids can augment K as dominant intracellular osmolytes but do not replace its function as an enzyme cofactor. K is also essential in yeast, and depletion induces autophagy, presumably as a mechanism to free up this limiting nutrient (Rangarajan et al., 2020).

3.4 Rubidium ($_{37}$Rb) and Cesium ($_{55}$Cs)

The heavier elements in group 1 include Rb and Cs. Francium ($_{87}$Fr) is too short-lived (22 minute half-life) and rare to be biologically relevant. Rb is relatively abundant both in the Earth's crust (at 90 ppm, comparable to Zn) and in seawater (18th most abundant element), but only rarely have beneficial roles been suggested. Cs (3 ppm) is 30-fold less abundant than Rb and ranks as the 45th most abundant element in the Earth's crust.

In some organisms facing K-limiting conditions, Rb may be able to substitute for K (Subbarao et al., 2003). The growth of sugar beets increased when Rb was supplemented to a K-deficient medium (El-Sheikh et al., 1967). Some halophiles rely on exceptionally high cytosolic concentrations of K to sustain growth. The archaeal halophile *Haloarcula marismortui* accumulates intracellular K to 2.4 M in medium amended with high K (120 mM) (Jensen et al., 2015). At low concentrations (8 mM) of K, the intracellular K level is reduced to ~1.4 M. If Rb or Cs are available these cations accumulate to levels of ~0.6 and 0.3 M, respectively, with a concomitant reduction in K (Jensen et al., 2015). This provides evidence for a potential beneficial role for both Rb and Cs in these specific laboratory conditions. It is not yet established if this type of substitution is relevant in any natural setting, since K is normally much more abundant than Rb.

The effects of Rb have also been characterized in mammals. At the cellular level, Rb can displace a fraction of intracellular K, but the sum of the two ions remains relatively constant (Kirk et al., 1984). Replacement of K by Rb (and even Cs) in rats can be dramatic, with Rb or Cs replacing up to ~40% of intracellular K in muscle tissue (Meltzer, 1991; Relman et al., 1957). In the plasma, however, Rb and Cs levels are maintained at less than 1% of the group I cations. This displacement is not without consequence, and both Rb and Cs are toxic (Meltzer, 1991; Relman et al., 1957). Overall, we suggest that Rb can be tentatively assigned as class (iv) since, in some environments, it could plausibly be of marginal benefit to some species.

A biological role for Cs seems less likely. Cs is produced in large-scale for use in drilling fluids used for petroleum extraction (Vidal et al., 2020). Radioactive ^{137}Cs is a by-product in commercial nuclear reactors, and contamination is an environmental concern in regions such as those affected by the 2011 accident at the Fukushima Daiichi Nuclear Power Plant. ^{137}Cs in soils can be bioremediated by absorption in plants and mushrooms (Avery, 1995; Duff & Ramsey, 2008) and ^{137}Cs in foods may be partially remediated by adsorption into intestinal bacteria that leads to elimination from the host (Saito et al., 2019). Although Cs is bioaccumulated by some organisms, likely through K uptake systems, we classify Cs as class (v) since it has no documented beneficial effect to cells under conditions likely to be present outside the laboratory.

4. Divalent Cations (group 2)

The group 2 elements are present in biological systems as the divalent cation. The primary focus is on magnesium ($_{12}$Mg) and calcium ($_{20}$Ca), which are common rock-forming elements that account for 2.33 and 4.15% of crustal material by weight, respectively (Figure 2). Mg (~52 mM) and Ca (~10 mM) are also abundant in the ocean. These two cations are essential for many enzymes, although they can occasionally be substituted with other cations. Of the other elements in the group [beryllium (Be), strontium (Sr), barium (Ba), and radium (Ra)], only Sr and Ba have beneficial roles.

4.1 Beryllium ($_4$Be)

Be (2.8 ppm) is one of the least abundant of the lighter elements in the crust (Figure 2); like Li, Be is not a significant product of stellar nucleosynthesis (Johnson, 2019). Be is often present as a divalent cation, but due to its small size and high charge density it also forms covalent complexes, and some have notable biological activities. For example, BeF_3^- anion is a phosphate mimic widely used in protein structural studies (Jin et al., 2017). Be is toxic to both animals and plants, and soil contamination can lead to a reduction in plant growth (Shah et al., 2016; Strupp, 2010). Toxicity likely arises, in part, from the ability of Be to compete for Mg and Zn binding sites in enzymes (Fromm, 2020) and its ability to catalyze structural changes in cell surface polysaccharides and glycoproteins (Buchner, 2020).

In humans, Be inhalation in industrial settings can result in a type of lung inflammation (pneumonitis) known as berylliosis (chronic beryllium disease), which can lead to lung cancer (Buchner, 2020; Perera et al., 2017). Lung inflammation has been linked, by both genetic correlation and structural studies, to the binding of Be to a class II major histocompatibility complex (MHC) protein (human leukocyte antigen HLA-DPB1) in combination with specific peptides (Clayton et al., 2014). This complex triggers T cell proliferation, inflammation, and granuloma formation (MacMurdo et al., 2020). In sum, Be has no known beneficial functions and is a toxic element (class (v)).

4.2 Magnesium ($_{12}$Mg)

Mg is a major cation universally essential for life (class (i)). Hundreds of enzymes require Mg to be catalytically active, including most reactions that use ATP or other nucleotides. Although total cellular Mg is often in the range of 100 mM (Nierhaus, 2014), ~90% of this is complexed by binding to NTPs, anionic molecules and nucleic acids (Sieg et al.,

2022). Mg plays an essential role in the assembly and function of the ribosome (Nierhaus, 2014). In rapidly growing cells, including many Bacteria and *S. cerevisiae*, the majority (>80%) of RNA is in the ribosome (rRNA). The folding of rRNA and ribosome assembly generally relies on charge neutralization of the RNA phosphate backbone by counterions. These include inorganic ions, polyamines, and the ribosomal proteins themselves.

Although Mg is an essential component of the ribosome, there is still controversy about the number and nature of the ribosome-associated cations. Analysis of one high resolution structure (from *Thermus thermophilus*; PDB 4V6F) reveals ~1400 ions in a translation initiation complex, initially assigned as Mg (Jenner et al., 2010). However, this assignment has been challenged. One recent study suggests ~1000 Mg and 367 K ions (Rozov et al., 2019). An alternative view, based on stereochemical constraints, suggests instead only ~200 specific Mg ions and ~700-800 monovalent ions, presumably K (Auffinger et al., 2020). While the precise numbers are not critical for our purposes, this highlights the challenge in assigning biologically relevant cations in large complexes like the ribosome.

No other cations can fully replace Mg in the structure and function of the ribosome. However, it is plausible that ribosome-associated counterions may have changed over time. For example, life evolved in an environment with higher ambient Fe and Mn concentrations, and these ions may have helped support ribosome function early in evolution (Bray et al., 2018). Indeed, the translation activity of *E. coli* ribosomes with limiting amounts of Mg can be restored by adding Fe or Mn, which bind to levels of ~500 ions per ribosome. Although Mg was not quantified in this study, the authors suggest that Fe or Mn may be able to largely substitute for Mg (Bray et al., 2018). The ability of Fe and Mn to bind directly to rRNA is also observed in vivo. In yeast strains with elevated cytosolic Fe, the production of reactive oxygen species (ROS) leads to rRNA fragmentation, suggestive of a direct association of Fe. Moreover, this effect can be ameliorated by supplementation with Mn, which likely competes for these same sites (Smethurst et al., 2020). Thus, other divalent cations (Fe, Mn) can partially substitute for the Mg requirement for ribosome assembly and function, but there is no evidence that the Mg requirement can be eliminated.

Pathogenic bacteria like *Salmonella* may be deprived of Mg during phagocytosis, making Mg deprivation an effective component of nutritional immunity (Blanc-Potard & Groisman, 2021). Phagocytic cells starve Bacteria of Mg after engulfment by using a transporter called NRAMP1 (natural resistance associated macrophage protein 1), which pumps Mg out of phagocytic vesicles (Cunrath & Bumann, 2019). Under conditions of low Mg, *Salmonella enterica* serovar Typhimurium adapts by reducing ribosome synthesis (Pontes et al., 2016). Elucidation of the molecular details has revealed a complex regulatory circuit that promotes the expression of Mg importers and inhibits both the F_1F_O ATP synthase and the synthesis of ribosomes. By reducing the level of both ATP and ribosomes in the cell, the cell reallocates Mg to sustain activity of the now diminished pool of ribosomes and other essential enzymes. A correlation between cytosolic Mg and ribosome levels is also seen in *B. subtilis* (Akanuma et al., 2014). In plants, Mg is an essential part of the abundant chlorophyll molecule and deficiency can reduce crop yield (Tanoi & Kobayashi, 2015). In sum, Mg is a critical ion with a multitude of roles in all organisms, including a universal requirement for translation.

4.3 Calcium ($_{20}$Ca)

Calcium (Ca) is a major cation essential for many Eukarya, including animals and plants. Although Ca is inextricably linked to cell physiology, Ca was largely rejected in favor of Mg as an intracellular divalent cation during life's evolution, perhaps because Ca forms insoluble precipitates with phosphates (Williams, 2006; Williams, 2000). However, this same property has been exploited to store Ca in intracellular vesicles known as acidocalcisomes (Docampo & Huang, 2016). These membrane vesicles are rich in phosphate (P_i), pyrophosphate, and polyphosphate complexed with Ca and other cations (Docampo & Moreno, 2011). Acidocalcisomes play important roles in both phosphate and Ca homeostasis, and are considered to be one of the earliest evolving intracellular organelles found from Bacteria to man (Docampo et al., 2005).

Unlike Mg, which is maintained at intracellular levels approaching ~10 mM, cytosolic Ca levels are typically very low (~100 nM). Most cells have active transport mechanisms to export Ca from the cell or into membrane-bound compartments (Clapham, 2007; Williams, 2006). The transient opening of Ca-channels in membranes can lead to a 10-fold or more increase in cytosolic Ca in milliseconds, which is sensed by proteins like calmodulin, which are characterized by so-called EF-hand Ca-binding motifs (Mohanta et al., 2019). Among the many Ca-activated enzymes are Ca-dependent kinases, which thereby couple two dominant classes of cell signaling: Ca fluxes and protein phosphorylation (Clapham, 2007).

The essentiality of Ca for multicellular Eukarya is unquestioned and its biological roles are numerous (Carafoli & Krebs, 2016; Clapham, 2007). In contrast, the requirement for Ca in the microbial world is far less defined. Nevertheless, Ca is frequently present in defined growth medium for both Bacteria and Archaea. For example, some minimal media for the cultivation of *E. coli* contain Ca (e.g. M9 medium) whereas others do not (e.g. M63 medium) (Keseler et al., 2021). Although both *E. coli* and *B. subtilis* can be grown in medium lacking added Ca, it remains possible that trace levels of Ca support growth. Indeed, studies using EGTA as a chemical chelator support a Ca requirement, albeit low, for both *E. coli* (Arakawa et al., 2000) and *B. subtilis* (Herbaud et al., 1998). However, since chelators are not entirely specific, interpreting such experiments is challenging. A tentative conclusion is that Ca, while often beneficial, may be dispensable for growth of many Bacteria and Archaea.

Bioinformatic approaches also support the notion that Bacteria and Archaea have a variable Ca requirement. Although EF-hand proteins and putative Ca transporters are common in the microbial world (Dominguez, 2004; Domínguez et al., 2015), their numbers are much lower than in multicellular eukaryotes (Marchadier et al., 2016). Bacteria often have the full set of proteins needed for Ca-mediated signaling, including Ca channels to allow passive import and efflux proteins that can reestablish a transmembrane Ca gradient (Domínguez et al., 2015; Lu et al., 2020). Most Ca transporters identified in Bacteria are implicated in efflux, and this can be important during pathogenesis (Rosch et al., 2008). In addition, energy-dependent Ca import pathways for have recently been defined and may be important in environments with low Ca availability (Gupta et al., 2017).

Ca is a regulatory signal in some microbes. For example, Ca serves as a signal triggering biofilm formation in marine *Vibrio* spp. (Park et al., 2015; Tischler et al., 2018) and in *Pseudomonas aeruginosa* (Broder et al., 2016). For host-associated Bacteria, the difference in Ca concentration in interstitial spaces compared to the cell cytosol can be a signal that regulates the expression of virulence determinants (King et al., 2020). In *E. coli*, voltage-gated Ca channels generate transient fluxes in cytosolic Ca levels that are important in the response to mechanosensation (a bacterial sense of touch) (Bruni et al., 2017). Given its wide-ranging roles, and the still uncertain and likely variable requirement for Ca in microbes, Ca is best assigned to class (ii).

4.3.1 Calcium and biomineralization—Ca is abundant in both marine and terrestrial environments and tends to form insoluble minerals that have been exploited throughout evolution. The most important Ca-minerals in biology are based on $CaCO_3$ (calcium carbonate) and $CaPO_4$ (e.g. hydroxyapatite) <Figure 4>. Hydroxyapatite-type minerals make up ~2/3 of the mass of bone in vertebrates and are present in near solid form as tooth enamel (Welborn, 2020).

$CaCO_3$ minerals synthesized by marine plankton play a major role in global elemental cycling. Calcification induced by cyanobacteria in mixed photosynthetic communities growing in shallow seas is thought to have contributed to the formation of stromatolites: biogenic, layered mineral accretions considered to be evidence of early life and dating to nearly 3 Ga (Couradeau et al., 2012). Although often considered as an extracellular process, in one early-evolving cyanobacterial lineage (Gloeobacterales) intracellular biominerals were found that contained Ca along with significant amounts of Mg, Sr, and Ba (Couradeau et al., 2012).

$CaCO_3$ exoskeletons became widespread around the time of the Cambrian explosion (~540 million years ago) and likely emerged multiple times in evolution (Gilbert et al., 2022). $CaCO_3$ crystallizes in multiple lattice types, with calcite (the most stable) and aragonite being most common in marine systems. The type of lattice that is formed can be controlled biologically and is influenced by ocean chemistry, which has varied over geologic time (Sandberg, 1983). When the ocean has relatively high levels of Mg (as at present), aragonite is easier to generate, whereas during periods with reduced Mg levels, calcite is dominant (Turchyn & DePaolo, 2019). Other cations are also found in $CaCO_3$ biominerals, although typically at lower levels than would be characteristic of an abiotic precipitation process, which suggests that the organism exerts selectivity at the sites of calcification (Gilbert et al., 2022).

The use of a $CaCO_3$ exoskeleton is seen in single-celled Eukarya including foraminiferans, coccolithophorids, algae, and dinoflagellates. The coccolithophores are unicellular phytoplankton surrounded by hard, mineralized plates (coccoliths) (Müller, 2019). The benefits of calcification may include protection against predation or viruses and protection from Ca toxicity when seawater Ca levels are elevated (Monteiro et al., 2016; Müller, 2019). Sedimentary layers formed from coccolithophores are abundant, and can account for large rock outcroppings including, most famously, the white cliffs of Dover in England. The foraminifera are single-celled amoeboid protozoa with a hard $CaCO_3$ shell

(test), often found in the benthic layers of marine or brackish waters (de Nooijer et al., 2014). Collectively, the marine microfossils that arise from the foraminiferans and coccolithophorids display enormous diversity and form a rich part of the fossil record that provides insights into the chemistry of the ancient oceans (Hayward et al., 2022). There are over 200 extant species of coccolithophores (Müller, 2019), and the foraminiferans are represented by nearly 9000 extant species, with more than 40,000 in the fossil record. Because of their abundance in ocean sediments, foraminiferans are a major component of the "*Globigerina* ooze" that covers one third of Earth's surface (Hayward et al., 2022). Much of this sediment is calcite, since aragonite-based exoskeletons (common in sea snails and some foraminifera) are more easily dissolved after sedimentation (Sulpis et al., 2022).

The extracellular precipitation of calcite has also been described in both Gram-negative and Gram-positive bacteria. Calcium interacts with and stabilizes anionic surface polymers, which can nucleate the formation of $CaCO_3$ minerals (Görgen et al., 2020). Biofilm formation *in B. subtilis* is enhanced in the presence of Ca, which form a $CaCO_3$ (calcite) mineral phase and strengthens the extracellular matrix (Keren-Paz & Kolodkin-Gal, 2020; Keren-Paz et al., 2022). Biogenic mineralization is being tested as a possible mechanism for the development of "self-healing" concrete: encapsulation of *Bacillus* spores in the concrete may allow cracks to seal themselves if exposed to the right conditions, or healing fluids containing bacteria that nucleate $CaCO_3$ precipitation may be used to treat fractured surfaces (Lee & Park, 2018). In addition to surface-associated mineralization, internal formation of amorphous $CaCO_3$ has been documented in *Achromatium* spp. (a gamma-proteobacterium) and in several species of cyanobacteria (Görgen et al., 2020). Formation of intracellular Ca-based minerals in cyanobacteria may sometimes be localized to a membrane-bound compartment, but the genetic basis of this is poorly understood (Blondeau et al., 2018; Couradeau et al., 2012). In sum, insoluble Ca precipitates have been broadly exploited in biology (Figure 4).

4.4 Strontium ($_{38}$Sr)

Strontium (Sr) and barium (Ba) have beneficial roles in several organisms (class (iv)). Because it is part of the same chemical group as Ca, Sr is commonly found as an element co-mineralized with Ca in $CaCO_3$ or $CaPO_4$ biominerals. For example, corals will precipitate Ca and Sr as carbonates in a ratio proportional to their presence in seawater, but also dependent on ambient temperature, which allows Sr/Ca ratios to serve as a measure of temperature in paleoclimatology (Smith et al., 1979).

Sr can also form skeletal structures surrounding certain protists. Radiolaria are a phylum of unicellular, predatory protists (Eukarya) characterized by mineralized exoskeletons and are closely related to foraminifera. While most Radiolaria use Si as the basis for their exoskeletons, those within the class Acantharea are defined by exoskeletons composed of celestite ($SrSO_4$) (Biard, 2022) <Figure 5>. There are over 150 recognized species of Acantharea, which have 10 to 20 radially arranged (star-shaped) skeletal elements known as spicules. The spicules are formed from $SrSO_4$ and sometimes include $BaSO_4$ (barium sulfate), with the precise arrangement and organization of the spicules used to define the various species (Decelle & Not, 2015).

The Acantharea can be abundant in ocean surface waters where they often associate with symbiotic photosynthetic algae and thereby contribute to primary productivity. Due to their selective use of Sr and Ba for biomineralization, they can, through sedimentation, reduce the levels of these elements in ocean surface waters and thereby contribute to their biogeochemical cycling (Decelle & Not, 2015). Compared to Ca (400 ppm), both Sr (13 ppm) and Ba (0.05 ppm) are at much lower levels in ocean waters, and the biological mechanisms that allow their concentration and precipitation are poorly understood. It is not clear if Acantherea require Sr or Ba for growth, and they are among the few organisms where Sr has a clear beneficial role (Raven & Knoll, 2010).

In animals, Sr may also play a role in biomineralization. In hatchling cephalopods, Sr appears to be required for statocyst formation and therefore normal development (Hanlon et al., 1989). In humans, Sr can be incorporated at low levels in bone, and strontium ranelate has been developed as a treatment for severe osteoporosis (Pors Nielsen, 2004). While the benefits of Sr in the treatment of osteoporosis and healing of bone fractures is well established, increased risks of heart problems have led to contraindications for some populations (Reginster et al., 2015). Sr and Ba can also be bioaccumulated by plants, and this offers a potential tool for soil bioremediation. However, uptake is associated with negative effects on plant fitness (Burger & Lichtscheidl, 2019; Gupta et al., 2018; Ribeiro et al., 2018).

4.5 Barium ($_{56}$Ba)

A small number of organisms selectively mineralize barite ($BaSO_4$) <Figure 6>. Barite is a denser mineral ($BaSO_4$ = 4.5 g/cm^3) than either celestite ($SrSO_4$ = 3.96 g/cm^3) or calcite ($CaCO_3$ = ~2.8 g/cm^3). This high mass density favors the use of barite in gravity-sensing statoliths (~1 μm in diameter) found in vacuoles in some freshwater green algae (charophytes) and in planktonic flagellates within the class Prymnesiophyceae (Krejci et al., 2011; Raven & Knoll, 2010). In the freshwater ciliate *Loxodes striatus* $BaSO_4$ statoliths (~3 μm) are enclosed in 3 to 4 membrane-bound vacuoles (Müller vesicles) and attached by a ciliary stick (Häder et al., 2017). Changes in cell orientation regulate cilia activity to allow cell reorientation (Figure 6). Whether barite is also used in Bacteria or Archaea is unexplored, although the soil microbe *Myxococcus xanthus* can precipitate $BaSO_4$ under appropriate conditions (González-Muñoz et al., 2003). $BaSO_4$ precipitates appear most common in marine systems, despite the very low concentrations of Ba, which suggests an active and selective biological concentration mechanism (Martinez-Ruiz et al., 2019).

5. Rare Earth Elements and the Lanthanides: Group 3

The rare earth elements (REEs) consist of scandium ($_{21}$Sc), yttrium ($_{39}$Y), and the lanthanides (collectively, Ln) and actinides (collectively, An). REEs share many of the same chemical and physical properties and are often found in an oxidation state of +3. REEs are used globally in many industries and are expected to be an emerging pollutant in the environment (Daumann et al., 2022; Tao et al., 2022). These elements are toxic to many organisms, and their beneficial roles often subtle (Ascenzi et al., 2020). Some Ln elements function as growth promoters in agriculture, although their beneficial role in plants remains

controversial. There is now strong evidence for beneficial roles of Ln elements in some microbes (Daumann et al., 2022; Picone & Op den Camp, 2019), and in rare cases they are essential for growth (Pol et al., 2014).

5.1 Scandium ($_{21}$Sc) and Yttrium ($_{39}$Y)

Scandium (Sc) is the smallest of the REEs, and many organisms can adsorb or bioaccumulate Sc. Sc can stimulate the production of microbial secondary metabolites (Syrvatka et al., 2022). For example, in *B. subtilis*, Sc stimulates the production of amylase, an extracellular enzyme, as well as bacilysin, an antibiotic (Inaoka & Ochi, 2011). In *Streptomyces* spp., a low concentration of Sc also promotes antibiotic expression (Kawai et al., 2007) and expression of secondary metabolite-biosynthetic gene clusters (Syrvatka et al., 2022; Tanaka et al., 2010). There is no evidence to suggest that these effects of Sc are beneficial, and they may result from stress responses induced by exposure to a toxic element.

Yttrium (Y) is chemically similar to the Ln elements. Although Y has no known biological roles, it has found great utility in medicine both in imaging compounds and for radiotherapy. In nature, Y is found as the ^{89}Y isotope, and a further 8 radioactive isotopes can be generated (from ^{85}Y to ^{93}Y) with half-lives from hours to months (Tickner et al., 2020). These are used in medical imaging (positron emission tomography) and radiotherapy (^{90}Y). Despite these applications, both Sc and Y are classified as class (v): of no known beneficial use in natural systems.

5.2 Lanthanides: Lanthanum ($_{57}$La), Cerium ($_{58}$Ce), Praseodyminium ($_{59}$Pr), Neodymium ($_{60}$Nd), and Samarium ($_{62}$Sm)

The lanthanides (Ln) comprise the 15 metallic elements from atomic number 57 to 71. Ln are now appreciated as beneficial nutrients for methylotrophs (Skovran et al., 2019; Tani et al., 2021) and can even be essential for growth (Pol et al., 2014). Methylotrophs are Bacteria that metabolize methane or methanol as an energy source using methanol dehydrogenase (MDH) as a key enzyme <Figure 7>. The first MDH proteins described in 1964 were Ca-dependent, and it was revealed only 4 decades later that MDH proteins frequently prefer or require Ln as cofactors (Daumann, 2019; Daumann et al., 2022). The role of Ln in biology is a very active area of research, as recently reviewed (Cotruvo, 2019; Daumann, 2022; Daumann & Camp, 2021; Featherston & Cotruvo, 2021).

In one model methylotroph, *Methylobacterium extorquens* strain AM1, the XoxF1 MDH uses Ln cofactors. In this and related species, methylotrophy is supported by a Ca-dependent enzyme when no Ln are available. Low levels (~10 nM) of Ln will shut off the Ca-enzyme and induce expression of the preferred Ln-dependent enzyme, XoxF1 (Chu & Lidstrom, 2016; Vu et al., 2016). This “lanthanide switch” provides the bacterium with metabolic flexibility depending on metal availability.

The best cofactors for XoxF are the lighter Ln, including lanthanum (La), cerium (Ce), praseodyminium (Pr), neodymium (Nd), and perhaps also samarium (Sm) (Daumann, 2019). Some methylotrophs, such as *Methylotenera mobilis* and *M. fumariolicum* SolV, can oxidize methanol using europium (Eu) or gadolinium (Gd) as cofactors, but the catalytic efficiency

is decreased compared to the lighter Ln elements (Jahn et al., 2018). Lanthanides are also essential for ExaF, a pyrroloquinoline quinone-dependent ethanol dehydrogenase (Good et al., 2016). A conditionally expressed, Ln-dependent alcohol dehydrogenase is present in both methylotrophs and the non-methylotroph *Pseudomonas putida* (Wehrmann et al., 2018).

Some methylotrophs produce lanmodulin, a 12 kDa Ln-binding protein with a postulated role in Ln import (Cotruvo Jr et al., 2018; Deblonde et al., 2020). Lanmodulin is encoded by a subset of Ln-utilizing Bacteria (*Methylobacterium, Methylorubrum* and *Bradyrhizobium*) but is apparently absent from other methylotrophs (Daumann et al., 2022). Lanmodulin undergoes a conformational change upon Ln-binding and retains activity even in highly acidic conditions (pH~2.5), high temperature (up to 95 °C), and molar amounts of competing metals. The ability of lanmodulin to bind tightly and selectively to Ln, and even to actinide elements, is likely to lead to new applications in both medicine and bioremediation (G. J.-P. Deblonde et al., 2021; Dong et al., 2021).

An alternative pathway for Ln acquisition has also been proposed. An operon encoding a putative Ln chelator has been identified in *Methylorubrum extorquens* AM1 (Roszczenko-Jasińska et al., 2020). By analogy with the role of siderophores in Fe uptake, the product of this operon has been christened a lanthanophore (Good et al., 2022; Zytnick et al., 2022). The chemical nature of the lanthanophore is still under investigation, but its import is thought to depend on a TonB-dependent outer membrane receptor (LutH), a periplasmic binding protein (LutA), and an inner membrane ABC transporter (LutEF) (Daumann et al., 2022). Once imported, Ln may be stored in association with polyphosphate, possibly in acidocalcisome-type vesicles (Good et al., 2022).

Lanthanides are also considered beneficial in plant and animal nutrition (Abdelnour et al., 2019; Tommasi et al., 2021). A feed additive for animal husbandry that contains La and Ce citrate salts (Lancer) has been approved in the European Union (Tommasi et al., 2021). Considering their beneficial (and in rare cases, essential) role in methylotrophs, and possible beneficial roles in other organisms, several Ln elements are here assigned to class (iv): beneficial to at least some species.

5.3 Actinide Elements

Among the actinide (An) series of heavy elements, only thorium ($_{90}$Th) and uranium ($_{92}$U) have isotopes sufficiently stable that they are still present naturally on Earth (Figure 2). ^{232}Th, with a half-life >14 billion years, is a stable (if rare) element. ^{238}U, with a half-life of >4 billion years, is present in the Earth's crust at levels comparable to Mo and is bioaccumulated by some organisms. U plays a central role in the nuclear energy industry since ^{235}U can undergo fission, and if sufficiently enriched this can become a self-sustaining chain reaction. Of the naturally occurring An elements, only U has been proposed to have a beneficial role in biology (class (iv)).

Some of the An elements can be synthesized in nuclear reactors and have potential applications in medicine. All actinium ($_{89}$Ac) isotopes are radioactive, vanishingly rare in the natural world, and have no known beneficial role (class (v)). Ac exists in >30 isotopes, with those from ^{222}Ac to ^{233}Ac having half-lives varying from seconds to days. ^{225}Ac, with

a half-life of 10 days, decays by alpha-particle emission and is under development for use in radiotherapy (Kostelnik & Orvig, 2019). The LanM protein binds tightly to Ln and An elements and provides a potential tool for enrichment and recovery of Ac for use in medicine (G. J.-P. Deblonde et al., 2021; Mattocks & Cotruvo, 2020). LanM can also form complexes with other actinides, including the americium ($_{95}$Am) and curium ($_{96}$Cm) ions (G. J. P. Deblonde et al., 2021), which are important constituents of radioactive waste from nuclear reactors. Although not important in nature, both Am and Cm can support methylotrophic growth under laboratory conditions (Singer et al., 2022).

5.3.1 Uranium ($_{92}$U)—Uranium, at 2.9 ppm in the crust, is a naturally occurring An comparable in abundance to tin (Sn). U can be found bound to proteins at low levels in at least some species. This is assumed to result from mismetalation of enzymes that normally function with other metal ions (Cvetkovic et al., 2010). U can have a beneficial use as an external electron acceptor in some Bacteria and is therefore assigned to class (iv). Gram-negative bacteria such as *Shewanella* and *Geobacter* can reduce U^{+6} to U^{+4} (Koribanics et al., 2015; Richter et al., 2012). The conductive pili of *Geobacter* are essential for extracellular reduction, and the reduced uranium preferentially precipitates at the cell surface and in the periplasm (Cologgi et al., 2011), which reduces accumulation within the cell (Kolhe et al., 2018; Rogiers et al., 2022). A growth-stimulatory effect of U^{+6} was seen for the thermophilic, gram-positive bacterium *Thermoterrabacterium ferrireducens* (Khijniak et al., 2005). Inclusion of U^{+6} salts in the medium stimulated growth ~2.5-fold, consistent with a direct role of U reduction in energy coupling. Similarly, a gram-negative Bacterium (*Burkholderia* sp.) is capable of uranium-respiration (Koribanics et al., 2015). Although U respiration is possible under suitable conditions, evidence for a growth-promoting effect of U in natural environments is still limited (Majumder & Wall, 2017).

6. Refractory Transition Metals (groups 4 through 6)

The transition metals in groups 4 through 6 include many considered refractory, an indication of their very high melting temperatures. There is a paucity of biologically important elements in this region of the periodic table. By far, the most important is molybdenum ($_{42}$Mo), the heaviest element that is widely found to be essential (class (ii)). However, vanadium (V) and tungsten (W) are also found as *bona fide* cofactors in some enzymes and have well-documented biological roles in specific organisms (class (iv)).

6.1 Group 4: The Titanium Group

The group 4 elements include titanium ($_{22}$Ti), zirconium ($_{40}$Zi), and hafnium ($_{72}$Hf). These elements have little relevance to biology. Anecdotal evidence suggests that Ti may have limited utility in some natural systems and can be tentatively included in class (iv) rather than class (v). Zi and Hf have no known beneficial roles (class (v)).

6.1.1 Titanium ($_{22}$Ti)—Titanium, at 5650 ppm, is an abundant element in the Earth's crust (9th most abundant), although it is largely present in insoluble oxides that limit its bioavailability. In seawater, the levels of Ti are exceptionally low (4 pM). However, levels as high as 100 μM have been noted in hot springs (Çobani & Valentine, 2022).

Although there are no organisms known to require Ti, it shares with V the property of being accumulated to a high level in some marine species (Zierden & Valentine, 2015). TiO_2 appears to play a structural role in some marine organisms in place of silica, SiO_2. Biomineralized TiO_2 has been reported in diatoms and some foraminifera (Cole & Valentine, 2006). Ti is concentrated from the environment, and TiO_2 forms a mineralized shell (test), indicative of an active concentration mechanism (Çobani & Valentine, 2022). Diatoms in culture conditions supplemented with Ti and limited for Si can produce mineralized cell walls (frustules) with up to 80% TiO_2 by weight (Jeffryes et al., 2008). The ability of diatoms and some foraminifera to use Ti may contribute to the depletion of this element from the ocean surface layers (Orians et al., 1990). Ti may also play a role in ascidians, which accumulate this element as well as V (Thompson et al., 2018; Zierden & Valentine, 2015). Some Bacteria have recently been found to liberate Ti from TiO_2 minerals and incorporate the released Ti into their metallome (Gallo et al., 2019). TiO_2 is very effective at absorbing ultraviolet radiation, and therefore serves as an effective sunscreen, which may contribute to its beneficial role in some organisms. For this same reason, TiO_2 nanoparticles have been adapted for photodynamic therapy in treatment of cancer (Youssef et al., 2017; Ziental et al., 2020). In medicine, Ti metal is most appreciated for its utility in implants due to its ability to bind well with bone and its biocompatibility (Kaur & Singh, 2019). Although there is still much to learn, we here assign Ti as a member of class (iv): beneficial to at least some species.

6.1.2 Zirconium ($_{40}$Zi) and Hafnium ($_{72}$Hf)—

Zirconium has been described as an enigma, since it is much more abundant in the crust (165 ppm) than Mo (1.2 ppm), bioaccumulates in both animals and plants, and yet seems have little beneficial or toxic effect (Ghosh et al., 1992). If it has any biological role, it remains to be discovered. Hf (3 ppm) is similar to Zi and is found co-crystallized in Zi-containing silicate minerals. Because of its large nucleus, Hf is very effective at neutron capture and is widely used in control rods in nuclear power plants. This same property may prove useful in medicine: Hf is currently in development, in the form of Hf oxide nanoparticles, for radiotherapy in cancer treatment (Scher et al., 2020). Both Zi and Hf are considered class (v): no known beneficial use in natural systems.

6.2 Group 5: The Vanadium Group

Among the transition metals in group 5, only V has known biological roles, and these are in specialized functions in some organisms (class (iv)). Niobium (Nb) is a critical element in manufacturing, commonly as a steel additive, but of little biological relevance. Tantalum (Ta) is industrially useful for production of metal alloys and is medically important for implants since it has excellent biocompatibility and does not evoke an immune response (Han et al., 2019). Neither Nb nor Ta have known biological roles (class (v)).

6.2.1 Vanadium ($_{23}$V)—

Vanadium, the 20th most abundant element in the Earth's crust (120 ppm), has restricted but well-defined uses in biology (Rehder, 2022). V is among the more abundant transition elements in seawater with a concentration of ~30 nM (Rehder, 2015). One major beneficial function is to allow the synthesis of an alternative nitrogenase when Mo is unavailable (Harwood, 2020), as discussed in section 6.3.2. In addition, a small

set of V-dependent enzymes have been described (Rehder, 2022). V biochemistry has a rich history, and it has even been suggested that V may be essential for some species (Crans et al., 2004). V has also been proposed to be a beneficial, or even essential, trace element for humans (Tripathi et al., 2018). However, the possible benefits of V are still a topic of debate (Harland & Harden-Williams, 1994; Rehder, 2013).

V is often present as an oxyanion (vanadate) and this species is the cofactor for a family of V-dependent haloperoxidases (VHPOs) in marine algae and some Bacteria (Wever et al., 2018). These enzymes play a presumably beneficial role in the generation of volatile organohalogen compounds in marine systems, and thereby affect the biogeochemical cycling of the halogens (Baumgartner & McKinnie, 2021; Wever et al., 2018). V is also accumulated to high levels (>300 mM) in certain marine invertebrates known as sea squirts (tunicates). V is found in complex with specific binding proteins (vanabins) within blood cells (vanadocytes) (Michibata et al., 2003; Ueki et al., 2015). Despite the presence of specific binding proteins, and a compartment specific accumulation (to levels 10 million-fold higher than in seawater), the physiological role of V in tunicates has not been satisfactorily explained (Rehder, 2015). In a possible example of elemental substitution, in some sea squirts V deficiency is correlated with accumulation of niobium ($_{41}$Nb) or even tantalum ($_{73}$Ta), but a role for these elements is also not established (Carlisle, 1958; Kokubu & Hidaka, 1965). Finally, some Bacteria can use vanadate as an electron acceptor in dissimilatory respiration (Rehder, 2015). In sum, we suggest that V is class (iv): beneficial to at least some species. The proposal that V may be an essential element for humans, while not discarded (Chellan & Sadler, 2015), has not gained wide support. It is therefore grouped with many other elements that may have a poorly defined beneficial effect.

6.2.2 Niobium ($_{41}$Nb) and Tantalum ($_{73}$Ta)—

Niobium (Nb) bioaccumulates in some marine organisms (Carlisle, 1958; Kokubu & Hidaka, 1965), but does not have a documented beneficial role. Tantalum (Ta) is an industrially important element, but the environmental fate and distribution of Ta is poorly understood, and there is little evidence for toxicity (and none for a beneficial role) (Filella, 2017). Although Ta may bioaccumulate in some marine sea squirts (to a level of 0.02% by weight), its biological relevance is not understood (Kokubu & Hidaka, 1965). Therefore, we assign both Nb and Ta to class (v).

6.3 Group 6: The Chromium Group

The group 6 elements are transition metals with known or potential biological roles. The role of Cr in biology is controversial, and although Cr was long considered essential for human biology, that status has been challenged. Both Mo and W are scarce elements in the crust (both estimated at ~1.2 ppm), whereas in seawater Mo is much more abundant than W (by >10^5-fold) (L'Vov N et al., 2002). A select set of Mo- and W-dependent enzymes have been described. Both Mo and W form chemically similar oxyanions, molybdate (MoO_4^{2-}) and tungstate (WO_4^{2-}), often coordinated to S in an organic dithiolate-containing pyranopterin cofactor to serve in redox enzymes.

6.3.1 Chromium ($_{24}$Cr)—

Chromium (Cr) was considered an essential trace metal for mammals for nearly 60 years, based largely on early studies in rodents (Vincent, 2013).

As a result, nutritional supplements containing this metal proliferated, with sales second only to Ca (Vincent, 2013). More recent work has led to the removal of Cr from the list of essential elements in human nutrition and has questioned whether it even has a beneficial role (Vincent, 2017). While it is possible that circulating Cr^{3+} may act to augment insulin signaling, any beneficial effect is likely adventitious and only apparent at doses not normally found in the diet (Vincent, 2015).

The interactions of Cr with cells are more commonly negative, with Cr^{6+} being particularly toxic (Gomathy et al., 2022). A diversity of microbes, including Bacteria and fungi, are able to reduce Cr^{6+} to less toxic Cr^{3+} (Guo et al., 2021), which may be of use in bioremediation of contaminated sites (Gutierrez-Corona et al., 2016). Whereas some toxic metals benefit cells by serving as electron acceptors in anaerobic respiration, in other cases reduction seems to be a detoxication mechanism. For Cr, the current consensus is that microbial reduction serves a detoxification function (Guo et al., 2021; Richter et al., 2012). At present, we place Cr in class (v), although it may be promoted to class (iv) if convincing evidence of a beneficial role is found.

6.3.2 Molybdenum ($_{42}$Mo)—Molybdenum (Mo) is the most important of the group 6 elements and is required for many organisms in all three domains of life (class (ii)). There is genomic evidence for Mo-dependent enzymes in 68% of Bacteria, 97% of Archaea, and 70% of Eukarya (Zhang & Zheng, 2020). Mo is most often found in enzymes as molybdenum cofactor, MoCo <Figure 8>. MoCo is a pyranopterin-based redox cofactor with Mo bound to two S atoms in a *cis*-dithiolene group (Metzger & Basu, 2022; Schwarz et al., 2009). MoCo is required for at least 50 enzymes across all three domains of life (Zhang & Gladyshev, 2008). There are four major MoCo-dependent enzyme families: sulfite oxidase, xanthine oxidase, dimethylsulfoxide reductase, and aldehyde:ferredoxin oxidoreductase (Schwarz et al., 2009).

In human biology, Mo is an essential trace nutrient. Humans have four MoCo-dependent enzymes: sulfite oxidase, xanthine oxidase, aldehyde oxidase, and mitochondrial amidoxime-reducing component (mARC). Although Mo deficiency does not occur naturally in humans, it has been observed in patients (Novotny & Peterson, 2018). Further, there are genetic diseases leading to defects in MoCo biosynthesis that lead to neurodegeneration and death in childhood (Atwal & Scaglia, 2016). MoCo is also essential for plants, at least during growth in most soils. The individual MoCo-dependent enzymes are each dispensable but can be conditionally essential depending on nutrient conditions. The cumulative effect of MoCo loss is a crippled plant that can only be kept alive under specific laboratory conditions (Mendel & Kruse, 2012). In contrast, in *S. cerevisiae* there are no MoCo-dependent enzymes and no Mo requirement (Mendel & Kruse, 2012).

From a global perspective, the most critical role for Mo is as a component of nitrogenase, where it is in an Fe- and Mo-containing metal cluster (FeMoCo; Figure 8c) with a formula of $MoFe_7S_9$ (Burén et al., 2020). Nitrogenase, a key enzyme in biogeochemical cycling due to its ability to fix atmospheric N_2 into ammonia, evolved ~3.2 Ga when the atmosphere was still anaerobic. Even today, nitrogenase is very sensitive to inactivation by molecular oxygen, and diazotrophs must develop mechanisms to shield nitrogenase from

inactivation by O_2. In the filamentous cyanobacterium *Anabaena,* nitrogenase is spatially separated from oxygenic photosynthesis by only being synthesized in periodically spaced, non-photosynthetic cells (heterocysts) within the filament. O_2 diffusion into these cells from adjacent photosynthetic cells is restricted by a thick cell envelope and by rapid O_2 consumption by respiration at the cell membrane (Poole & Hill, 1997). In aerobic Bacteria, respiration serves to maintain a low oxygen tension in the cytosol and thereby allows functioning of many O_2-sensitive enzymes, a mechanism christened a “respiratory shield” (Wofford et al., 2019). In unicellular diazotrophs, such as *Crocosphaera watsonii* (Masuda et al., 2022), nitrogen fixation (night) and photosynthesis (day) are instead separated in time (Saito et al., 2011; Stöckel et al., 2008). This reduces O_2-poisoning of the nitrogenase and additionally allows cells to recycle valuable Fe atoms from photosynthetic complexes needed during the day into nitrogenase as night. Expression of O_2-binding proteins of the globin family (cyanoglobins) may additionally help sustain high nitrogenase activity (Johnson & Lecomte, 2013). Finally, in the plant-rhizobium symbiosis, nitrogenase is protected by plant-produced leghemoglobin, a heme-containing O_2 scavenger that buffers O_2 to levels sufficient to support respiration, but not high enough to damage nitrogenase (Rutten & Poole, 2019).

It has been proposed that the intrinsic sensitivity of nitrogenase to inactivation by O_2 may account, at least in part, for the long lag between the evolution of oxygenic photosynthesis and GOE (~2.4 Ga; when atmospheric O_2 first accumulated), and the much later increase in O_2 levels to contemporary levels (~21% O_2) (Allen et al., 2019). During the intervening nearly 2 billion years (the Proterozoic eon) atmospheric O_2 is thought to have rarely exceeded ~2% (~10% of current levels), a phenomenon referred to as Proterozoic O_2 stasis. This stasis might have resulted from a global limitation for fixed nitrogen due to either Mo limitation or to a lack of mechanisms to shield nitrogenase from O_2-inhibition. In support of the latter idea, the cyanobacterial lineage is ancient, but heterocyst formation is not evident until the time of the Cambrian explosion at the transition from the Proterozoic to the Phanerozoic eon. At this time, land plants proliferated and were able to separate aerial photosynthesis from symbiotic nitrogen fixation in the soil, and O_2 levels rose to near current levels. Simultaneously, nitrogen-fixing microbes developed strategies to avoid O_2-inhibition (Allen et al., 2019).

When there is a scarcity of Mo, some organisms synthesize alternative forms of nitrogenase that replace Mo with V or use an Fe-only cofactor (Harwood, 2020). These alternative types of nitrogenase provide a back-up function since they are only found in Bacteria and Archaea that also express, usually as the preferred enzyme, a Mo-nitrogenase. The expression of alternative nitrogenases is often hierarchically regulated, with the V-enzyme expressed when Mo is absent, and the Fe-only enzyme expressed when both Mo and V are absent (Appia-Ayme et al., 2022; Harwood, 2020). The current consensus is that the Mo-containing nitrogenase is the ancestral form, and alternative metal utilization emerged later in evolution (Garcia et al., 2020; Mus et al., 2018).

6.3.3 Tungsten ($_{74}$W)—There is a small set of tungstoenzymes, including the W-containing oxidoreductase (WOR) family proteins. Similar to Mo, W-containing enzymes often rely on W bound to the pyranopterin cofactor (tungstopterin), although W is

often coordinated by two pyranopterins (Milojevic, 2022). The true tungstoenzymes include formate dehydrogenase and aldehyde:ferredoxin-oxidoreductases from Bacteria and Archaea, with the latter including methanogens, acetogens, and thermophiles (L'Vov N et al., 2002; Milojevic, 2022). There is overlap between enzymes that rely on MoCo as a cofactor and those that can use W. For some MoCo-dependent enzymes, binding of W to the pyranopterin results in enzyme inactivation, and for some others activity is present for both the Mo- and W-cofactored forms. However, for most WOR family proteins, only the W-form is active (L'Vov N et al., 2002; Schut et al., 2021).

Tungstoenzymes are evolutionarily ancient and perhaps evolved in the anaerobic and sulfidic environment of the Archean when W was more available than Mo (Hille, 2002). It is estimated that sulfide levels in excess of 10 μM can remove Mo by precipitation, which may have contributed to a preferential use of W in sulfidic environments on ancient Earth and today in some hot springs and volcanic regions (Buessecker et al., 2022). The GOE may have altered metal bioavailability and facilitated the replacement of W with Mo in some enzymes. Thus, tungstoenzymes found in obligate and often thermophilic anaerobes may be remnants of this ancient world. For example, in one hyperthermophilic Archaea, *Pyrococcus furiosus,* W accumulates to an intracellular concentration of 29 μM, primarily due to five W-dependent enzymes (Sevcenco et al., 2009). W is essential for cultivation of the Archaean *Wolframiiraptor gerlachensis* and genomic evidence reveals a widespread presence of tungstate (WO_4^{2-}) transporters and tungstoenzymes in related species of the *Wolframiiraptoraceae* family (Buessecker et al., 2022). Similarly, W is essential for growth of some representatives of the *Thermococcales* and *Thermoproteales*. In Bacteria, the only known acetylene hydratase is also a W-dependent enzyme. The prevalence of enzymes that selectively use acetylene is curious since acetylene is not naturally present at significant levels on Earth. This has led to the suggestion that acetylene hydratase may be a relic of the Archean eon, when acetylene may have been a more abundant constituent of the primordial reducing atmosphere (Kroneck, 2016).

Bacteria in the human microbiome have been found to encode WOR enzymes together with dedicated systems for W import (Schut et al., 2021). Studies of one representative organism (a member of the Clostridia class of Bacteria) revealed a W-dependent enzyme that oxidizes toxic aldehydes present to the comparatively innocuous carboxylic acids. These results suggest that dietary W, present at very low levels in most foods, could impact human health by allowing WOR enzymes to oxidize toxic aldehydes present in cooked foods (Schut et al., 2021).

Tungstoenzymes may also play a role in allowing specific metabolic processes to continue when Mo is limiting. For example, the sulfate-reducing bacterium *Desulfovibrio alaskensis* encodes two formate dehydrogenases: one requires W to function whereas the other can use either W or Mo. When Mo is present in the environment, the organism upregulates production of the Mo/W isozyme, and when only W is present in the medium, the W isozyme is synthesized (Mota et al., 2011). Another example of W functionally replacing Mo is in the Archean *Methanosarcina acetivorans*, which encodes Mo- and W-dependent forms of formylmethanofuran dehydrogenases (Rohlin & Gunsalus, 2010). The presence of

tungstoenzymes in the Bacteria and Archaea leads us to assign W to class (iv): beneficial to at least some species.

7. Transition Metals: groups 7 through 12

The six transition metals in the first period of groups 7 to 12 are all important cofactors for enzyme catalysis and electron transport. These elements include some that are essential for all (or nearly all) organisms across all three domains of life (Fe,Zn) and others that are essential for many organisms in all three domains (Mn,Co,Ni,Cu). The heavier elements in groups 7-12 are notable primarily for their toxicity and have only rarely been found to have beneficial roles in biology. Nevertheless, some heavier elements in these groups are subject to microbially-mediated biotransformation, and microbes may play a role in their biogeochemical cycling.

It is estimated that metalloproteins represent one third of all proteins, and nearly one half of enzymes. Of the six first-row transition metals, four are essential to both plants and animals (Mn,Fe,Cu,Zn). Humans additionally require Co, whereas some plants require Ni. The transition metals often function (sometimes interchangeably) as electrophilic centers in enzymes (most often as the divalent cation), in redox reactions, and in partnership with organic cofactors. The application of bioinformatic techniques to the ever-increasing set of genomes from all three domains of life has provided a powerful tool for understanding the use of metals by cells (Grosjean & Blaby-Haas, 2020; Zhang & Zheng, 2020).

The metal content of the cell, or quota, is partitioned between ions that are tightly bound, often as enzyme cofactors, and a mobile pool of bioavailable metal that can be used in the metalation of nascent enzymes (Foster et al., 2022). The avidity with which divalent transition metals bind to ligands is summarized as the Irving-Williams Series: $Mn^{2+} < Fe^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+} > Zn^{2+}$. Those ions that interact relatively weakly with ligands (Mn, Fe) may have a substantial pool of rapidly exchanging, hydrated ions in the cell. For example, in the model bacterium *B. subtilis*, the Mn^{2+} and Fe^{2+} quotas are often in the range of 500 μM averaged over the cell, with perhaps 1-2% of these ions in a rapidly exchangeable, labile pool (~10^4 atoms per cell) (Helmann, 2014). In contrast, for elements at the higher affinity end of the Irving-Williams series the binding affinities are such that there is no free (hydrated) metal present, and protein metalation involves ligand-exchange reactions between small molecule ligands or protein chaperones and nascent metalloproteins (Foster et al., 2022). Thus, the chemical stability with which ions bind to ligands affects the nature of the metal pools in the cell, and cellular sensors of metal status (metalloregulatory proteins and riboswitches) sense fluctuations around these buffered metal concentrations (Foster et al., 2022).

The low solubility and slow exchange kinetics of many metal complexes in the environment presents challenges to microbial nutrition. To enhance the solubility of metals and facilitate uptake, many microbes synthesize metal-selective chelators (metallophores) and cognate uptake systems (Reitz & Medema, 2022). This is a phenomenon first widely appreciated for Bacterial and fungal siderophores that enhance Fe(III) uptake (Chu et al., 2010). This same strategy extends to the use of zincophores for Zn uptake (Morey & Kehl-Fie, 2020)

and methanobactin for Cu uptake (Kenney & Rosenzweig, 2018b). The presence of high-affinity import systems complicates efforts to rigorously define the metal requirements for microbes. One approach, widely used in studies of marine organisms, is the use of chemical chelators to buffer metals at very low levels (e.g. Aquil and its successors), which requires consideration of both the thermodynamics and kinetics of metal speciation (Martocello et al., 2019). In humans, the production of molecules that tightly bind metals can also limit the growth of microbes within tissues and cells. Key metal-sequestering functions are provided by transferrin (Fe,Mn) (Liu et al., 2021; Vincent & Love, 2012), calprotectin (Mn,Fe,Ni,Zn) (Zygiel & Nolan, 2018), and siderocalins (binding of Fe-siderophore complexes) (Sia et al., 2013). Collectively, these and other mechanisms contribute to innate immunity through a mechanism known as nutritional immunity (Murdoch & Skaar, 2022).

7.1 Manganese ($_{25}$Mn).

In Earth's crust, Mn (950 ppm) is the 12th most abundant element (and 5th most abundant metal) (Horning et al., 2015). Mn is widely used in biology across a vast spectrum of organisms and is therefore a class (ii) element (Alejandro et al., 2020; Balachandran et al., 2020; Bosma et al., 2021). Globally, one of its most essential roles is in oxygenic photosynthesis, leading to a high Mn requirement in photosynthetic Bacteria and Eukarya, including all plants. The oxygen-evolving complex (OEC) within photosystem II contains a complex metal cofactor (Mn_4CaO) that removes electrons from water and is therefore responsible for the genesis of virtually all O_2 in our atmosphere (Barber, 2016; Oliver et al., 2022). In addition to its role in the photosynthetic reaction center, Mn functions as a cofactor for numerous other enzymes in plants (Alejandro et al., 2020). Studies in *Arabidopsis* suggest that nearly 400 enzymes might contain Mn, but only ~20% are confirmed to be active with Mn as a cofactor (Alejandro et al., 2020). In many cases the preferred cofactor is not established and a unique dependence on Mn is not known. Indeed, in addition to the OEC, only two plant enzymes are known to exclusively depend on Mn, manganese superoxide dismutase (MnSOD) and oxalate oxidase (Alejandro et al., 2020). Thus, Mn may be generally beneficial and able to activate a wide range of metalloproteins, but it is uniquely essential for only a handful. In plant nutrition both Mn limitation and excess are common, depending on the type of soil and Mn bioavailability.

Mn is also a required element for animals and many microbes. The key roles of Mn in human biology are as enzyme cofactors for MnSOD, arginase, glutamine synthetase, and glycosyltransferases (Balachandran et al., 2020). In humans, Mn deficiency is rare. When in excess, Mn can cause neurological effects (manganism). Bacteria vary in their preference for metalating enzymes with Mn or Fe, with some groups having a more Fe-centric metabolism, and others relying more heavily on Mn (Bosma et al., 2021). This variability extends even to the level of individual enzymes, with Bacteria encoding Fe-dependent SODs (FeSOD), Mn-dependent SODs (MnSOD), or cambialistic enzymes that can function with either metal (Frye et al., 2022). Many Bacteria have no documented requirement for Mn, while for others it is essential. Mn is sometimes used as a substitute for Fe in Fe-limited conditions to allow essential processes in the cell to continue (Merchant & Helmann, 2012). For example, the replacement of FeSOD with MnSOD is a widespread iron-sparing mechanism in Bacteria, algae, and diatoms (Peers & Price, 2004). In *E. coli* facing Fe deprivation, an alternative,

Mn-utilizing RNR is expressed to replace the Fe-dependent RNR, allowing the essential process of DNA replication to continue (Andrews, 2011).

7.2 Iron ($_{26}$Fe)

Iron (Fe) is the single most abundant element of our planet, making up >30% by weight. Much of this Fe is partitioned into the core region (88% Fe), responsible for Earth's magnetic field. On Earth's surface, Fe is the 4th most abundant element (after O, Al, Si) making up 5.63% (56,300 ppm) of the continental crust (Figure 2). This high abundance of Fe is quite literally a universal property since Fe is the heaviest element formed through fusion reactions in the heaviest stars (nucleosynthesis) and therefore Fe accumulates as stars burn; all heavier elements require the collapse of massive stars into neutron stars, visible on Earth as supernovae (Domagal-Goldman et al., 2016). In striking contrast with its terrestrial abundance, Fe is largely depleted from vast regions of the ocean's surface waters and this can be a major limitation on primary productivity (Moore et al., 2013). Because Fe is a ubiquitous presence in biological systems it is intimately involved in the biogeochemical cycling of other elements (Kappler et al., 2021).

Fe is essential for almost all organisms. The only known exceptions are Bacteria (*Lactobacillus* spp. and *Borrelia burgdorferi*) that grow in severely Fe-limited environments and are thought to have completely dispensed with an Fe requirement (Posey & Gherardini, 2000). *Myoplasma genitalium*, a genome-reduced human pathogen, has also lost or replaced many Fe-dependent enzymes and may no longer require Fe for growth (Peralvarez-Marin et al., 2021). Although long considered a universally essential element for life, these rare exceptions suggest that Fe is a class (ii) element.

In catalysis, Fe can function as an electrophilic center (a Lewis acid) or as a redox center with the interconversion of ferrous (Fe^{2+}) and ferric (Fe^{3+}) species. Fe^{2+} is easily oxidized in aerobic environments, and this oxidation contributes to the production of reactive oxygen species (ROS) such as superoxide and hydrogen peroxide. This ready oxidation often leads to the formation insoluble oxides and hydrates (similar to rust), which contributes to the very low availability of Fe in aerated environments.

As an agile redox catalyst, Fe is the most versatile redox-active metal ion in biology. Fe is present, on average, in ~4% of encoded proteins in Bacteria and ~1% in Eukarya. In humans, Fe is estimated to be present in ~2% of all proteins, half of which are heme proteins (Zhang & Zheng, 2020). These values vary widely and in early evolving organisms, including representative Archaea, Fe can be more prevalent as a cofactor than Zn (Ferrer et al., 2007). Note that these values reflect the number of unique proteins encoded by each genome that are thought to contain Fe and do not take into account relative protein abundance.

Many Fe-containing proteins are conserved across the tree of life, suggesting an ancient origin (Andreini et al., 2009). Notable Fe-dependent enzymes include the cytochromes and other heme proteins (Figure 8a), iron-sulfur (FeS) cluster-containing enzymes, and proteins with mono- or dinuclear Fe centers. Heme-containing enzymes are ubiquitous in biology, and hemoproteins play a major role in electron transfer reactions. Heme also

functions in sequestration of O_2 by leghemoglobin to support symbiotic N_2-fixation in root nodules (Rutten & Poole, 2019) and in binding and delivery of O_2 to tissues in mammalian hemoglobin. Fe may also be coordinated with inorganic sulfide ion (S^{2-}) in FeS clusters. FeS clusters are most commonly found in two types, Fe_2S_2 and Fe_4S_4, and function as electron transfer cofactors and in regulating protein stability and activity (Lill, 2009). More complex arrangements with other metals are also common, as seen for example in the FeMo cofactor used in nitrogenases (Figure 8c).

In addition to its catalytic role, Fe^{2+} can serve to nucleate the folding of stable protein domains, much as Zn^{2+} does in Zn-finger proteins. For example, *Ferroplasma acidiphilum*, a member of the Archaea that grows in very low pH environments where Fe^{2+} is highly soluble, has an Fe-enriched proteome. Many proteins that would in other organisms use Zn instead contain Fe, which may function as an “iron rivet” to stabilize protein structure or in catalysis (Ferrer et al., 2007). Fe has also found other uses in biology. In magnetotactic Bacteria, intracellular arrays of magnetite (Fe_3O_4) crystals are formed as a mechanism to sense the Earth’s magnetic field (Figure 6). Phylogenetic comparisons suggest that magnetotaxis is an ancient trait that evolved during the Archaean eon more than 3 Ga (Lin et al., 2017). The ability to sense the magnetic field, together with other cues, allows directional swimming to find more favorable environments across oxic-anoxic gradients (Goswami et al., 2022; Müller et al., 2020).

Given the many important roles of Fe in biology, and the potentially toxic effects of Fe in contributing to ROS production, organisms must devote considerable resources to Fe homeostasis. Obtaining sufficient Fe is a challenge for many microbes that therefore produce high affinity organic chelators (siderophores) to solubilize Fe^{3+} in a form readily recognized for import (Chu et al., 2010; Malavia et al., 2017). In mammals, Fe is tightly bound by ferritins inside cells and by transferrin in the blood, and immune cells release proteins (calprotectin) that can sequester Fe and other metals from microbes (Murdoch & Skaar, 2022). The molecular mechanisms of Fe trafficking in humans have now been clarified allowing an integrated view of Fe fluxes at the cellular, organ, and systemic levels (Katsarou & Pantopoulos, 2020; Maio et al., 2021). In the Eukarya, the mitochondria play a central role in cellular Fe homeostasis as the major sites of heme and FeS cluster biogenesis (Mühlenhoff et al., 2015). Indeed, even intracellular pathogens that have reduced genomes have retained remnants of mitochondria (mitosomes) to sustain FeS synthesis (Lill et al., 2015).

While Fe is essential in plants, animals, and most microbes, the specific enzymes and functions that are essential (rather than beneficial) in any given organism are not always obvious. In many organisms, Fe likely has multiple essential roles and there is no way to adapt to its absence. We can also ask which specific types of Fe cofactor are essential. For example, FeS cluster assembly is an evolutionarily ancient process that is essential in Eukarya and in many microbes (Esquilin-Lebron et al., 2021; Vinella et al., 2009). However, it has been possible to engineer *E. coli* strains where FeS cluster assembly is dispensable. Although *E. coli* is predicted to encode >100 FeS proteins, only the two involved in isoprenoid biosynthesis are essential under all conditions (Trotter et al., 2009). By replacing these steps in the endogenous pathway with enzymes from the alternative

mevalonate pathway, it was possible to generate strains that no longer required FeS cluster biogenesis for growth (Tanaka et al., 2016). *B. subtilis* has also been engineered to render FeS biogenesis dispensable (Yokoyama et al., 2018). Since most organisms in all three domains of life encode proteins for FeS biogenesis, it is likely that organisms that no longer require (or at least benefit from) synthesis of this cofactor are rare.

Similarly, we can ask how frequently cells may have dispensed with a requirement for heme and heme-enzymes. Heme can be assembled by multiple pathways found in all three domains of life (Kořený et al., 2022; Layer, 2021). Those organisms that cannot synthesize heme may acquire heme from a symbiotic partner or, in the case of some pathogens, obtain heme from the host (Choby & Skaar, 2016). However, in selected anaerobic, fermenting Bacteria (some Clostridia and Thermotogales) and Archaea (methanogens), there is no apparent requirement for heme (Ducluzeau & Nitschke, 2016; Kořený et al., 2022).

Since Fe has so many essential roles in cell physiology, those conditions that lead to Fe limitation can have grave consequences. Fe has a myriad of uses in our cells with ~2% of human genes encoding Fe proteins distributed between heme proteins (48%), FeS cluster proteins (17%), and non-heme, non-FeS proteins (35%) (Zhang & Zheng, 2020). However, most of the 5 g of Fe in the human body is in hemoglobin (~70% of the body's Fe content), and the characteristic signature of Fe-limitation is a reduction in red blood cells (anemia). Fe deficiency is a widespread nutritional problem affecting well over 1 billion people and ranks among the leading health burdens in many countries (Pasricha et al., 2021).

Fe limitation is a concern in certain agricultural sectors due to its central role in electron transfer during photosynthesis and its poor bioavailability in alkaline soils (Briat et al., 2015). In *Arabidopsis*, over 1000 proteins are thought to contain Fe, including 446 heme proteins, 204 FeS proteins, and an additional 330 non-heme, non FeS proteins (Przybyla-Toscano et al., 2021). Fe-limitation leads to chlorosis, which can be remedied with Fe fertilizers. Limitation for Fe is also common in marine systems and is thought to limit primary production by phytoplankton in roughly one-third of surface waters (Moore et al., 2013; Tagliabue et al., 2017).

Fe limitation can be either an acute or chronic stress, and many organisms employ mechanisms of elemental economy to reduce Fe demand (Merchant & Helmann, 2012). Fe-sparing responses involve replacement of Fe proteins by alternative enzymes (using either organic cofactors or other metal ions) and a reduction in synthesis of low-priority Fe enzymes to allow Fe use by those pathways most critical for life (Blaby-Haas & Merchant, 2013; Brault et al., 2015; Oglesby-Sherrouse & Murphy, 2013). As just one example, replacement of abundant FeS-containing ferredoxins with flavodoxins is a classic signature of Fe-limitation in phytoplankton (Roche et al., 1996).

7.3 Cobalt ($_{27}$Co)

Although much less abundant in the crust than Fe or Mn (Figure 2), cobalt (Co) is a moderately abundant element (25 ppm): comparable to Ni (84 ppm), Cu (60), and Zn (70 ppm). The levels of these biologically important transition metals are even lower in the surface waters of the ocean (< 1 ppm) due to both limited solubility and their important role

as nutrients. Phytoplankton and other abundant organisms in the surface waters sequester nutrients and much of this biomass is ultimately transported to lower levels of the ocean system by sedimentation (Morel & Price, 2003).

Co is required by many Bacteria and Archaea and a subset of the Eukarya, with plants and many fungi being notable exceptions (class (ii)). A bioinformatic survey of over ~750 species concluded that Co is likely beneficial or essential for 76% of Bacteria, 96% of Archaea, and 31% of Eukarya (Zhang & Zheng, 2020). Those Bacteria that appear to not use Co often have reduced genomes or are host-associated. Among the Archaea, only the symbiotic Nanoarchaeota have lost all genes associated with Co-utilization. In the Eukarya, Co appears to no longer be used by many fungi, arthropods, and the streptophyta clade of plants (Zhang & Zheng, 2020).

The majority of Co-dependent enzymes rely on a complex organic cofactor (cobalamin; Figure 8b) with Co held within a corrinoid ring with a variable 5^{th} (lower) ligand (often a benzimidazole or purine) and 6^{th} (upper) ligand that participates in catalysis (often a methyl or adenosyl group) (Osman et al., 2021). Cobalamin biosynthesis requires nearly 30 separate steps, and this complex pathway is only found in selected Bacteria and Archaea. For example, *Salmonella enterica* synthesizes cobalamin but *E. coli* does not. A survey of 11,000 sequenced bacterial genomes revealed that ~37% have the complete pathway, but many more species have partial pathways (Shelton et al., 2019). Humans are unable to synthesize cobalamin and must acquire this nutrient from their diet, which led to its designation as vitamin B_{12}.

The sharing of cobalamins and their precursors (cobamides) in microbial communities is commonplace. In the *Bacteriodetes*, often found in the complex community of the animal gut microbiome, only 0.6% of sequenced species have the complete synthetic pathway, yet 96% have cobamide-dependent enzymes (Shelton et al., 2019). In marine systems, a requirement for B_{12} in both algae and diatoms may be met by an obligate association with Bacteria (Amin et al., 2012; Croft et al., 2005). Although many fungi do not contain recognizable B_{12}-dependent enzymes, early-branching fungal lineages contain both B_{12}-dependent enzymes and cobalamin-modifying proteins (Orłowska et al., 2021). While not an essential element for plants, Co has been suggested to have beneficial effects, including the stimulation of N_2-fixation by symbiotic bacteria and possibly for metalation of some enzymes that can also use other metal ions as cofactors (Hu et al., 2021). No unique and non-redundant role of Co has been identified in land plants and many fungi, and these organisms appear to have no Co requirement (Zhang et al., 2019).

Cobalamin-dependent enzymes catalyze three main types of reactions: isomerization, methyl transfer, and dehalogenation. In human biology, vitamin B_{12} deficiency leads to pernicious anemia (Green et al., 2017). Humans have two B_{12}-dependent enzymes: methyl-cobalamin is a required cofactor in methionine synthesis and adenosyl-cobalamin functions in methylmalonyl-CoA mutase. The roles of cobalamin in Bacteria and Archaea are more diverse, with a total of 15 identified cobamide-dependent enzyme types (Shelton et al., 2019). Co is also essential for growth of the abundant marine cyanobacterium *Prochlorococcus*, and this requirement cannot be met by Zn (Saito et al., 2002). Careful

measurements of the growth requirement suggest that fewer than 20 Co atoms are sufficient to sustain growth (compared to >5000 atoms of Fe), likely due to the role of Co-pseudocobalamin in NrdJ, a component of the essential ribonucleotide reductase (RNR) that supports DNA synthesis, and in the MetH methionine biosynthesis enzyme (Hawco et al., 2020). In many other cyanobacteria, both functions have been replaced by Co-independent enzymes. Indeed, the ability of organisms to dispense with a Co requirement by replacement with alternative enzymes, and to conditionally express the B_{12}-independent version as needed, is a widespread adaptation.

Co also serves as a cofactor in some non-corrin enzymes. For example, Co may serve in place of Zn as a cofactor for carbonic anhydrase, a key enzyme in support of photosynthetic carbon fixation, as observed in some diatoms and algae (Yee & Morel, 1996). As a result, Co can serve to reduce the Zn requirement for growth (Kellogg et al., 2020). In *Salmonella*, Zn-deficiency can also be compensated by provision with Co, which can sustain the activity of Zn-dependent enzymes and replace Zn in some ribosomal proteins that normally contain a structural Zn (Ammendola et al., 2020). Thus, Co may be generally beneficial in Zn-sparing responses.

7.4 Nickel ($_{28}$Ni)

Nickel (Ni) is essential for plants and beneficial (or conditionally essential) for many Bacteria and Archaea. Ni-enzymes are most widely used in anaerobic Bacteria and Archaea, which reflects the fact that Ni was prevalent in ancient environments (Hausinger, 2022). In most organisms, there are only a handful of Ni enzymes (Zhang et al., 2009), nearly all of which mediate reactions that either generate or consume biologically relevant gases (CO, CO_2, CH_4, H_2, NH_3, and O_2) (Alfano & Cavazza, 2020; Ragsdale, 2009). Among ~750 analyzed Bacterial species, nearly 60% contain Ni-dependent enzymes including representatives of most Bacterial phyla (Zhang & Zheng, 2020). The most common Bacterial Ni-dependent enzymes are urease, Ni-Fe hydrogenase, carbon monoxide dehydrogenase, and a Ni-dependent superoxide dismutase SodN. Ni enzymes were even more common in Archaea, being found in 83% of genomes and commonly include urease, Ni-Fe hydrogenase, carbon monoxide dehydrogenase, and methyl-coenzyme M reductase (Zhang et al., 2009). These enzymes can deploy Ni^{2+} as a Lewis acid (electrophilic center), as seen in urease and glyoxalase I, or use redox chemistry as seen in NiSOD, Ni-Fe hydrogenase and CO dehydrogenase (Maroney & Ciurli, 2014).

In Eukarya, Ni utilization is less common, with 32% of species encoding Ni-dependent enzymes (Zhang & Zheng, 2020). Urease is the only commonly occurring Ni-dependent enzyme, and Ni utilization is most commonly a trait of fungi and plants. The requirement for Ni in urease has been suggested to account for the essential role of this element in plant physiology, but Ni may also be a cofactor for glyoxalase I, important in the degradation of the toxic metabolite methylglyoxal (Fabiano et al., 2015). Ni is important in some marine diatoms and genomics studies implicate NiSOD as one key Ni-dependent enzyme (Dupont et al., 2008; Twining et al., 2012). Many marine cyanobacteria express a NiSOD that can reduce Fe demand by supplanting FeSOD (Dupont et al., 2008). Phylogenetic arguments suggest that in the Archean, and prior to the GOE, cyanobacteria may have

utilized a CuZnSOD, and only much later (at the end of the Proterozoic) did NiSOD become widespread (Boden et al., 2021).

Ni plays a particularly important role in the physiology of the human pathogen *Helicobacter pylori*, a Gram-negative bacterium that lives in the acidic environment of the stomach (Kumar et al., 2022). In this environment, Ni-dependent urease is critical to help moderate local pH by production of NH_3 (Gaddy & Haley, 2015). Urease activity requires specific pathways for Ni acquisition from dietary sources. Since Ni levels in animal tissues are low, *Helicobacter* spp. that live in the stomachs of carnivores have had to adapt to Ni deficiency. In *H. mustelae*, which colonizes ferrets, Ni-deficiency leads to the expression of an alternative Fe-containing urease to replace Ni-urease (Stoof et al., 2008). As these examples illustrate, Ni is a broadly beneficial element for many organisms (class (ii)), but in many applications the corresponding Ni enzymes can be replaced by alternative metalloenzymes.

7.5 Copper ($_{29}$Cu)

Copper (Cu) is widely, but not universally, employed as a versatile redox cofactor in all three domains of life and is (together with Fe and Zn) among the most ubiquitous metals in biology (class (ii)). In the Archean eon, Cu was largely absent from aqueous systems since the reduced Cu^+ ion precipitates as insoluble Cu_2S in sulfide-rich environments. With the increase in O_2 after the GOE, more soluble Cu^{2+} became available, and cuproenzymes became more prevalent. This history is reflected in the current distribution of Cu enzymes, which are present in ~80% of Bacteria (missing completely in several phyla), ~50% of Archaea, and >95% of the Eukarya sampled (Zhang & Zheng, 2020). Within the Eukarya, the only organisms lacking identifiable Cu transporters and cuproproteins are some protozoan parasites (Zhang & Zheng, 2020).

Across all three domains of life, Cu is most common in aerobic respiratory chains, where it is critical to the reduction of O_2 by the cytochrome oxidase complex. Other major redox roles for Cu include CuZnSOD and a variety of oxidases, many of which function outside the cell. One notable class of Cu-dependent oxidase is the lytic polysaccharide monooxygenases (LPMO) found in many fungi and some Bacteria (Johansen, 2016). LPMO enzymes play a central role in the degradation of lignocellulose and are therefore critical for the decomposition of plant matter. The evolution of LPMO enzymes may have led to the end, ~300 million years ago, of the Carboniferous Period and its associated coal deposits (Johansen, 2016), although this model has been challenged (Nelsen et al., 2016). Thus, Cu is most frequently implicated in reactions involving O_2 and in other electron transfer reactions.

Cu homeostasis has been well studied in the model alga *C. reinhardtii*, where it is critical for respiration and conditionally used in plastocyanin. Plastocyanin is a small, Cu-containing protein that serves as an electron carrier in photosynthesis in cyanobacteria, many green algae, and plants. Under Cu-limited conditions, plastocyanin can be replaced by cytochrome c_6 (a heme-dependent electron carrier) to spare Cu for cytochrome oxidase, the essential terminal enzyme for respiration (García-Cañas et al., 2021; Merchant et al., 2020). Cu is also important in Bacteria that can grow on methane, and some methanotrophs switch between a soluble Fe-dependent methane monooxygenase and a membrane-localized Cu-

dependent version depending on Cu availability, a process dubbed the “copper switch” (A. A. DiSpirito et al., 2016; Ross & Rosenzweig, 2017). In response to Cu, the particulate methane monooxygenase is produced and localized to intracytoplasmic membranes derived from the inner membrane (Alan A. DiSpirito et al., 2016).

In addition to its utility as a redox cofactor and electron carrier, Cu can be toxic if not carefully managed within the cell (Ladomersky & Petris, 2015). Cu sits at the apex of the Irving-Williams series, which reflects the high avidity with which Cu binds to ligands. As a result, Cu can displace other metals resulting in enzyme mismetalation and protein aggregation (Barwinska-Sendra & Waldron, 2017). Cu import into cells, transfer between cell compartments, insertion into enzymes, and export from the cell is all tightly regulated to prevent toxicity (Guengerich, 2018).

In Bacteria, Cu is generally restricted to enzymes in the membrane, periplasm, or external to the cell; cytosolic Cu-binding proteins are rare (Giachino & Waldron, 2020). Studies in the yeast *S. cerevisiae* led to the discovery of Cu chaperones that guide Cu into selected cuproproteins (Robinson & Winge, 2010). Metallochaperones are increasingly appreciated for their roles in metal homeostasis, including GTP-dependent chaperones for targeting metalation of enzymes by Ni, Zn, Co, and Fe (Chen & O'Halloran, 2022; Edmonds et al., 2021; Vaccaro & Drennan, 2022). Bacteria may also produce chelators (chalkophores) to assist with Cu acquisition (Kenney & Rosenzweig, 2018a). For example, *Mycobacterium tuberculosis* synthesizes a diisonitrile lipopeptide Cu-chelator in response to Cu limitation (Buglino et al., 2022).

During infection, the mammalian host can either limit access to Cu or use the toxicity imposed by excess Cu to kill pathogens (Culbertson & Culotta, 2021; Garcia-Santamarina & Thiele, 2015; Samanovic et al., 2012). The use of Cu intoxication by eukaryotic cells predates the rise of multicellular animals; even protozoa deploy Cu as a bioweapon (Hao et al., 2016). The antimicrobial properties of Cu have long been appreciated and are an active area of medical research (Arendsen et al., 2019). In agriculture, Cu-based antimicrobials came to prominence with the discovery by French vintners that $CuSO_4$ solutions (Bordeaux mixture) protect against fungal pathogens (Lamichhane et al., 2018). Cu-based compounds continue to be widely used in agriculture as antimicrobials, although they are increasingly regulated.

Cu is essential for humans, and mutations in genes encoding two homologous Cu transporters can lead to either Cu overload (Wilson’s disease) or to Cu deficiency (Menkes’ disease) (Bandmann et al., 2015; de Bie et al., 2007; Hordyjewska et al., 2014; Zlatic et al., 2015). Dysregulation of Cu metabolism is also implicated in the etiology several common neurodegenerative diseases, including Alzheimer’s, Parkinson’s, and amyotrophic lateral sclerosis (Giampietro et al., 2018). Since Cu is required for cell growth, impeding access to Cu has been exploited in new strategies for cancer therapy (Li, 2020; Shanbhag et al., 2021).

In sum, Cu is one of the most versatile metal cofactors in biology, especially valued for its redox chemistry and its essential role in aerobic respiration. Yet, this same active redox

chemistry, coupled with its high avidity for ligands, necessitates tight regulation of Cu import and trafficking.

7.6 Zinc ($_{30}$Zn)

From our present vantage point, Zn is the only transition metal that appears to be essential for all life (class (i)) (Zhang et al., 2019). Whether further investigation of life's diversity, particularly in the Bacteria and Archaea, challenges this rarefied status remains to be seen. Under biological conditions, Zn is not redox active and Zn^{2+} functions as an electrophilic center (Lewis acid) in enzymes and nucleates protein folding in Zn-finger proteins. There is nothing unique about this function, which in many enzymes can be assumed by other divalent metals such as Fe (Ferrer et al., 2007), Co (Yee & Morel, 1996), or Cd (Tang et al., 2014; Xu & Morel, 2013). Indeed, many Zn-dependent enzymes can be replaced by enzymes that use a different metal or use metal-independent chemistry (Zhang & Gladyshev, 2010).

Bioinformatics has been used to estimate the Zn content of various proteomes (Andreini et al., 2009), and the results are available in several databases (Zhang & Zheng, 2020). These studies predict that ~9% of all proteins encoded in Eukarya bind Zn, with a somewhat lower level of ~5% in representative Bacteria and Archaea. The higher level in Eukarya reflects, in part, a large diversification of Zn-finger containing transcription factors.

Because of its essentiality, Zn deficiency can limit cell growth. It is estimated that the human body contains 2 to 3 g of Zn that populates 300 distinct enzymes and 2000 transcription factors. Deficiency is thought to affect nearly one in five people globally (Chasapis et al., 2020), and in its more severe and chronic forms can lead to anemia, hypogonadism, and dwarfism (Roohani et al., 2013). Our immune systems have exploited the universal requirement for Zn to restrict bacterial growth through nutritional immunity (Murdoch & Skaar, 2022). The metal-chelating protein calprotectin is released by neutrophils and tightly sequesters Zn (as well as Mn and Fe) to create a metal-restricted environment for bacteria within tissues. Zn shares with Fe the property of being a common growth-limiting nutrient for phytoplankton in ocean surface waters (Kellogg et al., 2022; Morel & Price, 2003). Zn is also a critical nutrient in agriculture and in some soils is limiting for plant growth leading to chlorosis and stunted growth (Stanton et al., 2022).

The immediate cellular response to Zn limitation is an increase in expression of high affinity transporters to import Zn from environmental sources. Zn import may additionally benefit from the production of Zn chelators (zincophores), high affinity Zn ligands that function like siderophores in Fe import (Bellotti et al., 2021). Small molecule zincophores related to the plant metabolite nicotianamine have been identified in Bacteria and fungi and are postulated to be an ancient adaptation to Zn limitation (Laffont & Arnoux, 2020; Morey & Kehl-Fie, 2020). In contemporary plants, nicotianamine is thought to be involved in metal trafficking within and between tissues (Olsen & Palmgren, 2014). In *Mycobacterium tuberculosis*, another type of Zn-chelator, a kupyaphore, is postulated to assist in Zn acquisition and perhaps resistance to excess Zn (Mehdiratta et al., 2022).

In addition to import, Zn-limited cells mobilize Zn from intracellular stores. Depending on the organism, Zn may be stored in the thiol-rich protein metallothionein, mobilizable ribosomal proteins, or membrane-bound compartments (vacuoles). For example, in *S. cerevisiae* the Zn quota under replete conditions is ~2.3 x 10^7 atoms per cell, with ~60% stored in the vacuole (Wang, Weisenhorn, et al., 2018). The remaining Zn is largely protein associated and distributed among >200 distinct proteins. Under Zn deficient conditions the proteome is remodeled, the Zn quota drops more than 2-fold, and many Zn-dependent enzymes lack a bound metal ion (they are apoproteins). The combination of increasing import capacity and Zn mobilization can delay the onset of Zn limitation, but ultimately growth ceases in the absence of Zn.

In some systems it has been possible to infer those processes that are most susceptible to Zn depletion by identifying functions that are selectively induced in Zn-deficient cells. As a mechanism of elemental economy, many cells express Zn-independent enzymes to maintain their metabolism even in the face of Zn limitation. In *B. subtilis* Zn-deficient cells become limited for folate due to the failure of the Zn-dependent GTP cyclohydrolase I (FolEA) enzyme (Chandrangsu et al., 2019). Under severe Zn limitation, cells induce expression of an alternative, Zn-independent isozyme (Sankaran et al., 2009; Shin & Helmann, 2016). Analysis of the Zn deprivation response in the highly metal tolerant Bacterium *Cupriavidus metallidurans* has also been revealing (Nies, 2022b). This organism has an optimal Zn quota of 7 x 10^4 ions, and with ~2 x 10^4 ions growth becomes Zn-limited. Under this condition at least one abundant Zn-requiring metalloprotein (the RpoC subunit of RNA polymerase) is aberrantly folded and appears in inclusion bodies (Herzberg et al., 2014). This is representative of one effect of Zn limitation (misfolding of enzymes requiring a structural Zn ion) but does not imply that RNAP activity is limiting for growth. In general, it is common for Zn-independent enzymes and pathways to be induced to mitigate the effects of Zn limitation.

Insights into the physiological consequences of Zn deprivation have also emerged from studies of Zn chaperones belonging to the COG0523 family of GTPases (Edmonds et al., 2021). For example, in *B. subtilis* cells maintain FolEA activity by expression of a specific Zn metallochaperone (ZagA) that functions to deliver Zn to FolEA as a high priority destination (Chandrangsu et al., 2019), and when this can no longer be sustained a Zn-independent FolEB is induced (Shin & Helmann, 2016). Similarly, in *Acinetobacter* spp., a Zn metallochaperone supports activity of an enzyme critical for riboflavin synthesis (Nairn et al., 2016). In *C. metallidurans*, several Zn metallochaperones are present, and these appear to function in both metal delivery and metal storage (Bütof et al., 2019). In the Eukarya, COG0523 chaperones define the Zn-regulated GTPase metalloprotein activator (ZNG1) family and direct Zn to the critical enzyme methionine aminopeptidase in both *S. cerevisiae* (Pasquini et al., 2022) and in vertebrates (Weiss et al., 2022).

Zn limitation is also common in ocean surface waters. One key role of Zn in this environment is as a cofactor for carbonic anhydrase (CA), an abundant enzyme needed for the rapid equilibration of carbonic acid with CO_2 required for carbon fixation by RuBisCO. In Zn-limiting environments many phytoplankton sustain carbonic anhydrase activity with Co, Mn, or even Cd (see section 7.7.4) (Jensen et al., 2019; Morel et al., 2020). This

substitution allows cells to sustain high rates of photosynthesis and spares precious Zn for other vital functions. Members of the ZNG1 family chaperones have also been detected in diatoms, presumably as an adaptive response to Zn (and possibly Co) limitation in surface waters (Kellogg et al., 2022). However, the identity of the client proteins for these metallochaperones is not yet known.

7.7 Heavier Metals

The heavier elements within groups 7 to 12 are all metals of industrial relevance, but infrequently used in biology. Of the 12 elements in this region of the periodic table, only cadmium (Cd) has a beneficial role in nature (class (iv)). The others are class (v), with no documented beneficial role.

7.7.1 Technetium ($_{43}$Tc) and Rhenium ($_{75}$Re)—The heavier group 7 elements are technetium ($_{43}$Tc) and rhenium ($_{75}$Re). Tc is radioactive and does not occur naturally on Earth. The longest-lived Tc isotope has a half-life of 4.2 million years, and since our solar system formed ~4.5 Ga, there is essentially no Tc remaining from stellar nucleosynthesis. The very low level of Tc on Earth arises instead as a fission product from the decay of uranium ($_{92}$U). Tc salts can be reduced by microbes, which offers a potential mechanism for bioremediation of Tc-contaminated sites (Icenhower et al., 2010). Although not a beneficial element in nature, one metastable Tc isotope (^{99m}Tc) is the single most widely used radioisotope in medicine due to its short half-life (~6 hours) and low energy gamma emission that enables many imaging procedures (Duatti, 2021). Re is also one of the rarest elements on Earth and, like other elements of higher atomic number, is a primordial product formed through mergers of neutron stars, an intrinsically rare event (Johnson, 2019).

7.7.2 The Platinum Group Metals (Ru,Os,Rh,Ir,Pd,Pt)—The platinum-group metals (Ru,Rh,Pd,Os,Ir,Pt) from groups 8-10 are among the least abundant elements in Earth's crust (Figure 2). These metals do not readily form oxides and are siderophilic (iron-loving) elements that partitioned into the Fe-rich core of the Earth during planetary formation. All the elements in this group are considered noble metals based on their low reactivity. Within group 8, ruthenium ($_{44}$Ru) and osmium ($_{76}$Os) are notable for their toxicity to both microbes and mammalian cells (Meier-Menches et al., 2018; Southam et al., 2017). The heavier group 9 elements rhodium ($_{45}$Rh) and iridium ($_{77}$Ir) are also toxic, a trait that may be harnessed for anti-cancer therapies (Sohrabi et al., 2021). Some Bacteria, or bacterial consortia, can reduce Rh^{3+} to the metal to aid in bioremediation and metal recovery (Ngwenya & Whiteley, 2006). The group 10 elements palladium ($_{46}$Pd) and ($_{78}$Pt) also form toxic complexes and some, such as cis-platin for cancer chemotherapy, are medically useful. Both Pd^{2+} and Pt^{+4} can be subject to microbial reduction to the elemental metals, which may prove useful in biologically-mediated recovery of these valuable metals from waste streams (Zhuang et al., 2015).

7.7.3 Silver ($_{47}$Ag), and Gold ($_{79}$Au)—Both silver (Ag) and gold (Au) are precious coinage metals and of technological relevance. Silver (Ag) has long been appreciated for its antimicrobial properties (Rai et al., 2012), and bacterial mechanisms for resistance include exporters to pump toxic Ag ions from the cytosol (Mijnendonckx et al., 2013). Both Ag and

Au are also subject to biotransformation by microbes (Banik et al., 2022; Pradhan & Turner, 2022). Some Bacteria and fungi can reduce Ag^+ to generate Ag^0 nanoparticles (AgNP) (Guilger-Casagrande & Lima, 2019), which have a number of developing uses in medicine (Burdușel et al., 2018; Eckhardt et al., 2013; Rai et al., 2012). Gold (Au) ion can be reduced to metallic Au^0 by Bacteria such as *Burkholderia contaminans* (Wang et al., 2022).

7.7.4 Cadmium ($_{48}$Cd) and Mercury ($_{80}$Hg)—Cd and Hg are notable primarily for their toxicity. Both are extremely thiophilic metals and bind to sulfur containing metabolites and cysteine-rich proteins, often with toxic results. In animals, Cd can induce expression of the thiol-rich metal buffering protein metallothionein, and the ability of metallothionein to bind Cd can help mitigate toxicity (Nordberg & Nordberg, 2022). However, there are no beneficial uses for Cd documented in animals. In contrast, Cd has been confirmed as a biologically relevant cofactor for some carbonic anhydrases (CA) in marine microbes and is therefore a class (iv) element.

Efficient photosynthesis relies on CA to allow rapid production of CO_2, a required substrate for RuBisCO. Although most families of CA require Zn, some diatoms express a Cd-utilizing carbonic anhydrase (CDCA) that can function with either Zn or Cd <Figure 9>. This enables cells to sustain their metabolism even in Zn-depleted regions of the open ocean (Morel et al., 2020; Xu & Morel, 2013). This mechanism has been described in detail in the diatom *Thalassiosira weissflogii*, where a ζ-class CA (CDCA) functions with Cd, and an alternative δ-class enzyme can use Co. Recently, a new class of CA was described that can use Mn in place of Zn, further expanding the ability of diatoms to sustain growth when faced with Zn limitation (Jensen et al., 2019).

Divalent Cd can also substitute for Zn in other proteins, at least in vitro (Tang et al., 2014). However, this is not known to occur in cells and is of uncertain biological relevance. In contrast to Cd, Hg has no known beneficial role in biology (Selin, 2009). Mercuric ion is detoxified by many microbes by reduction to more volatile metallic Hg or by methylation (Yu & Barkay, 2022).

8. Groups 13-16: Metals and Metalloids

The non-metals in these groups include the essential macronutrients that, together with hydrogen, make up the CHNOPS macronutrients of life (section 2). The remaining elements in groups 13 through 16 include metals and metalloids. Three metalloids have essential or beneficial roles in biology (B,Si,Se); the remaining elements are mostly noted for their toxicity rather than any beneficial effects (Figure 1).

8.1 Group 13: The Boron ($_5$B) Group

Group 13 includes the metalloid boron ($_5$B) and four metals: aluminum ($_{13}$Al), gallium ($_{31}$Ga), indium ($_{49}$In), and thallium ($_{81}$Tl). These elements are commonly found as trivalent ions. As noted earlier, B (10 ppm in the crust) is scarce compared to other elements of low atomic number (Figure 2), although it is enriched in the form of hydrated borate oxyanion (borax) in deposits left by evaporation of transient lakes. In contrast, Al is the third most abundant element in the lithosphere by weight (8.23% or 82,300 ppm), after O (46.1%) and

Si (28.2%). Aluminum is an industrially important metal with over 60 million tons produced annually. Production of metallic Al is not limited by access due to ample deposits of Al-rich minerals, but by the high input of electricity required for production of the metal. Despite its abundance in nature, Al concentrations are very low in living systems, which have largely rejected but not eliminated this metal from cells (Pogue & Lukiw, 2014). Gallium ($_{31}$Ga) is moderately abundant in the lithosphere (19 ppm), comparable to many of the essential transition elements (Figure 2). In contrast, indium (In) and thallium (Tl) are scarce in the crust (both <1 ppm).

8.1.1 Boron ($_5$B)—Boron (B) is an essential element for plants (class (iii)), where it is a critical constituent of cell walls (Gonzalez-Fontes, 2020; Wimmer et al., 2020). B is particularly adept at coordination to vicinal hydroxyl groups (Bolaños et al., 2004), and this allows the formation of complexes between B and polysaccharides (rhamnogalacturonan) in plant cell walls (O'Neill et al., 2001). The essentiality of B has been challenged and an alternative view is that B functions to nullify the toxicity of phenylpropanoids through sequestration (Lewis, 2019). This suggestion led to a lively debate that highlights the challenge in defining the boundary between essential and beneficial roles (McGrath, 2020). Many plant biologists favor the view that B is beneficial, and most likely essential, for plants. B is widely used as a soil amendment, and the pathways of borate uptake and transport are well studied (Sharma et al., 2022; Yoshinari & Takano, 2017).

B is present largely as boronic acid in the ocean, at concentrations of ~4-5 ppm, and is conditionally essential for some marine organisms (Carrano et al., 2009). Essential roles for B have been proposed for algae, diatoms, and cyanobacteria. Compared to other trace elements, physiological studies to demonstrate the essentiality of B are straightforward. Early studies documented that the cyanobacterium *Nostoc muscorum* becomes chlorotic (loss of chlorophyll) when grown with low levels of B (Eyster, 1952). However, it was noted that care must be taken to use appropriate glassware since growth in Pyrex (borosilicate) glassware precluded detection of B deficiency (Eyster, 1952), a result that highlights the capacity of microbes to scavenge needed elements from seemingly recalcitrant sources. The cyanobacterium *Anabaena* sp. PCC 7119 also exhibits a loss of chlorophyll content under B-deficiency, although this may be a secondary result of a defect N_2 fixation (Mateo et al., 1986). One critical role of B in filamentous cyanobacteria may be to stabilize the cell wall of the N_2-fixing heterocysts to prevent oxidative inactivation of nitrogenase (Bonilla et al., 1990).

B may also have roles in other marine microbes. When the molecular structure of the *Vibrio harveyi* autoinducer 2 (AI-2) molecule bound to its receptor (LuxP) was determined, it was serendipitously found to contain B (Chen et al., 2002). Autoinducers are molecules produced and sensed by Bacteria as a way of monitoring their population density (Mukherjee & Bassler, 2019), and AI-2 was identified as a furanosyl borate diester. The LuxP receptor in this study is only found in marine organisms (*Vibrio spp.*) (Zhang et al., 2020), suggesting that these organisms sense extracellular AI-2 that has spontaneously bound to borate ion, an abundant constituent of seawater (Bolaños et al., 2004). In contrast, other Bacteria sense AI-2 through a different family of receptors that preferentially bind AI-2 that lacks B (Miller et al., 2004; Zhang et al., 2020). Thus, Bacteria have adapted to the form of AI-2 most

prevalent in their environment. Thus, the ability of *Vibrio* spp. to recognize AI-2 bound with B is advantageous, but not a specific, essential role of B.

8.1.2 Aluminum ($_{13}$Al)—Aluminum is notable as being one of the most abundant elements on Earth, yet one that has been widely ignored by living systems. Because of its high abundance in most soils, Al is found at trace levels throughout living systems, but with little apparent benefit or harm. There are no dedicated systems for Al uptake, trafficking, or storage, and no Al-dependent enzymes (Exley & Mold, 2015). Al is therefore a stealth element, with few biologically relevant interactions and no well-documented biochemical activities.

Most of the research on Al in biology has been dedicated to exploration of its toxicity at high levels, as well as the mechanisms by which plants and animals are able to tolerate high Al in the environment (Chandra & Keshavkant, 2021). Humans have caused an increase in Al in soils through mining, and increased bioavailability in acidic soils can be problematic (Pilon-Smits et al., 2009). There has been some discussion of whether environmental exposure, from sources such as cookware and vaccines, could be detrimental to human health. However, food intake remains the major source of exposure for most individuals and concerns about toxicity have abated over time for all but those with the highest occupational exposures (Goullé & Grangeot-Keros, 2020; Lidsky, 2014).

In the oceans, the presence of Al can lead to modest increases in the growth of diatoms and other phytoplankton. This is postulated to result from an ability of extracellular Al-superoxide complexes to reduce ferric iron to the more soluble and bioavailable ferrous form. In addition, Al may also lead to an increase in the sedimentation of organic matter and thereby impact both the C and P cycles (Duhamel et al., 2021; Zhou et al., 2018). Low levels of Al may be beneficial for plant growth, and Al is often bioaccumulated from acidic soils. The benefits of Al remain controversial, but may relate to an ability to deter herbivores, prevent Fe toxicity, or increase antioxidant defenses (Bojórquez-Quintal et al., 2017; Pilon-Smits et al., 2009). Al may also alter the composition of the plant-associated microbiome to favor beneficial Bacteria, and thereby indirectly contribute to plant health (Jiang et al., 2022; Muhammad et al., 2018). Based on this suggested beneficial effect for plant physiology, Al can be tentatively assigned as class (iv).

8.1.3 Gallium ($_{31}$Ga)—Gallium ($_{31}$Ga) is not known to have a beneficial or nutrient role in biology and is therefore a class (v) element. Gallium forms a trivalent ion that can replace Fe in some contexts and thereby interfere with Fe metabolism (Chitambar, 2016). Compounds containing $_{31}$Ga been developed for a variety of medical applications, including as anticancer agents. Galliumcan be bound to siderophores to serve as antimicrobials that interfere with Fe metabolism, and a similar strategy using porphyrins may target pathogens that access heme iron (Centola et al., 2020; Goss et al., 2018; Mouriño & Wilks, 2021). Gallium nitrate ($Ga(NO_3)_3$) has antibacterial activity and has shown promise in the clinical treatment of *Pseudomonas*, a common lung-associated pathogen in cystic fibrosis patients (Goss et al., 2018). Since gallium nitrate is already an FDA-approved treatment for hypercalcemia in cancer patients, adoption of this therapy could be relatively rapid.

8.1.4 Indium ($_{49}$In) and Thallium ($_{81}$Tl)—

Neither In nor Tl have any documented beneficial role in biology (class (v)). Indium is a significant component of electronic waste (e-waste), and this has raised concerns about its toxicity (White & Shine, 2016). Tl is considered highly toxic and, although present naturally at low levels, it can be highly enriched in contaminated soils near mining and smelting activities. It is bioaccumulated by some plants in the mustard family, which could be of use in bioremediation (Vejvodová et al., 2022).

8.2 Group 14: The Carbon Group

The group 14 elements include C (section 2.2), the metalloids silicon ($_{14}$Si) and germanium ($_{32}$Ge), and the metals tin ($_{50}$Sn) and lead ($_{82}$Pb). Apart from C, none of these elements are widely used by cells. However, Si is very important for some microbes for biomineralization (class (iv)). Ge, Sn, and Pb are noted for their toxicity and are class (v) elements.

8.2.1 Silicon ($_{14}$Si) and Si Biomineralization—

Silicon (Si) is the second most abundant element (after O) in Earth's crust due to an abundance of silicate (SiO_4)-based minerals, yet Si is essential or beneficial for very few organisms (class (iv)). The Si budget of the oceans consists primarily of inputs from weathering of continental crust and transport by rivers. These inputs are balanced by removal, primarily in near coastal regions, by sedimentation of marine organisms that biomineralize a silicate exoskeleton (Tréguer & De La Rocha, 2013). Diatoms are the single most important class of organisms that generate biogenic Si (hydrated silica; $SiO_2{\cdot}nH_2O$) in their shells (frustules) <Figure 10>, but Si is also used by some radiolarians, flagellates, and sponges. Biogenic silica is often referred to as opal, and the sedimentation of dead diatoms has the picturesque name of opal rain. Diatoms account for ~40% of ocean primary productivity and, as a result, the ocean Si and C cycles are intimately linked (Tréguer et al., 2018). Since it is estimated that roughly half of all photosynthetic carbon fixation occurs in the oceans (Field et al., 1998), diatoms alone account for ~20% all C fixed into organic matter on Earth.

In diatoms and radiolarians, Si plays a critical structural role and is essential for growth. Diatoms make silica-based cell walls, a fascinating process proposed to involve specialized micron-sized compartments (silica deposition vesicles or SDVs). However, recent evidence suggests that the mineralization process (silicification) may occur outside the cell cytoplasm (Mayzel et al., 2021). Thus, there may be multiple pathways for Si deposition, or the SDVs may play a support role in Si storage (Hildebrand et al., 2018). Recent studies reveal that Si-limitation facilitates viral infection and subsequent death of diatoms (Kranzler et al., 2019). Because of the essentiality of Si to the diatom lifecycle, diatoms have evolved mechanisms to acclimate to Si limitation. When Si-limited, diatoms may decrease Si content by decreasing frustule thickness, although this can lead to an increased vulnerability to predators (McNair et al., 2018).

Si is also beneficial to most plants and has a role in plant stress responses, growth, and defense mechanisms (Sharma et al., 2021). Therefore, Si has been classed as quasi-essential (broadly beneficial but not essential) (Epstein, 1999; Rodrigues & Datnoff, 2015). As a major component in most soils, plants have ample access to Si and accumulate Si as ~0.1%

to 15% of dry weight, depending on species and growth conditions (Farooq & Dietz, 2015). This is higher than some essential elements (including Ca, Mg, S and P). However, some plants are considered Si "excluders" and have no growth defect with much lower Si content (down to 0.0006%) (Epstein, 1999). In the specific case of horsetails (*Equisetum* spp.) Si is essential, but this is the exception, and most plants can complete their lifecycle in the absence of Si (Epstein, 1999). Most plant-associated Si is present in microscopic (typically ~10 to 30 μm) mineralized, quartz-like inclusions known as phytoliths. These can be both inside cells or deposited on cell walls, but the process of silicification is not well understood (Kovács et al., 2022). Si availability can be important under drought stress conditions and in plant defenses (Wang et al., 2021).

Plants take up Si from the soil as the neutral hydrate silicic acid [$Si(OH)_4$] and have dedicated transporters both for import and excretion (Gaur et al., 2020). The silicic acid importer, named Lsi1, is a member of the evolutionarily ancient aquaporin family of transporters found in all three domains of life (Deshmukh & Bélanger, 2016). Related transporters, collectively defined as the Nodulin26-like intrinsic proteins (NIPs), have been designated as metalloido-porins to reflect their roles in transport of silicic acid and related metalloids across membranes (Pommerrenig et al., 2015).

In humans, Si increases the strength of bones and connective tissue and may have other beneficial effects, but these are still under study (Farooq & Dietz, 2015; Rondanelli et al., 2021). However, because Si is ubiquitous in plant-based foods, dietary insufficiency is not observed and there is no official recommendation for daily intake (Rondanelli et al., 2021).

8.2.2 Germanium ($_{32}$Ge)—Germanium (Ge) is immediately below Si in the periodic table and has a related chemistry. In soils, it is commonly present as germanic acid ($Ge(OH)_4$), a silicic acid analog. Ge is most noted for its detrimental effects on living systems. However, low levels of Ge added to animal feed has been suggested to increase fitness. The mechanism behind these effects is not well understood, but may involve beneficial effects on immune function (Li et al., 2017). There are no reported instances of Ge deficiency leading to health effects in animals. In plants, Ge can be toxic in excess (Sharma et al., 2021), but low levels may delay the onset of B deficiency, perhaps by increasing the mobility of borate (Rosenberg, 2008).

Like Si, Ge forms oxides (GeO_2) that can sometimes be found in biogenic SiO_2 minerals such as phytoliths in plant tissues (Kaiser et al., 2020). Ge is ~10^4 less abundant than Si, so even when present it is a very minor component. Ge can also be incorporated at low levels during silicification in diatoms and sponges, but without any apparent benefit. Indeed, Ge may interfere with silicification in some instances, and in high concentrations can cause morphological and other defects (Mayzel et al., 2021; Moura & Unterlass, 2020). This inhibition is postulated to involve incorporation of Ge oxides that then acts to block further Si incorporation (a Ge-capping model) (Marron et al., 2016). In sum, Ge is not essential for any organism, and beneficial effects remain anecdotal. We here assign Ge as a class (v) element.

8.2.3 Tin ($_{50}$Sn) and Lead ($_{82}$Pb)—

Neither tin (Sn) nor lead (Pb) have any documented beneficial roles in biology (class (v)). Sn is a trace element in many organisms, presumably due to adventitious uptake. Although Sn was once suggested to be essential for humans, it is no longer even considered beneficial (Chellan & Sadler, 2015). Similarly, Pb is of no known beneficial use and is toxic to most organisms. Toxicity due to environmental Pb contamination, including in lead-containing paints and contaminated drinking water, remains a major health concern requiring careful remediation (Collin et al., 2022).

8.3 Group 15: The Nitrogen Group

The nitrogen group includes two elements that are essential for all life (N and P) as considered in section 2. The remaining elements in this group include arsenic ($_{33}$As), antimony ($_{51}$Sb), and bismuth ($_{83}$Bi). These elements are more noted for their toxicity than for their rare beneficial roles, which are only seen in selected microbes that take advantage of the redox properties of some As and Sb anions.

8.3.1 Arsenic ($_{33}$As) and Antimony ($_{51}$Sb)—

Both arsenic (As) and antimony (Sb) are commonly found as oxyanions and are subject to biologically-mediated redox reactions. Arsenate-reducing and arsenite-oxidizing microbes play a major role in the biogeochemical cycling of As (Biswas & Sarkar, 2022). Similarly, antimony-oxidizing bacteria oxidize antimonite to antimonate, and the reverse reaction can also be microbially catalyzed (Deng et al., 2021; Li et al., 2016; Liu et al., 2022).

Metalloid oxidation can support chemolithotrophic growth: As^{3+} or Sb^{3+} can serve as an electron donor to provide reducing equivalents for the fixation of CO_2 into organic matter (Deng et al., 2021; Shi et al., 2020). As may also be used in Bacteria for the synthesis of organoarsenicals as antibiotics. Arsenicals have a long history in medicine, extending at least to the time of the ancient Greeks (Paul et al., 2022). The recent discovery of arsinothricin as a bacterially produced organoarsenical antibiotic provides one example of a beneficial role for As in microbes (Li et al., 2021). Given their ability to participate as electron donors for chemolithotrophs and acceptors for anaerobic respiration, both As and Sb can be considered as class (iv) elements, with some utility to selected microbes.

8.3.2 Bismuth ($_{83}$Bi)—

Bi is a low abundance heavy metal present in the crust at levels (8.5 ppb) somewhat greater than gold (Au), but less than selenium (Se). Bi was one of the earliest metals to be discovered and is often present in ores as sulfides or oxides. Until 2003, Bi was considered the heaviest stable element in the periodic table. However, the natural ^{209}Bi isotope does decay by alpha-particle emission (as predicted by theoreticians), but decay is extremely slow (a half-life longer than the age of the universe). Chemically, Bi has properties similar to Th and Pb, but with less toxicity (Kanatzidis et al., 2020). Bi has no known beneficial role, although Bi compounds have a long history in medicine (Li et al., 2019). Bismuth subsalicylate is widely used for gastrointestinal distress, as and anti-diarrheal, and other formulations have been developed for the treatment of problematic *Helicobacter pylori* infections (Griffith et al., 2021). For our purposes, we assign Bi as class (v).

8.4 Group 16: The Oxygen Family

Group 16 includes the essential non-metals oxygen ($_8$O) and sulfur ($_{16}$S) (section 2), the nutrient metalloid selenium ($_{34}$Se), the rarely beneficial metalloid tellurium ($_{52}$Te), and the biologically irrelevant metal polonium ($_{84}$Po).

8.4.1 Selenium ($_{34}$Se)—Selenium (Se) is essential for many organisms from all three domains of life (class (ii)). Se functions most commonly to replace S in selenocysteine (Sec) and in a modified base (5-methylaminomethyl-2-selenouridine; mnm5Se2U) found in the wobble position of specific tRNAs. In both pathways, hydrogen selenide (H_2Se) is first phosphorylated by selenophosphate synthetase (SelD) to generate selenophosphate. Selenophosphate is a substrate for both SelA, which converts a tRNA-bound cysteine to Sec, and SelU, which replaces S in 2-thiouridine-containing tRNAs with Se.

Selenoproteins represent a small set of proteins that have a site-specific substitution of Sec in place of a Cys residue (replacing a S atom with Se), often in an enzyme active site. Sec itself is synthesized from Cys after charging of a specific Sec-tRNA. After conversion to Sec, this charged tRNA binds with the help of a dedicated elongation factor to ribosomes at specific UGA stop codons in response to specific signals. These RNA-associated signals (selenocysteine insertion sequences; SECIS) vary between organisms and bind to accessory proteins that direct co-translational Sec insertion (Wells et al., 2021). Most selenoproteins have a single Sec in a catalytic role, as in glutathione peroxidase. Because of its mechanism of co-translational insertion, and the presence of a cognate codon, Sec is considered the 21st proteogenic amino acid in biology.

Many Se enzymes are redox active. Sec is a much stronger nucleophile than Cys, which increases catalytic efficiency. Sec can be reversibly oxidized to the selenenic acid (Sec-SeOH), analogous to the oxidation of Cys to sulfenic acid (Cys-SOH). A key distinction, however, is that S oxidation often continues further to the sulfinic acid (Cys-SO_2H) and sulfonic acid (Cys-SO_3H); these over-oxidation reactions are much less common with Sec and re-reduction is more favorable (Reich & Hondal, 2016). These catalytic advantages provide a selective pressure to retain the extra machinery needed for selenoprotein synthesis.

The full suite of biologically important Se-containing compounds has yet to be revealed. Bioinformatic studies have revealed that *selD* genes are commonly found closely associated with *selA*, *selU*, and several genes of poorly characterized function (Kayrouz et al., 2022). This suggests that there may be other pathways that use selenophosphate for biosynthesis. One SelD homolog (SenC) initiates a pathway (involving also the SenA and SenB proteins) that uses an early intermediate in synthesis of the low molecular weight thiol ergothioneine and generates the Se analogue, selenoneine (Kayrouz et al., 2022). In this pathway, SenB generates an unusual selenosugar (N-acetyl-1-seleno-β-D-glucosamine; SeGlcNAc). SenA then combines this Se donor with N-trimethylated histidine (hercynine) to form the unstable intermediate hercyncyl-SeGlcNAc selenoxide, which spontaneously forms the product selenoneine. This gene cluster is present in more than 800 Bacteria, including many proteobacteria and actinomycetes.

Se biochemistry is a feature of many Bacteria, Archaea, and Eukarya. Sec biosynthesis is energetically costly, with an estimated 25 ATPs required each Sec incorporated (Reich & Hondal, 2016), and Sec usage has been lost from many lineages. The presence of in-frame "stop" codons and associated SECIS elements allows sites of Sec insertion to be predicted based on genomic information. Genome analyses reveal that ~20% of Bacteria incorporate Sec in their proteomes and another ~10% use Se in tRNA or have substituted Se in place of S in more complex cofactors (Wells et al., 2021; Zhang & Zheng, 2020). The most prevalent Sec-containing bacterial enzymes are formate dehydrogenase and glycine reductase. In the Archaea, Se usage is rarer with less than 12% of genomes (mostly within the Methanococcales, Methanopyrales, and Lokiarchaeota) encoding Sec-containing proteins (Zhang et al., 2019; Zhang & Zheng, 2020). There appears to be a correlation between Sec-utilization and a facultative or anaerobic lifestyle (Zhang & Zheng, 2020). One hypothesis suggests that Se utilization is related to the evolution of antioxidant defenses (Reich & Hondal, 2016).

Selenoproteins are essential for vertebrates (with 25 distinct selenoproteins in humans) and are found in many plants. Mutational studies in mice reveal that at least four selenoproteins (including thioredoxin reductases and a gluthathione peroxidase) are essential (Santesmasses et al., 2019). Since selenoproteins are found in unicellular Eukarya, vertebrates, and some early evolving fungi, it is currently thought to be an ancestral trait that has been lost in many clades (Mariotti et al., 2019; Santesmasses et al., 2020). It is unknown why it has persisted in certain lineages for 3.5 Ga and has been lost in others (Wells et al., 2021).

Many land plants, insects, and fungi do not contain the Sec-insertion pathways. Instead, land plants are notable for the synthesis of free selenomethionine (SeMet), considered a dietary antioxidant for humans. SeMet synthesis initiates with the import of selenate (SeO_4^{2-}) through sulfate uptake transporters or selenite (SeO_3^{2-}) mediated by phosphate transporters. A glutathione-dependent pathway then allows synthesis of hydrogen selenide (H_2Se), which is used instead of hydrogen sulfide (H_2S) by cysteine synthase. This then leads to Sec and ultimately to SeMet (Nasim et al., 2021). In contrast with Sec, which is incorporated with high efficiency at specific sites in proteins, SeMet can be incorporated stochastically at a low level in place of Met during translation. In sum, the major role of Se in biology is in place of S in amino acids.

Some anaerobic Bacteria are capable of dissimilatory respiration of Se (Oremland, 2020). Reduction of selenate to selenite has been widely reported, and reduction of selenite has also been observed (Wells et al., 2019). Selenotrophs such as *Sulfurospirellum barnesii*, *Bacillus selenitireductens*, and *Bacillus arseniciselenatis* respire Se-oxyanions to support growth.

8.4.2 Tellurium ($_{52}$Te)—Tellerium (Te), like S and Se, can adopt oxidation states ranging from −2 to +6, with the most common ions being +6 (tellurate, TeO_4^{2-}) and +4 (tellurite, TeO_3^{2-}). Although it is one of the rarest elements in the lithosphere (77^{th} in abundance at 0.001 ppm), in some areas Te can be concentrated to high levels (Zare et al., 2017). High Te is present near some deep sea hydrothermal vents and microbes from this extreme environment respire using dissimilatory tellurate and tellurite reduction (Csotonyi et al., 2006). Genomic studies suggest that this is a common mode of energy generation in this

unusual environment and is found in diverse genera including *Shewanella*, *Pseudomonas*, and *Vibrio* spp. (Maltman et al., 2016; Maltman & Yurkov, 2019; Presentato et al., 2019).

The tellurite anion (TeO_3^{2-}) can also be toxic to microbes, possibly due to imposition of oxidative stress (Chasteen et al., 2009). Genes implicated in resistance to Te are associated with efflux, methylation, the production of volatile compounds, or reduction leading to the formation of a black Te^0 precipitate (Kessi et al., 2022). The formation of Te nanoparticles often occurs in the cytoplasm, and likely depends on glutathione as a reductant (Kessi et al., 2022; Vávrová et al., 2021). Although most biological transformations of Te ions seem to be directed at detoxification, Te is of clear physiological benefit to some Bacteria from extreme environments such as deep sea hydrothermal vents (Maltman & Yurkov, 2019; Presentato et al., 2019). Therefore, we assign Te as a class (iv) element.

8.4.3 Polonium ($_{84}$Po)—Po is one of the rarest elements in the biosphere (estimated as a million-fold less abundant than Te), and each of the dozens of isotopes are radioactive. The major isotope found naturally is ^{210}Po (138 day half-life), which is continually produced through the decay of ^{238}U and ^{222}Rn. It has no beneficial roles in biology and is acutely poisonous due to it radioactive emission of tissue-damaging alpha particles (Ram et al., 2019). Po is therefore a class (v) element.

9. Group 17: Halogens

The halogens are electronegative elements and include fluorine ($_9$F), chlorine ($_{17}$Cl), bromine ($_{35}$Br), and iodine ($_{53}$I). Astatine ($_{85}$At) is vanishingly rare and radioactive and of no relevance to biology (class v). The halogens commonly exist as the anion (halide), but also form covalent bonds in organohalogens.

The halogens are both abundant and bioavailable compared to many elements of comparable mass. In the Earth's crust, abundance decreases with atomic number with F (585 ppm) > Cl (145 ppm) > Br (2.4 ppm) > I (0.45 ppm). Fluoride is a component in many minerals, where it can substitute for hydroxide anion. On the same scale, seawater is exceptionally rich in Cl (1.9×10^4 ppm), followed by Br (65 ppm), F (1.4 ppm), and I (0.05 ppm). The relative paucity of F in seawater reflects its ability to be incorporated into $CaCO_3$ minerals (Carpenter, 1969). F is also incorporated into calcium phosphate minerals (apatite), to generate fluoroapatite. Thus, biomineralization plays an important role in the depletion of F from ocean waters (Schlesinger et al., 2020).

Of the halides, Cl anion is by far the most important and the only one considered to be essential for cell physiology. However, the other halides may have beneficial and sometimes even essential functions. For example, Br and I are essential trace elements in human biology. Most microbes do not require halides to survive, but for selected species Cl is essential, and some species synthesize secondary halogen-containing metabolites (organohalogens).

9.1 Fluorine ($_9$F)

Fluorine is not known to be essential for any organism and is noted primarily for its toxicity (Johnston & Strobel, 2020). Nevertheless, F may have beneficial roles in some Bacteria, plants, and animals and is therefore class (iv). In human biology, F helps strengthen the apatite mineral that makes up tooth enamel, which decreases dental caries (Aoun et al., 2018). Dietary sources of F can include tea, seafood, fluoridated toothpaste, and drinking water.

Fluorinated natural products are still exceptionally rare (Chan & O'Hagan, 2012) and the benefit to the organism is often not obvious (Carvalho & Oliveira, 2017). For example, several genera of tropical and subtropical plants from Africa, Australia and South America produce fluoroacetate, which is toxic to mammals due to its ability to be converted to fluoroacetyl-CoA and then to fluorocitrate, a potent inhibitor of aconitase (Leong et al., 2017). From the perspective of the plant, this can presumably be viewed as a beneficial role for F. Some *Streptomyces* spp. produce fluorinated compounds with antimicrobial activity, including 4-fluorothreonine and the F-containing compound nucleocidin produced by *S. cattleya* (Zhu et al., 2015).

Fl toxicity has been documented in animals, plants, and microbes (Zuo et al., 2018). Many Bacteria and Archaea have evolved specific defense systems for the export of fluoride (Johnston & Strobel, 2020). These were originally identified by their association with a conserved, RNA-based regulatory element (riboswitch) that was found to serve as a sensor of fluoride anion (Baker et al., 2012). Fluoride export systems (FEX) have been documented in three model fungi (*Neurospora crassa, Saccharomyces cerevisiae, and Candida albicans*) (Li et al., 2013) and in plants (Banerjee & Roychoudhury, 2019).

9.2 Chlorine ($_{17}$Cl)

Chlorine (Cl), in the form of the chloride anion, is the most biologically relevant halide and is essential for both plants and animals. This is perhaps not surprising since Cl is the single most abundant solute in seawater, with a concentration of >19 gm per liter. In contrast, in the lithosphere Cl is less abundant than Fl. Since Cl is not essential for many Bacteria and Archaea, we assign Cl as a class (iii) element.

In animals, Cl is found in extracellular fluid as a counter ion to positively charged cations like K and Na. Since Cl is largely excluded from the cytosol, there is typically a transmembrane Cl ion gradient. Early nutrition studies using rats and chicks established that Cl deficiency has severe effects on organismal physiology. Chicks, for example, required 0.15% Cl by weight in their feed for maximal growth, and when fed a diet with <0.02% Cl they exhibited numerous symptoms, including nervous system dysfunction (Leach & Nesheim, 1963). Supplementation with Br, but not other halides, could restore the growth rate of Cl deficient chicks, but could not correct the nervous system defects. This likely reflects, at least in part, the irreplaceable role of Cl anion in neuronal cation-chloride cotransporters (Kaila et al., 2014). Indeed, the cation-chloride cotransporter family, and in particular K^+-Cl^- cotransporters, emerged very early in evolution, with representatives throughout the Eukarya and in some Archaea (Hartmann et al., 2013). In humans, Cl-

dependent transporters are found throughout the body, and numerous genetic diseases have been linked to defects in this important protein family (Poroca et al., 2017).

Cl anion also participates in other important physiological processes in humans. For example, gastric acid (HCl) is secreted by parietal cells in the epithelial lining of the stomach to aid in food digestion, and the strong oxidant hypochlorous acid (HOCl) is generated by activated neutrophils to aid in the killing of bacteria at sites of infection (Ulfig & Leichert, 2021). In addition to HOCl, it is estimated that ~10% or so of the hypohalous acid produced under physiological conditions is HOBr (Chapman et al., 2009). Cl is also an essential micronutrient for plants (Broyer et al., 1954), critical for the proper functioning of photosystem II, for the opening and closing of the stomata to control cell turgor and volume, and in action potentials and currents (Raven, 2017). Cl deficiency results in wilting of leaves at their edges, and eventual curling, chlorosis, and necrosis.

Unlike plants and animals, Cl does not appear to be essential for many microbes. A survey of 44 Bacteria did not reveal any with a demonstrable Cl requirement, although in 11 cases, Cl was beneficial under osmotic stress conditions (Roeßler et al., 2003). In *E. coli*, a well characterized Cl^-/H^+ antiporter plays an important role in survival under severe acid stress: an influx of Cl^- can drive export of H^+ from the cytosol (Chavan et al., 2020; Matulef & Maduke, 2007; Miller, 2021). In some obligate halophiles, including members of both Bacteria and Archaea, Cl is essential (Müller & Oren, 2003). For example, in some Archaea (Halobacteriaceae) molar concentrations of Na and Cl are pumped into the cells by cotransport as osmolytes. Even in halophiles, the requirement for Cl varies widely (Müller & Oren, 2003). Thus, Cl is beneficial in this context. Cl-containing secondary metabolites (organochlorine compounds) are produced by some species of marine and soil bacteria, fungi, and phototrophic eukaryotes and are presumed to be beneficial (Atashgahi et al., 2018).

9.3 Bromine ($_{35}$Br)

Bromine (Br) is only known to be essential for animals, due to a key role in assembly of some collagen fibers. Specifically, Br is used in hypobromous acid, which functions in the formation of crosslinks essential for collagen function, as documented in depletion studies in *Drosophila* (McCall et al., 2014). Hypobromous acid is used for the formation of sulfilimine crosslinks in collagen IV by peroxidasin, a heme-containing oxidase. These crosslinks are crucial for integrity of basement membranes and therefore tissue development in animals (McCall et al., 2014). This is the only known role for Br in animals.

Br is actively concentrated by some marine algae. Bromide anion is present in seawater at a level 650-fold lower than Cl. However, certain macroalgae (seaweed) concentrate Br to very high levels. In studies of algae from the sea of Japan, many red and brown algae were found to contain ~0.1% Br (% dry weight), and two species of red seaweed (*Polysiphonia japonica* and *Neorhodomela larix*) accumulated Br to >3% (Saenko et al., 1978). This high concentration implies a beneficial role.

There is some evidence to suggest that in plants Br can partially substitute for Cl under low Cl conditions (Ozanne et al., 1957). Since Cl is an essential micronutrient for plants,

this could allow an elemental sparing effect. However, at 2.4 ppm, Br is 60-fold less abundant than Cl in the lithosphere, so the relevance in most natural settings is not obvious. V-dependent bromoperoxidases may also play a beneficial role in microbes by incorporation of Br into secondary metabolites (Cabrita et al., 2010). Since Br is essential in many multicellular animals, due to its specialized role in collagen crosslinking, and beneficial for some other organisms, we assign Br as class (iii).

9.4 Iodine ($_{53}$I)

Iodine (I) has beneficial interactions with selected organisms and is essential for mammals (class (iv)). Although present at low concentrations in the Earth's crust, seawater contains ~60 μg per liter, often exceeding the level of essential micronutrients like Fe, Zn, and Mn. Even so, it is the least abundant halide in seawater (Venturi, 2011)

In mammals, I is present in thyroxine and triiodothyronine, thyroid hormones that control the metabolic rate of the body and are essential for growth and development. Deficiency can cause hypothyroidism, goiter, and other diseases. Societal remedies for I deficiency include the iodization of table salt, which helps humans meet their daily requirement. Although not required for plants, I may play a beneficial antioxidant role in some aquatic plants (Medrano-Macías et al., 2016).

Most beneficial roles of I are associated with the synthesis of organoiodine compounds. Indeed, I-containing molecules have been described in more than 100 species, including marine bacteria and cyanobacteria, various algae, and diverse animals (Dembitsky, 2006). Their biological roles are largely unknown, although some may have antimicrobial activity. It has been suggested that V-dependent haloperoxidases evolved as an ancient protection mechanism against ROS (Leblanc et al., 2015; Venturi, 2011). Haloperoxidases consume H_2O_2 as substrate using halide ions as reductants and, in the process, can generate organohalogen compounds. This chemistry is well studied in brown algae (kelp). The macrophytic algae *Laminaria* concentrates I from seawater, with ~0.5 μM iodide (I^-) and iodate (IO_3^-), by more that 10^4-fold to millimolar levels (~1% by dry weight). In this species, ~80% is retained as iodide ion, and is postulated to function as a cellular osmolyte (Nitschke & Stengel, 2014), in addition to its suggested role as an antioxidant (La Barre et al., 2010).

10. Essential Elements Revisited

Having completed this survey of the biological roles of elements, we can return to the questions that motivated this review: *What is the minimum set of elements essential to sustain life?* and *Which elements have a beneficial role in biology, and which are either ignored, adventitiously accumulated, or consistently deleterious*? One key conclusion is that the set of elements essential for all life is reduced when one moves beyond the purview of mammalian (or human) physiology and plant biology to also consider the Bacteria and Archaea. Conversely, the set of elements that may be of physiological benefit keeps expanding as more biology is revealed.

Determining the metal ion requirements across the tree of life is a particular challenge, complicated by the presence of very high affinity and efficient uptake systems and the challenges of creating rigorously defined growth media. It is often insufficient to prepare medium using the highest purity reagents, since microbes are adept at scavenging trace nutrients, even from the walls of their culture vessels! For example, in chemostat studies of *E. coli* grown under Zn limitation, the culture vessel was prepared by acid-washing and treatment with chemical chelators to strip any bound metals from the surface. Nevertheless, the Zn-limited cells routinely contained much more Zn than added to the culture medium, presumably by actively leaching Zn from the glassware (Graham et al., 2009), and this effect decreased with repeated culturing as the vessel become more and more depleted of associated Zn. Similarly, leaching of B from borosilicate (pyrex) glassware complicated early efforts to explore the biological role of B in cyanobacteria (Eyster, 1952). In a third example, the serendipitous exposure to traces of V in steel (present in the plunger of a Hamilton syringe) pointed to a role for V in supporting activity of a purified haloperoxidase (Leblanc et al., 2015; Vilter, 1995).

In addition to the challenge of creating metal-limiting conditions, many metalloenzymes can interact with more than one transition metal with variable effects on activity. The situation is further compounded since metal ions may exchange during purification, which can lead to misleading assignments of the cofactor. In such cases, it has been challenging to know which ion is the true cofactor in vivo, or even if there is only one. Most famously, some superoxide dismutases (SOD) can function with either Fe or Mn and are designated as cambialistic (Frye et al., 2022; Valenti et al., 2022). However, this general principle applies to many classes of enzymes (Eom & Song, 2019; Smethurst & Shcherbik, 2021). Further, limitation for one metal can often be compensated by the presence of another, often due to the activity of an alternative enzyme with distinct metal preferences (Merchant & Helmann, 2012). Because of these complexities, and significant uncertainty in defining metalloproteomes (Cvetkovic et al., 2010), it is often challenging to define the precise set of metal ions that are required for cells.

Another challenge in investigating the biological roles of the elements is that so many can be present in cells, perhaps due to adventitious accumulation. Using high sensitivity analytical techniques, including inductively-coupled plasma-based methods (ICP-AES and ICP-MS) (Becker et al., 2014; Lobo et al., 2018) and laser-induced breakdown spectroscopy (Busser et al., 2018), it is possible to measure atomic composition with exquisite sensitivity. The ability to simultaneously monitor many elements has given rise to new research strategies including “metallomics” and “ionomics” (Haraguchi, 2017; X. Y. Huang & D. E. Salt, 2016). These approaches can provide insights into compensatory interactions between elements (Jeyasingh et al., 2017). However, their high sensitivity presents challenges; in one study 74 out of 78 stable elements could be detected in salmon (Haraguchi et al., 2008), and 60 or more elements have been reported in human tissues (Chellan & Sadler, 2015). The presence of elements does not necessarily indicate a beneficial role; uptake may be adventitious. For example, sub-stoichiometric amounts of (presumably) non-physiological cofactors (e.g. Pb, U) may be found adventitiously bound to enzymes (Cvetkovic et al., 2010), and some abundant elements (e.g. Al) are ubiquitous in cells and tissues, but of little obvious function.

10.1 Essential Elements for Humans

Remarkably, the precise suite of elements required in human biology is still controversial and may include as many as 25 elements (Chellan & Sadler, 2015; Maret, 2016; Zoroddu et al., 2019). However, some elements previously considered essential are now thought to be adventitiously accumulated. One recent compilation has defined a core set of 20 elements as essential for humans (Maret & Blower, 2022). This excludes Cr, one of the last elements to be disputed (Vincent, 2017). A current consensus list of 20 essential elements in human nutrition includes the 6 bulk elements (CHNOPS), 4 ions from groups 1 and 2 (Na,K,Mg,Ca), 6 metals (Mo,Mn,Fe,Co,Cu,Zn), the non-metal Se, and three halide ions (Cl, Br, I) (Maret & Blower, 2022). Humans require some elements that are not widely required by organisms from other domains of life. These include Br for collagen crosslinking (McCall et al., 2014) and I for production of thyroid hormone (Opazo et al., 2020). Neither is needed for the viability of mammalian cells per se; they function instead at the tissue or organismal level.

Multivitamin/multimineral supplements are formulated to address possible nutritional deficiencies and are a lucrative industry ($30 billion dollars per annum in the USA) (Manson & Bassuk, 2018). For people with medically documented deficiencies, mineral supplements are of clear value. For example, menstruating women may benefit from supplemental Fe (Percy et al., 2017), and vegetarians may benefit from vitamin B_{12}, the biologically relevant form of Co (Rizzo et al., 2016). However, many commercially available supplements contain numerous elements that are rarely deficient in the diet. A typical formulation might include K,Ca,Fe,Cl,Cr,Cu,I,Mg,Mn,P,Se,Zn,B,Ni,Si, and V. Despite being routinely consumed by a large fraction (~40%) of the US population, the health benefits of mineral supplements are unclear for most healthy people. Current recommendations, and those health conditions that might benefit most from supplementation, have been summarized elsewhere (Manson & Bassuk, 2018).

10.2 Essential Elements for Plants

For vascular plants, 17 elements are essential (Hell & Mendel, 2010). Unlike animals, plants do not require Na, Co, Se, or Br, but they do require Ni. The 17 essential elements for plants include the 6 bulk elements (CHNOPS), 3 ions from groups 1 and 2 (K,Mg,Ca), 6 metals (Mo,Mn,Fe,Ni,Cu,Zn), boron (B), and 1 halogen (Cl). Co is an additional proposed essential element (Hu et al., 2021), which would bring the total to 18. Plants require B, an element not commonly required by other forms of life, for cell wall function (Gonzalez-Fontes, 2020; Wimmer et al., 2020).

Plant tissues often contain a great diversity of elements. Ionomics studies have been used to assess the natural variation in elemental accumulation in the model plant *Arabidopsis thaliana* (Campos et al., 2021; X.-Y. Huang & David E. Salt, 2016). Some of the commonly detected elements (e.g. Al, Co, Na, Se, Si) are thought to be beneficial, and others may accumulate adventitiously (Pilon-Smits et al., 2009). The ability of plants to accumulate toxic elements (e.g. As, Cr, Ni, Cd, V, Pd, U) has also been exploited for bioremediation (phytoremediation) of contaminated soils (Aihemaiti et al., 2020; Reeves et al., 2018; Vaid et al., 2022; Yaashikaa et al., 2022). In one dramatic example, plants endemic to New

Caledonia and adapted to Ni-rich soils can accumulate Ni-citrate in levels of up to 25% dry weight, resulting in a blue-green sap (Reeves et al., 2018).

10.3 A Proposed Minimal Set of Essential Elements

As we learn more about life's vast diversity, and when we include the Bacteria and Archaea, our assessment of essential elements becomes more restricted. We speculate that the minimal requirement to support a viable cell may include only 9 *specific universally essential* elements together with a variable set of *beneficial* elements (functional redundancy). Current evidence suggests that the shared essential elements include the six bulk elements (CHNOPS), a monovalent cation (K), a divalent cation (Mg), and Zn to act as an electrophilic catalyst. In addition to these 9 elements (CHNOPS,K,Mg,Zn), most or all cells likely require one or more of the remaining transition metals (Mn,Fe,Co,Ni,Cu), and many organisms have additional essential elements (e.g. Ca,Se,Mo).

Of the six first-row transition metals, only Zn has a strong claim to being universally essential (Zhang & Zheng, 2020). Although widely used as an electrophilic center, Zn is limited in that it is not redox active. In some Archaea, it has been noted that Fe can functionally replace Zn in many enzymes, with "iron-rivets" replacing Zn fingers in protein folding in *Ferroplasma acidiphilum* (Ferrer et al., 2007). This widespread use of Fe in place of Zn is consistent with the higher availability of Fe during early evolution (Williams, 2012). Whether access to Zn was required for the very first cells is an open question, and it is conceivable that some contemporary microbes retain a Zn-independent physiology. The role of Zn in catalysis can be substituted by other metals in many enzyme families.

The other transition metals are all widely used in biology, but not essential for all life (Zhang & Zheng, 2020). Fe is often included in lists of essential elements, but this view is challenged by the lack of an Fe requirement in some Bacteria, including lactobacilli and *Borrelia burgdorferi* (Posey & Gherardini, 2000). In those rare cases where Fe is not required, Mn plays a much more important and presumably essential role in cell physiology. This suggests the possibility that while neither Fe nor Mn is universally essential, life may require access to at least one of these two ions. Cu is essential for aerobes, but Cu has been reported to be dispensable for growth of at some fermenting Bacteria, such as the lactobacilli (Bruyneel et al., 1989). In conclusion, we can hypothesize that while metal ions *collectively* provide essential life functions, no single metal ion may be absolutely required for all life.

10.4 An Expanding Suite of Beneficial Elements

In contrast with the shrinking list of universally essential elements, the list of elements with a beneficial function in biology has expanded in recent years. For example, Cd serves in place of Zn in the Cd-utilizing carbonic anhydrase (CDCA) in some marine diatoms (Lane & Morel, 2000; Xu & Morel, 2013). Similarly, the lanthanides were recently revealed to serve a beneficial role as enzyme cofactors in Bacteria (Featherston & Cotruvo, 2021; Skovran et al., 2019). Since it is difficult to prove a negative, and the diversity of life is vast, we should proceed with caution when ruling out a beneficial biological role for any specific element. While some class (iv) elements have very specific beneficial roles (e.g. V,W,Cd,Si),

for others the benefits are still poorly understood or not known to be relevant in nature (e.g. Li,Rb,Al).

10.5. The Elements of Life: A Web-Based Resource

Our understanding of the elements and their roles in living systems continues to evolve; new beneficial roles continue to be revealed, and elements once considered critical are now considered of little importance. To account for this changing landscape, we have developed a companion website for this review. *Elements of Life* is a moderated, public database that provides an accessible platform for exploring the biological role of elements (https://elementaleconomics.wixsite.com/website). The home page displays a periodic table that categorizes elements by *class*: (i) essential for all life, (ii) essential for many organisms in all three domains of life, (iii) essential or beneficial for many organisms in at least one domain, (iv) beneficial (and rarely, essential) to at least some species when present, and (v) of no known beneficial use. Viewers can click on the essential and beneficial elements to learn more about each element's major functions in biology, environmental and health impacts, and notable elemental sparing mechanisms (Merchant & Helmann, 2012). We welcome suggestions on this resource and have provided a *Feedback* page. We hope that this web resource will be a useful educational tool and spur interest in this fascinating intersection between chemistry and biology.

11 Elements of Life: Peering into the Future

Contemporary life represents a snapshot in time. The totality of life (the biosphere) is restricted to a thin layer near the Earth's surface. At present, it is estimated that life has a total mass of ~2.2 teratons (~10^{18} g) (Elhacham et al., 2020). This corresponds to ~550 gigatons (Gt) of carbon (5.5 x 10^{17} g), 80% of which is accounted for by terrestrial plants (Bar-On et al., 2018). The vast majority of the remaining 20% is microbial (mostly Bacteria), with animals accounting for less than 1%. Microbial life dominates metabolic activity in most habitats and represents an estimated 90% of the ocean's biomass (Cavicchioli et al., 2019). Importantly, marine phytoplankton contribute an estimated 50% of photosynthesis (primary production) worldwide (Cavicchioli et al., 2019). The composition of the biosphere changes over time, as amply illustrated by the fossil record. The Earth has witnessed at least half a dozen major mass extinction events, including one thought to be triggered by a major asteroid impact at the end of the Cretaceous period ~66 million years ago leading to the extinction of non-avian dinosaurs (Chiarenza et al., 2020). Study of how life has adapted to past episodes of climate change may provide insights into what our future holds (Payne & Clapham, 2012).

The Earth is widely considered to have now entered a new epoch, the Anthropocene, reflecting the large changes to our planet resulting from human activity (Malhi, 2017). This includes the ongoing extinction of large numbers of species, sometimes called the sixth extinction (Kolbert, 2014). Our collective impact on our planet is underlined by the rapid anthropogenic changes in our atmosphere due to the use of fossil fuels. As a result, CO_2 levels have increased by >30% in the last century. The total mass of the anthropogenic (human-built) environment (including roads, buildings, and other structures) is estimated

to soon surpass the total biomass on Earth (Elhacham et al., 2020). The impact of the human species on the biosphere is hard to foresee, but some trends are clear. Climate change will increase average temperatures and elevated CO_2 levels will lead to ocean acidification, thereby impacting the carbon cycle and, through effects on diatoms, the ocean silica cycle (Taucher et al., 2022). Ocean acidification may also trigger a calcification crisis (Hönisch et al., 2012), although it has been suggested that the decrease in nannoplankton due to past episodes of ocean acidification may be overestimated (Slater et al., 2022). Microbial life plays a disproportionate role in global nutrient cycling, and discussions of climate change, its implications, and possible mitigation strategies will need to explicitly consider these activities (Cavicchioli et al., 2019).

Humans are also altering the biosphere by the mobilization and concentration of large amounts of industrially relevant metals. The latest compendium of “critical minerals” released by the United States Geologic Survey includes 50 elements, ranging from Aluminum (Al) to Zirconium (Zr), as “serving an essential function in the manufacturing of a product, the absence of which would have significant consequences for the economy or national security” (Burton, 2022a). Globally, efforts to recover 25 of the most commercially important minerals involves the processing of ~37.6 billion metric tons of ore annually: the “equivalent of almost 7,000 Great Pyramids of Giza” (Burton, 2022b). One measure of how dispersed elements are in the lithosphere is the rock-to-metal ratio, which refers to the magnitude of enrichment required to generate a pure metal from an ore (Nassar et al., 2022). For abundant metals (Al, Fe, Cr) little enrichment is required, whereas for the platinum group metals (Pt,Pd,Ru,Rh,Ir), the amount of enrichment may be a million times higher. As these elements are enriched to high levels of purity and later released into the waste stream, we provide a new opportunity for life to exploit previously rare resources (Zhuang et al., 2015). Whether this will lead to the evolution of new beneficial uses for previously ignored elements is an open question.

We should not underestimate the ability of life to exploit newly available resources, both molecular and elemental. Laboratory evolution experiments have led to the emergence of a methylotroph with a greatly increased capacity to use gadolinium (Gd), a heavy Ln element, and to acquire this element from a Gd-containing contrast agent used for magnetic resonance imaging (Good et al., 2022). Organoflourine compounds are rare in the natural world but represent an abundant and recalcitrant environmental contaminant. Not only do some soil Bacteria catabolize these compounds, they can also incorporate metabolites into fatty acid synthesis leading to the production of fluorinated phospholipids (Xie et al., 2022). These results highlight how xenobiotic compounds in the chemical waste stream may lead to novel ways of integrating elements into metabolism. The evolution of new uses for elements may be accelerated by efforts in synthetic biology to capitalize on the ability of microbes to develop new chemistries (Haas & Nikel, 2022; Reed & Alper, 2018). As we continue to inventory the scope and diversity of microbial life, scientists will likely uncover new and unexpected functions for elements, and our perception of the elements of life will itself evolve.

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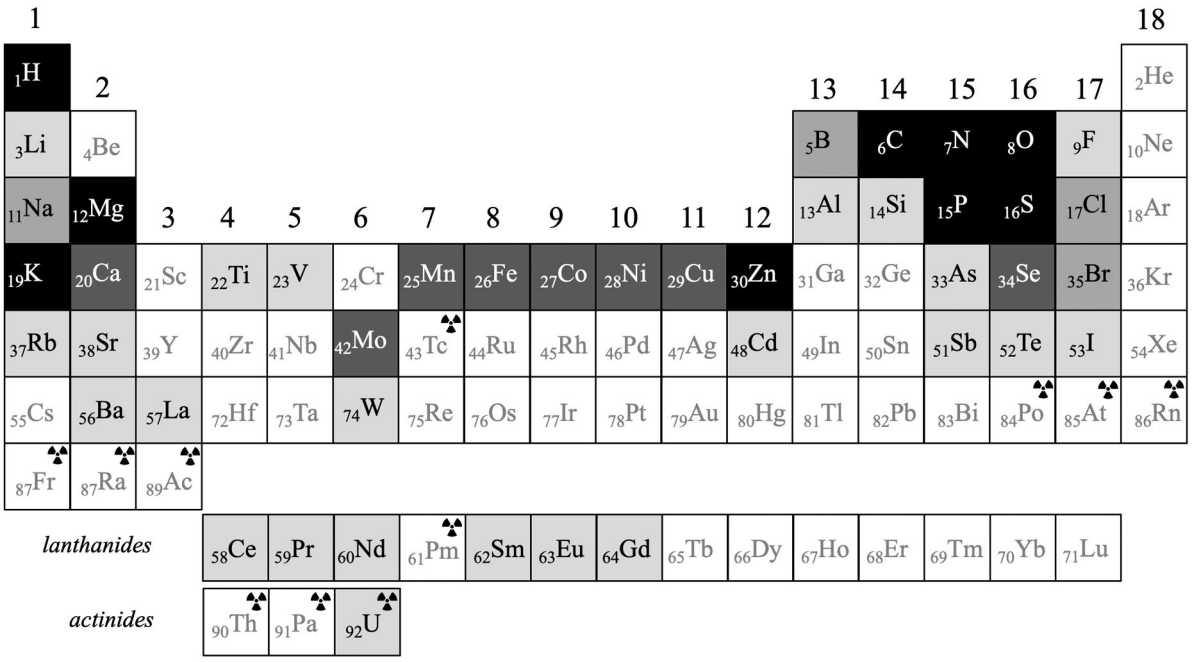

Figure 1. A biocentric periodic table of elements.

The chemical elements are organized into 18 groups (columns) and are shaded to indicate their importance in biology. The elements essential for all life are class (i): indicated with a black background and include the bulk macronutrients (CHNOPS), two ions (K,Mg) and one transition metal (Zn). Class (ii) elements (essential for many organisms in all three domains of life) are in white font with a dark grey background. The class (iii) elements (essential or beneficial for many organisms in at least one domain) are in black font with a dark grey background. An additional 23 elements are assigned as class (iv) (beneficial to at least some species) have light grey shading. All remaining elements are currently assigned as class (v): of no known biological benefit and are in grey font against a white background. Radioactive elements with no stable isotope are indicated (☢).

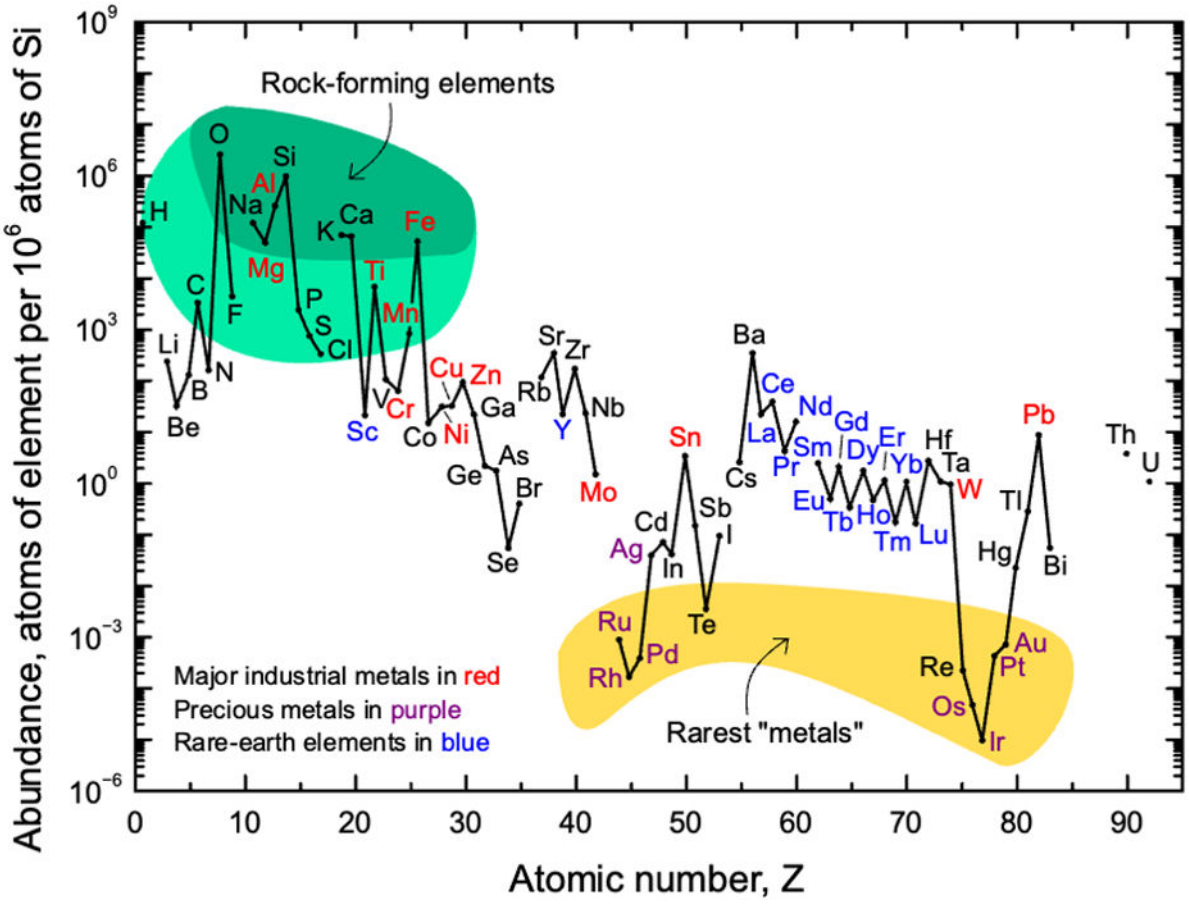

Figure 2.

Relative levels of the naturally occurring elements from hydrogen ($_{1}$H) to uranium ($_{92}$U) in the Earth's upper (continental) crust. Abundance is on a $\log_{10}$ scale relative to silicon ($_{14}$Si), arbitrarily set to 10^6. The decline in abundance from lighter to heavier elements reflects a similar pattern in the interstellar gases that condensed to form our solar system ~4.5 Ga. The rarest metals are those that dissolved well into molten iron (siderophilic) and were depleted from the surface when they partitioned into Earth's iron core during our planet's formation. Note that atomic numbers are indicated by subscripts, and mass by superscripts. There are gaps in this chart that correspond to the 6 noble gases ($_{2}$He, $_{10}$Ne, $_{18}$Ar, $_{36}$Kr, $_{54}$Xe, $_{86}$Rn), and 8 unstable (radioactive) elements of low natural abundance: technetium ($_{43}$Tc), promethium ($_{61}$Pm), polonium ($_{84}$Po), astatine ($_{85}$At), francium ($_{87}$Fr), radium ($_{88}$Ra), actinium ($_{89}$Ac), and protactinium ($_{91}$Pa). This leaves 78 naturally occurring elements of defined abundance. There is general agreement on the abundance as reported in several sources (see https://en.wikipedia.org/wiki/Abundance_of_elements_in_Earth%27s_crust for a comparison). In this text, we will use the value derived from (Haynes, 2016).

Image credit: https://commons.wikimedia.org/wiki/File:Elemental_abundances.svg. *(public domain)*

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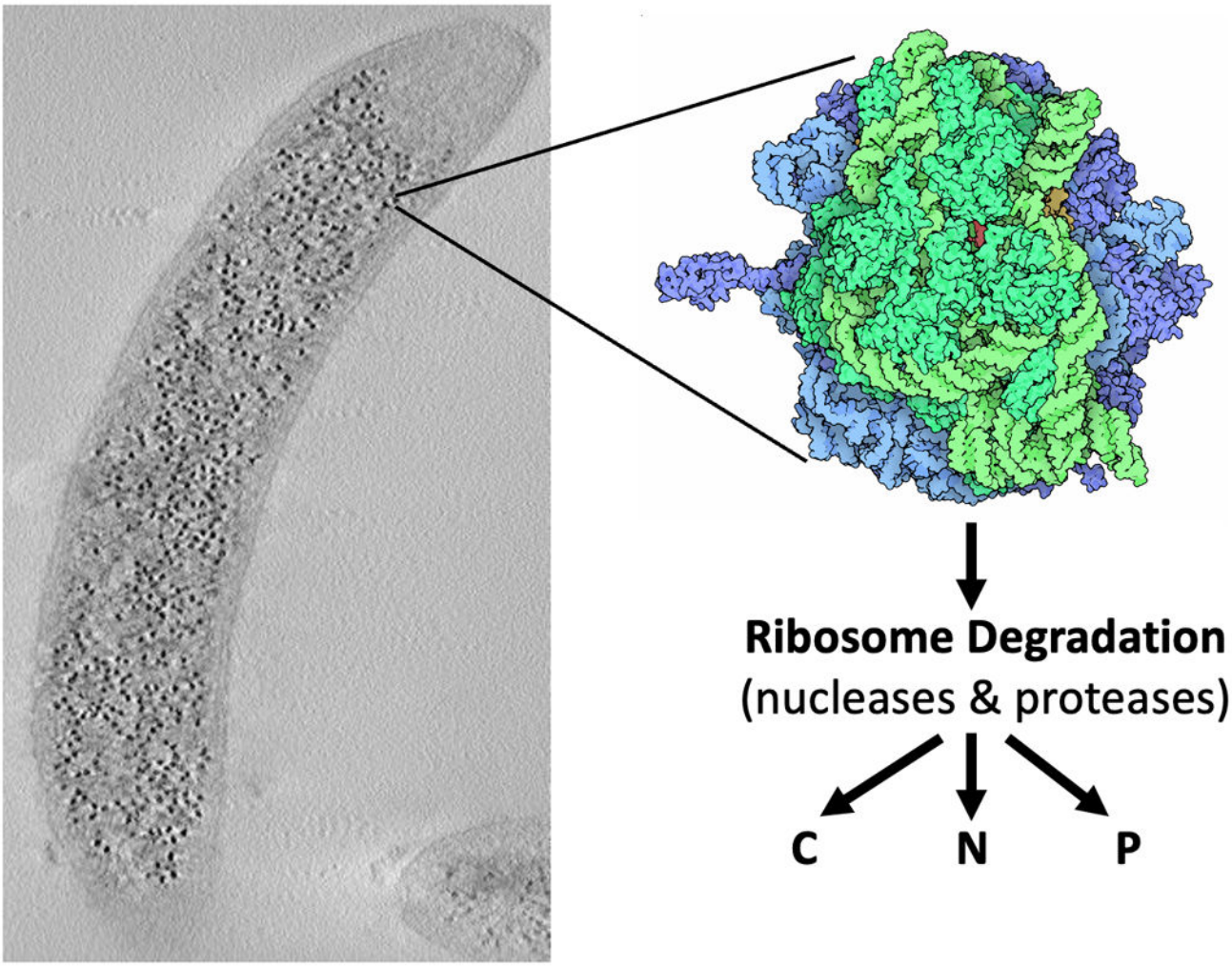

Figure 3. Recycling of limiting macronutrients by ribosome turnover.

Ribosomes are a major macromolecular constituent of bacteria (accounting for ~25-40% of dry weight), with $>10^4$ ribosomes per growing cell. Here, ribosomes are seen as the electron dense dots in a *Caulobacter crescentus* cell as imaged by electron microscopy. The ribosome itself is a complex assemblage of both RNA and proteins, with a small subunit (green) and large subunit (blue) that assemble to form the complete ribosome. Each ribosome has an abundance of C,H,N,O,P with lesser amounts of S,Mg,K, and Zn.

Image credits: left image, L. Shapiro, H. McAdams (2012) https://doi.org/doi:10.7295/W9CIL40123; public domain). Watercolor by David Goodsell; https://pdb101.rcsb.org/motm/121; public domain).

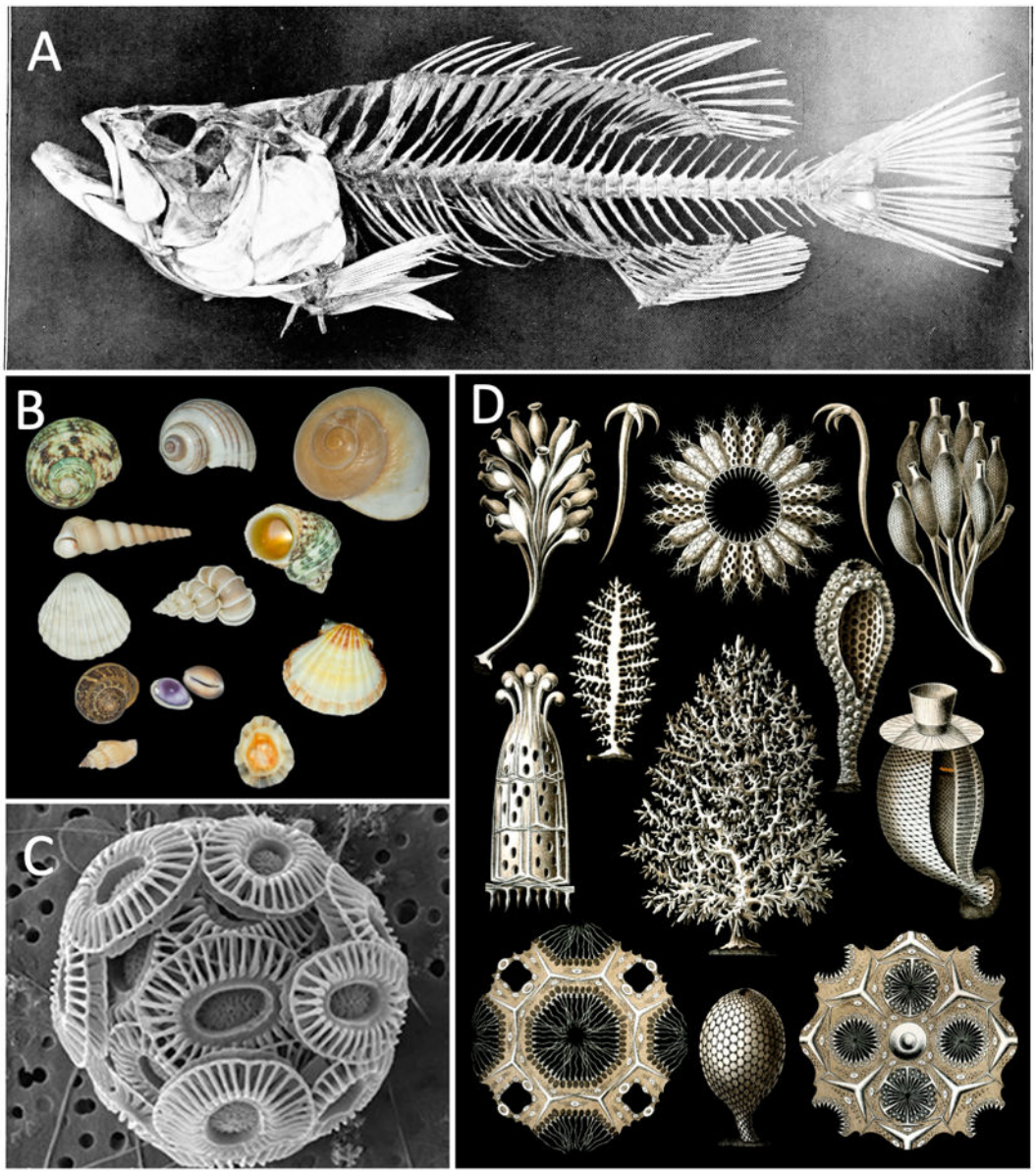

Figure 4. Ca-based biomineralization in biology.

A. Hydroxyapatite ($Ca_5(PO_4)_3OH_2$) accounts for the bulk of bone mass in vertebrates, here represented by the skeleton of the black bass. Calcite ($CaCO_3$) is the major structural component for numerous organisms including **B**. mollusk shells (~95-99% $CaCO_3$ by weight), **C**. the microscopic coccolithophore *Emiliania huxleyi* (diameter = 7 μm) where $CaCO_3$ forms the mineralized shell (or "coccosphere"), and **D**. calcareous sponges (Phylum: Porifera; Class: Calcarea).

Images are all public domain; credits: A. The skeleton of the black bass; 1900 (Robert W. Shufeldt); B. Mollusk shells (Zachi Evenor); C. scanning electron micrograph of *Emiliania huxleyi* (Dr. Jeremy Young) and D. drawing by Ernst Haeckel (Kunstformen der Natur, 1904).

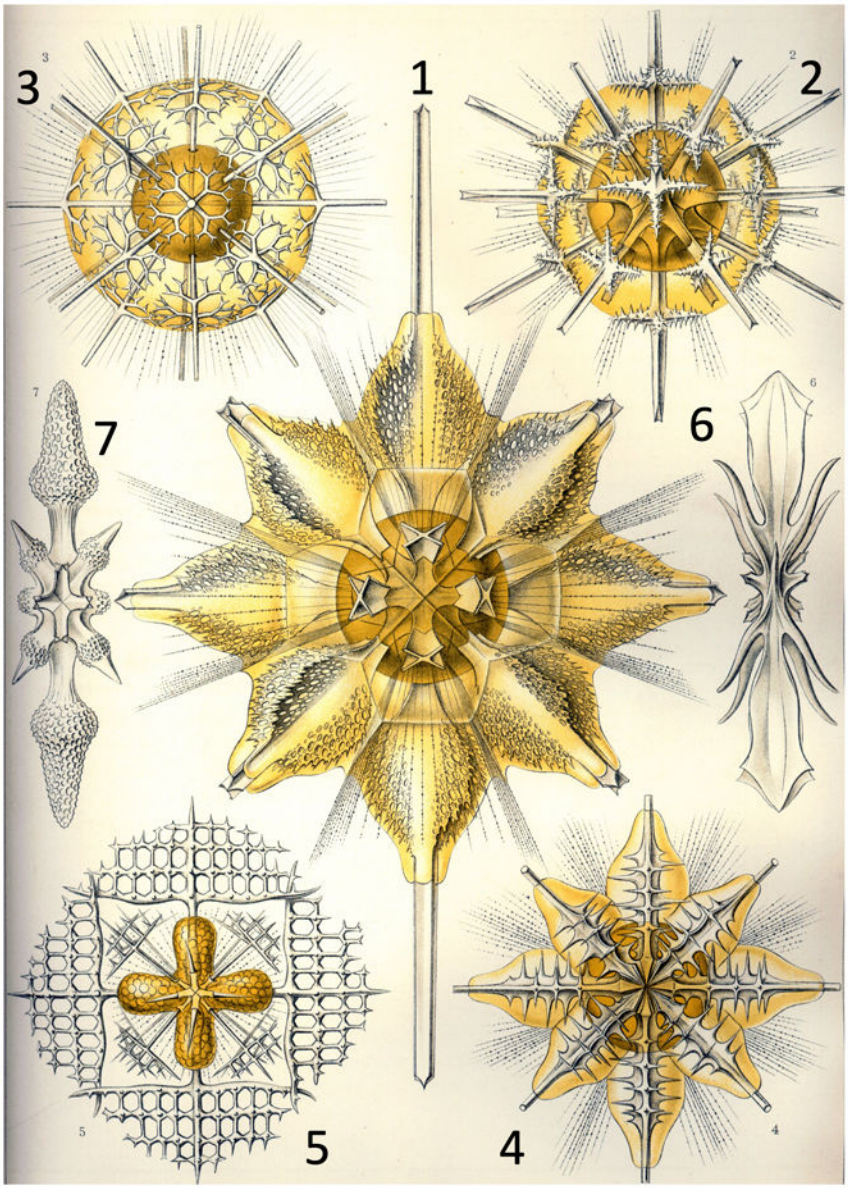

Figure 5. Sr-based biomineralization in biology.

Within the Phylum Radiolaria, the class Acantharea are small (0.2 to ~2 mm in size) marine plankton that use celestine ($SrSO_4$) for their hard shells. Shown here are drawings from Ernst Haeckel (Kunstformen der Natur, 1904, plate 21) of 1. *Xiphacantha ciliata* (Haeckel) = *Xiphacantha* sp., 2 *Xiphacantha spinulosa* (Haeckel) = *Stauracantha spinulosa* (Haeckel, 1860), 3 *Stauracantha quadrifurca* (Haeckel) = *Phyllostauridae* sp.?, 4. *Pristacantha polyodon* (Haeckel), 5. Lithoptera dodecaptera (Haeckel), 6. Acantholonche peripolaris (Haeckel) = *Gigartaconidae* sp.?, core spicule, and 7. *Acantholonche favosa* (Haeckel) = *Gigartaconidae* sp.?, core spicule.

Image credit: Ernst Haeckel, Kunstformen der Natur (1904), plate 21: Acanthometra This is a public domain image.

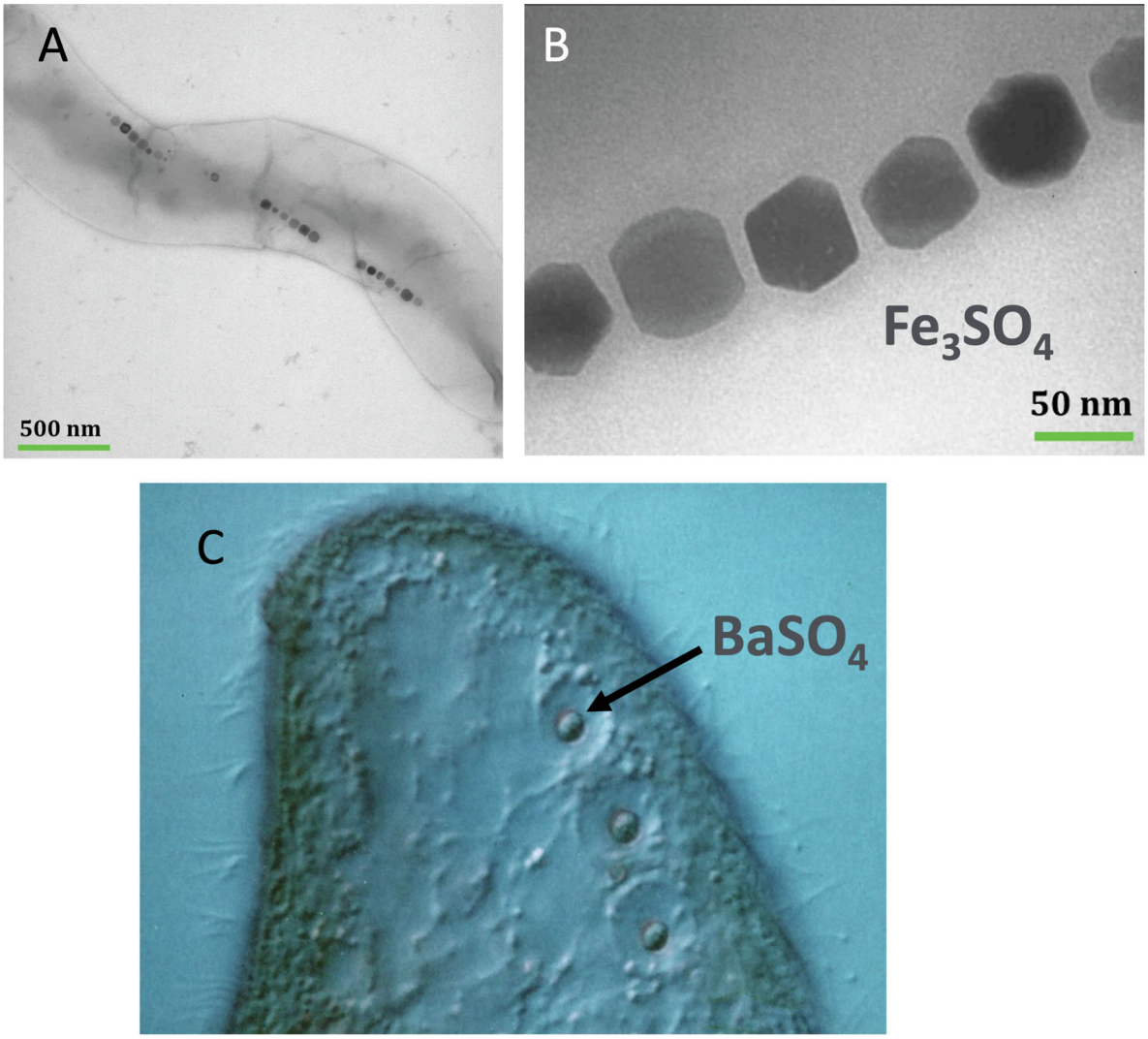

Figure 6. Intracellular biominerals and cellular taxis.

A. In the Bacterium *Magnetospirillum magneticum* linear arrays of magnetite (Fe_3O_4) crystals (enlarged in **B**) allow cells to swim directionally in response to the magnetic field (Ginet et al., 2011). **C.** The ciliate *Loxodes striatus* contains membrane-bound vesicles with barium sulfate ($BaSO_4$) concretions (3 μm diameter) fixed to a microtubular structure to serve as statoliths (courtesy N. Rieder), adapted from (Häder et al., 2017)

Image credits. A and B: image modified under a CC license from (Ginet et al., 2011). C. image adapted from (Häder et al., 2017) under a CC BY 4.0 license.

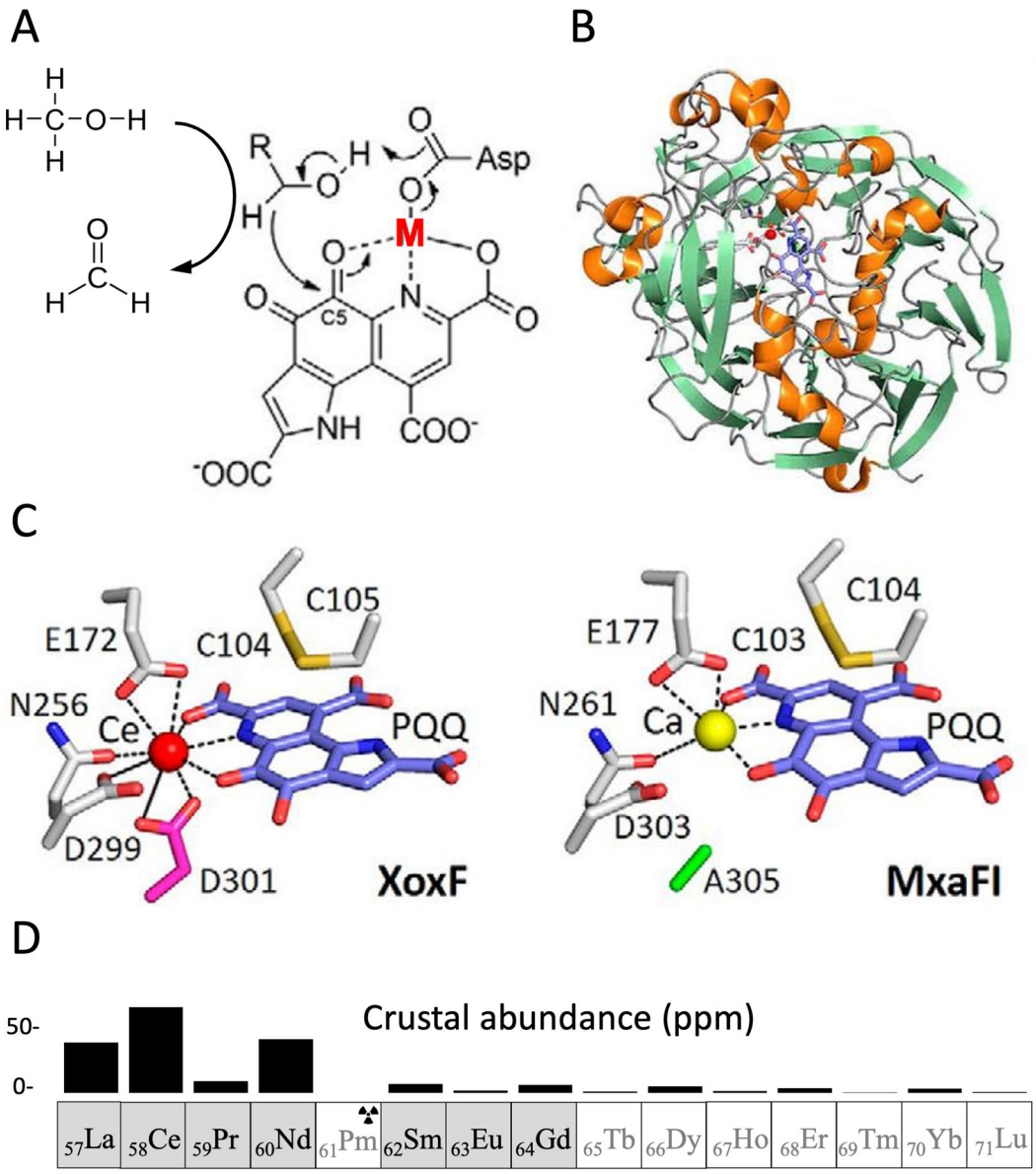

Figure 7. Biology of the lanthanide elements.

Lanthanides (Ln) serve as a cofactor for one family (XoxF) of methanol dehydrogenase (MDH), whereas a second family (MxaF1) uses Ca. MDH allows methyltrophs to use methanol (CH_3OH) as sole carbon and energy source. **A**. Catalytic mechanism of alcohol oxidation. The reactive C5 carbonyl of PQQ and Asp are required for catalysis in coordination with the bound metal cofactor (red M). **B.** Overall structure of a Ln-dependent MDH. The *Methylobacterium extorquens* AM1 XoxF1 (PDB entry 6OC6) is shown with β-sheets in green, α-helices in orange, and coils in gray, and the bound La^{3+} in red. **C**. Close up of active-site structures of Ce-bound *Methylacidiphilum fumariolicum* SolV (PDB code 4MAE) XoxF and Ca-bound MxaFI from *Methylobacterium extorquens* AM1 (PDB code 1W6S). PQQ in blue, Ce in red, Ca in yellow, Also shown is a Cys disulfide and a conserved Asp (D301, pink in XoxF) that is an Ala (green) in MxaFI. Panels A-C adapted from (Good

et al., 2020). **D**. The lanthanide series elements (shaded as in Figure 1) showing the relative crustal abundance of each element (Haynes, 2016).

Image credits. Panels A-C adapted from (Good et al., 2020) under a CC license.

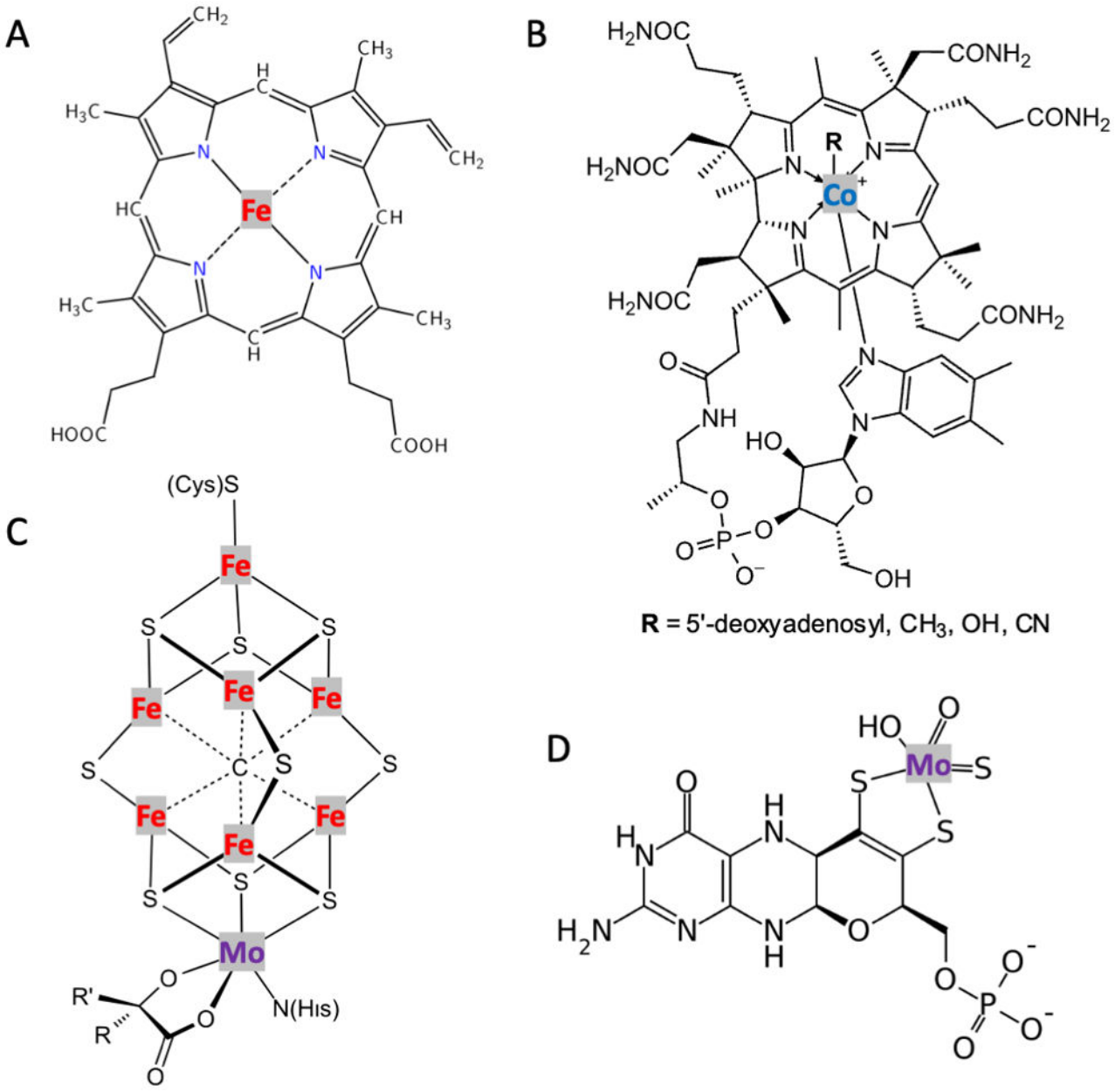

Figure 8. Representative metal-dependent enzyme cofactors.

A. Heme consists of a porphyrin ring with a central Fe atom. Related porphyrins replace the central Fe with Mg (chlorophyll) or Ni (F_{430} cofactor found in methanogenic Archaea) (Hausinger, 2019). **B**. Most Co-dependent enzymes have Co bound in cobalamin, where the R group is either deoxyadenosine in AdoCbl, or methyl in MeCbl. **C**. Most nitrogenase enzymes use an FeMo cofactor (FeMoCo) with formula Fe_7MoS_9C. One Fe (top) is anchored to the protein by Cys. FeMoCo contains 9 sulfides and a central C (carbide) atom, in which C is bonded directly to 6 Fe atoms (as far as is known, the sole instance of this type of bonding in biology). Mo is attached to three sulfides and to the protein by a His residue. The V-containing nitrogenases use a very similar cofactor (FeVCo) in which V replaces Mo, and one S is replaced by a carbonate ion (Hausinger, 2019). **D**. Most Mo-dependent enzymes

have Mo bound to two S atoms in a polycyclic pyranopterin known as molydopterin. The Mo may be replaced by W in tungstoenzymes.

Image credits: Wikimedia commons (public domain), 994px-Heme.svg.png, FeMoco_cluster.svg, Cobalamin_skeletal.svg, Molybdenum cofactor.svg.

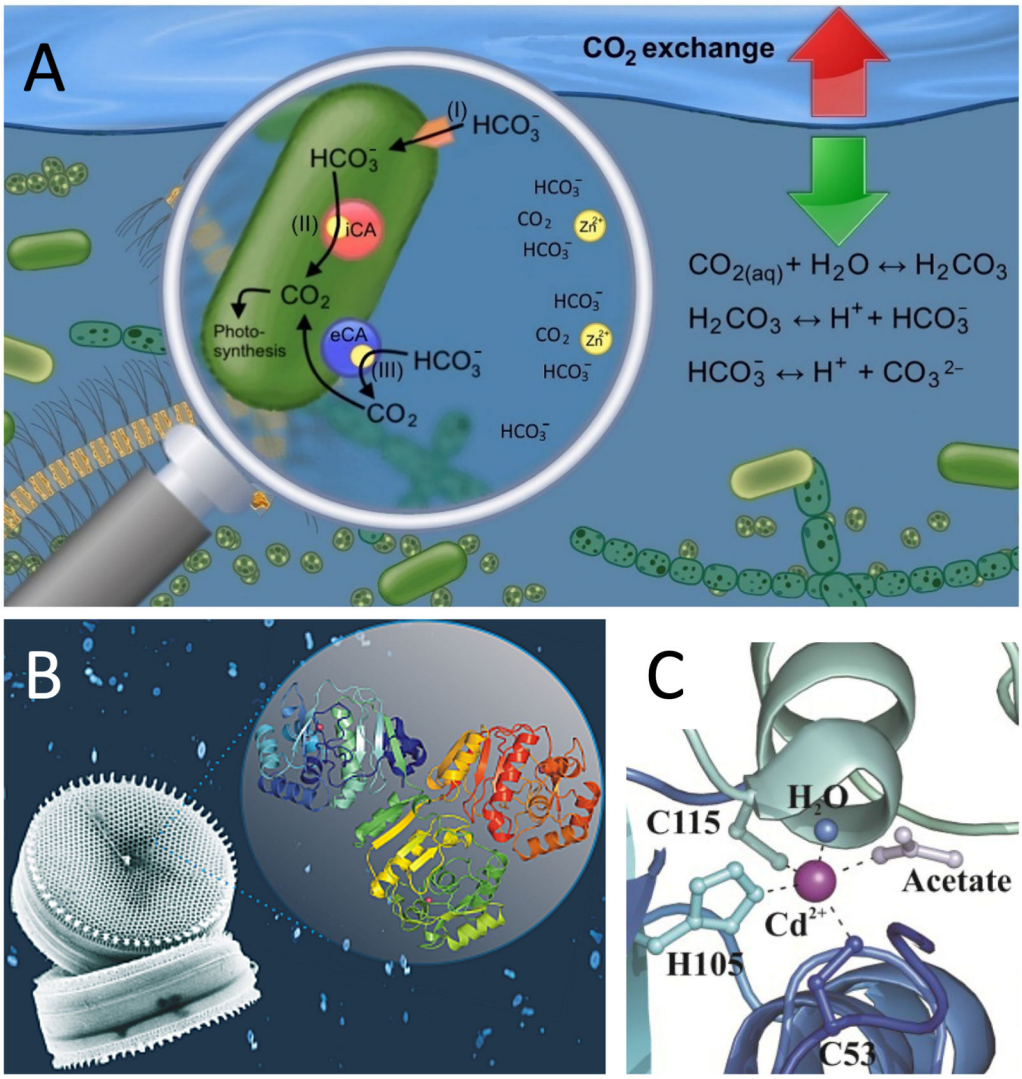

Figure 9. A biological role for Cd.

A. At the ocean surface atmospheric CO_2 dissolves and is hydrated to form carbonic acid. Optimal photosynthesis requires a carbon-concentrating mechanism (CCM) that relies on carbonic anhydrase (CA). CA are Zn-metalloenzymes that allow rapid generation of CO_2 from carbonic acid for use by rubisco. Carbonic acid import (i) and internal carbonic anhydrases (iCA, ii) serve this role. Alternatively, CO_2 may be generated by external carbonic anhydrase (eCA) followed by diffusion through the cell membrane. Adapted from (Mustaffa et al., 2021) under license CC BY 4.0. **B.** Cd functions as an alternative active site cofactor in Cd-utilizing carbonic anhydrase (CDCA) in some marine diatoms. The Cd-utilizing carbonic anhydrase (CDCA; right in ribbon diagram) is one of the major CA enzymes in the diatom *Thalassiosira weisflogii* (left in SEM image). **C**. Enlarged view of the CDCA active site with the Cd ion in purple. Panels B and C adapted from (Alterio et al., 2015), under license CC BY 4.0.

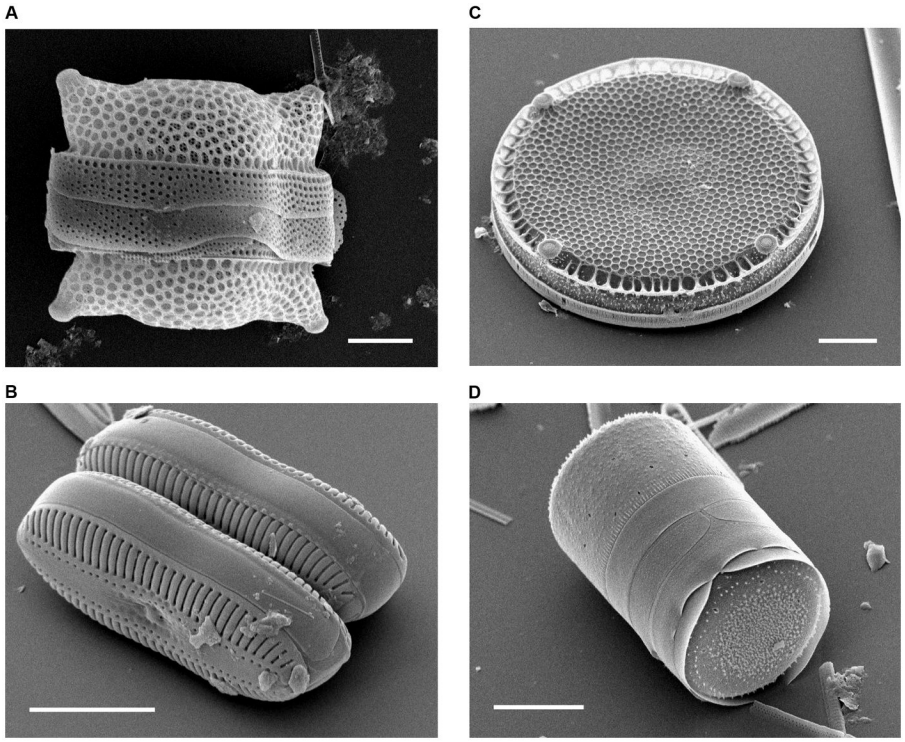

Figure 10. Si-based biomineralization in diatoms.

Biogenic silica (hydrated silica ($SiO_2 \cdot nH_2O$) as found in **A.** Frustule of a centric diatom, *Biddulphia reticulata* showing valves and girdle bands (size bar = 10 μm). B. Frustula of a two whole pennate diatom, *Diploneis* sp. size bar = 10 μm). **C**. A single valve of a centric diatom *Eupodiscus radiatus*. (size bar = 20 μm) (D. Frustule of a centric diatom, *Melosira varians*, showing valves and girdle bands (size bar = 10 μm). Scanning electron micrograph images courtesy of Mary Ann Tiffany, San Diego State University as published under a CC license in (Bradbury, 2004)).

Table 1.

The most widely used elements in biology[1] (classes i and ii)

class i		■ = Indisputably essential ■ = Presumed essential (no counterexamples known) ● = Essential or beneficial for many organisms **Known or presumed essential for all organisms**
symbol	**Domain[2] A B E**	
C	■ ■ ■	CHNO; Basis for all life chemistry and macromolecules
H	■ ■ ■	Cells vary from 65-90% H_2O by weight
N	■ ■ ■	CHNO together account for ~96-98% of most cells
O	■ ■ ■	
P	■ ■ ■	Essential for nucleic acids, phospholipids, nucleotides, etc.; ~1% of cell mass
S	■ ■ ■	Essential for proteins (Cys,Met), cofactors, etc.; ~0.2% of cell mass
K	■ ■ ■	Major intracellular monovalent cation (K^+)
Mg	■ ■ ■	Major intracellular divalent cation (Mg^{2+})
Zn	■ ■ ■	Major intracellular transition metal (Zn^{2+}); electrophilic catalyst in enzymes and nucleates protein folding in Zn-fingers and other proteins
class ii		**Essential for many organisms in all three domains**
Ca	● ● ■	Ca is widely used for cell signaling and biomineralization; broadly beneficial but essentiality unclear for many microbes
Mo	● ● ●	A,B,E: Mo-dependent enzymes (using MoCo) in a majority but not all species in each domain; essential for plants and animals, but not yeast.
Mn	● ● ■	E: essential for plants and animals; B,A: essential for many but not all species
Fe	● ● ■	B,A,E: essential for nearly all life, but rare exceptions are known in the Bacteria
Co	● ● ●	B,A,E: bioinformatics supports a broad distribution of Co-dependent enzymes
Ni	● ● ●	B,A,E: bioinformatics supports a broad distribution of Ni-dependent enzymes
Cu	● ● ●	B,A,E: bioinformatics suggests Cu-dependent enzymes in most organisms in all 3 domains
Se	● ● ●	B,A,E: bioinformatics supports a broad distribution of Se-dependent enzymes

[1] Assignments presented here should be considered a current educated guess and are subject to revision.

[2] Elemental utilization in Bacteria (B), Archaea (A), and Eukarya (E) is summarized.

Table 2.

Beneficial elements in biology[1] (classes iii and iv)

class iii		□ = beneficial (or essential) for many organisms (mechanism known) ▨ = beneficial for a few organisms (mechanism poorly understood) ❋ = beneficial: supports biomineralization in selected organisms ⌘ = beneficial: supports chemolithotrophy as electron donor/acceptor ▨ = beneficial roles possible, but no described examples **Essential or beneficial for many organisms in at least one domain**
symbol	**Domain[2] A B E**	
Na	□ □ □	E: essential for animals, but not most plants; B,A: requirement varies (where known)
B	▨ ▨ □	E: essential in plants for cell wall stability; B: B-containing secondary metabolites
Cl	□ □ □	E: essential for plants and animals; B,A: requirement varies (where known)
Br	▨ ▨ □	E: essential in multicellular animals for collagen formation; B: Br-containing secondary metabolites
class iv		**Beneficial for at least some species**
Li	▨ ▨ ▨	E: beneficial effects of Li on mood in human, B: possible sparing role in microbes, although relevance to natural settings is not established
Rb	▨ ▨ ▨	Possible sparing effect on K nutrition, but relevance in nature not shown
Sr	▨ ▨ ❋	E: Acantharea (a group of radiolarian protozoa) use $SrSO_4$ for their shells
Ba	▨ ▨ ❋	E: Some green algae use $BaSO_4$ crystals as statoliths for gravity-sensing
(Ln)[3]	▨ □ ▨	B: Many methylotrophs use (Ln) elements in methanol dehydrogenase
(An)[4]	▨ ⌘ ▨	B: U can support chemolithotrophic growth
Ti	▨ ▨ ❋	E: Some diatoms and foraminifera have tests of TiO_2, Ti accumulated in tunicates
V	□ □ ▨	B,A: V-cofactored nitrogenases, E; V-dependent haloperoxidases
W	□ □ ▨	B,A: W-cofactored enzymes often replace Mo-dependent functions
Cd	▨ ▨ □	E: Cd is a cofactor for carbonic anhydrase in some marine diatoms
Si	▨ ▨ ❋	E: diatoms use $SiSO_4$ for their shells (frustules)
As	▨ ⌘ ▨	B: As can support chemolithotrophic growth
Sb	▨ ⌘ ▨	B: Sb can support chemolithotrophic growth
Te	▨ ⌘ ▨	B: Te can support chemolithotrophic growth
F	▨ ▨ ▨	B: synthesis of F-containing secondary metabolites; E: plants make fluoroacetate, likely for defense; beneficial for tooth enamel in animals
I	▨ ▨ □	B,E: synthesis of l-containing secondary metabolites; E: mammals, required for thyroid hormone
Al	▨ ▨ ▨	E: postulated to be a beneficial element for plants

[1] Assignments presented here should be considered a current educated guess and are subject to revision.

[2] Elemental utilization in Bacteria (B), Archaea (A), and Eukarya (E) is summarized.

[3] Ln refers collectively to the lanthanide group of elements with atomic numbers 57 to 71.

[4] An refers collectively to the actinide group of elements with atomic numbers 89 to 103.