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MINIREVIEW

Microbial Genomics and the Periodic Table

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Extensive knowledge of microbial metabolism has been earned through more than a century of reductionist study. There is now basic understanding of how cultivated bacteria transduce the chemical energy of a growth substrate into the work and biosynthetic processes that underlie both survival and replication. This includes an appreciation that microorganisms can metabolize many chemical substances that exist only due to the efforts of synthetic chemists (34). These direct observations of microbial metabolism, and the molecular diversity inferred from microbial genome sequencing, point to the great breadth of microbial metabolism that exists in nature.

In this age of genomics and the inherently new perceptions of metabolic networks thus engendered (101), it is worth pointing out the obvious: microbial cells are not made up of information; they are made up of atoms. The atoms in a microbial cell are determined only partly by genome-encoded transporters; they are also determined by the extracellular environment. For example, *Deinococcus radiodurans* accumulates more or less of the elements iron and manganese, depending on their relative concentrations in the extracellular environment. If the manganese concentration is above a threshold, *D. radiodurans* will oxidize its carbon source, glucose, via the glycolytic pathway (145). Below the threshold concentration, the pentose phosphate pathway is used.

Substitution of manganese for iron is also important in the bacterial pathogen *Borrelia burgdorferi*, the causative agent of Lyme disease. The *B. burgdorferi* genome project has revealed the absence of iron-containing membrane proteins and annotated genes encoding proteins such as superoxide dismutase that are predicted to contain manganese rather than iron (97). The absence of iron and iron-containing proteins is proposed to allow *B. burgdorferi* to survive in a host that restricts iron, an action that normally limits microbial growth and thus prevents infection. In this way, the *B. burgdorferi* genome may have evolved by eliminating the requirement for what is usually an essential element.

Furthermore, an element required by some bacteria may be toxic to others. For example, tungsten is a required nutrient for some hyperthermophilic archaea (64) but 300 strains of iron-oxidizing bacteria are strongly inhibited by sodium tungstate (125). So, if we wish to study how the genome directs the cell, we need to know what atoms are present in the vicinity of the cell and how the cells respond to complex mixtures of the chemical elements and compounds.

In the period from 1930 to 1970, there was a strong interest in how biological systems respond holistically to the chemical elements, largely in the context of studies on microbial, plant, and animal nutrition (106, 118, 121). This led to the identification of major elements that commonly participate in metabolic processes within diverse microbiological systems, specifically H, C, O, N, P, S, Cl, K, Na, Ca, Mg, Se, Zn, Fe, Mn, Cu, Co, Ni, and Mo. In the last 70 years, much effort was expended to establish the precise mechanisms by which these elements mediate specific biological functions. However, with this expansion of knowledge, information has become fragmented into separate domains. For example, more recent reviews have focused on such topics as the microbial disposition of (i) heavy metals (91); (ii) metalloid compounds (8, 42, 88); and (iii) specific classes of organic compounds, including organosulfur compounds (61) and nitrogen heterocyclic compounds (40).

Most recently, focus on the complete constellation of elements found in microbes has taken on a new imperative in the light of efforts in genomics-based reconstruction of the cellular machinery, microbial remediation of complex environmental mixtures, and understanding microbial individuality. Reductionism has brought us to the point that this information can be interfaced with genomics, but the effort will further require a compilation of how microbes respond to all of the chemical elements. There have been reviews that address the issue of element essentiality, transformation, and toxicity more broadly (42, 113); the present review seeks to extend those efforts. This review does not discuss in any detail the role of transition metals in microbial metabolism, a topic that has been covered in numerous books and reviews (72, 86, 137). Rather, we focus on integrating research on the most common biological elements and those that are most rare, but for which biological roles have recently been identified.

INTERPLAY AMONG ELEMENTS

A microorganism's genes persist under selective pressure to facilitate the cell's survival in a complex and often changing chemical environment. Genes relevant to the acquisition of carbon, nitrogen, sulfur, phosphorus, major cations, chloride, zinc, and transition metals function in concert; all of those needs must be met for survival of the organism. Genomics is increasingly revealing this interplay. For example, an operon in

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Salmonella enterica serovar Typhimurium involved in magnesium uptake is regulated by the *pho* system, which is involved in the cell's response to phosphate starvation (28). This seems perplexing at first consideration, but makes sense when one considers cell chemistry holistically. The many intracellular molecules containing the pyrophosphate group, such as ATP, exist mainly complexed with Mg^{2+}. In fact, in vitro kinase assays use Mg-ATP as the phosphoryl-donating substrate (87).

Another example of how the genome and environment interact is differential metal binding to enzymes. Dai et al. (27) have shown that an isolated enzyme, the product of a single bacterial gene, has alternate enzymatic activities depending on whether the enzyme complexes Fe^{2+} or Co^{2+}. Both of the reactions are physiologically relevant. Thus, one must look to what Da Silva and Williams call the metallome when considering the function of specific genes within a bacterium's genome (28). The metallome is the complete complement of the alkali elements, alkali earth elements, zinc, transition metals, and metalloid elements; collectively this consists of as many as 50 elements. The present review focuses on the metallome, excluding the biologically common transition metals as mentioned above, and what is known about how cells respond to, and metabolize, those elements and their compounds.

CATALOGING INFORMATION ON MICROBIAL INTERACTION WITH THE ELEMENTS

Increasingly, efforts are emerging to depict metabolism in the context of the full constellation of chemical elements. A recent book, *The Biological Chemistry of the Elements: the Inorganic Chemistry of Life* (28), discusses the properties of the elements in the context of their selection and use by biological systems, but the focus is on mammalian biochemistry. In his book *Post-Genome Informatics*, M. Kanehisa discusses the flow of information in biological systems, from (i) the elements, (ii) to compounds, (iii) to genomes, (iv) to enzymes, and (v) to organisms (58). A World Wide Web database developed by Kanehisa and his coworkers, KEGG (44), shows a periodic table with links from 21 chemical elements to information on biological interactions with those elements that includes enzymes, transporters, and metabolic maps. A search of the related LIGAND chemical database on 21 June 2002 provided information on 43 chemical elements.

In another example, the World Wide Web-based University of Minnesota Biocatalysis/Biodegradation Database (UM-BBD) has focused on cataloging the diversity of microbial transformation reactions derived from published scientific literature (34). The UM-BBD's organizational framework is centered on depicting enzymatic transformations of distinct chemical elements and functional groups. The chemical functional groups, as defined by more than a century of research in synthetic chemistry, are collections of atoms that undergo specific chemical reactions such as reduction and/or oxidation, addition and/or elimination, or hydrolysis. Most metabolism databases deal almost exclusively with only a limited number of chemical elements, principally carbon, hydrogen, oxygen, nitrogen, phosphorus, and sulfur. In contrast, the UM-BBD has long included information on the microbial metabolism of inorganic and organic substances containing mercury, arsenic, silicon, tin, lead, selenium, tellurium, fluorine, chlorine, and bromine. Most recently, the UM-BBD has been expanded to contain information on microbial interactions with 77 chemical elements. This information can be accessed holistically via a standard periodic table representation of the chemical elements (Fig. 1A). For each of the 77 chemical elements covered, a hypertext link takes the user to further information on the microbial biochemistry of that element.

In the case of metals and metalloid elements, element pages describe how each undergoes oxidation, reduction, or perhaps coordination by specific microbes or their proteins. In the case of reactions, there are links to specific reaction pages. An example of a reaction page that is accessible from the element page for the radioactive element technetium is shown in Fig. 2. Technetium was first characterized in 1937, having been made in quantities sufficient to study via a newly built cyclotron (6). Yet, microbes are now known to change the oxidation state of the pertechnetate anion (70), showing the plasticity of biological systems to handle new chemical elements. The potential for microbes to reduce technetium to less-mobile oxidation states may have an impact on long-term environmental health, as isotopes such as technetium-99 have half-lives as long as 212,000 years.

MICROBIALLY FOCUSED DEPICTION OF THE ELEMENTS AND THEIR METABOLISM

A variety of schemes have evolved to arrange the chemical elements in a meaningful array (80), but the forerunner of the modern periodic table of the elements is generally credited to Sergei Mendeleyev (6). In 1869, Mendeleyev organized the elements into columns and rows for the purpose of teaching the properties of the elements to a chemistry class at St. Petersburg University. This fundamental organization of the chemical elements has persisted to the present as one of the most well-known and successful schemata in science. The organization imposed by Mendeleyev's periodic table facilitated the discovery of concepts related to chemical bonding, electron shells, electronic orbitals, and ultimately quantum theory.

The most widely used format for the periodic table of the elements was not developed with biology in mind, and thus different renderings may offer a better linkage between chemical properties and biological function. One such permutation presented here is a spiral representation of the chemical elements (Fig. 1B). A spiral elemental chart is not new and in fact dates back to the 1880s (80). However, it has been elaborated on here to best illustrate the biological roles and connectedness of the elements for their functions in microorganisms. For example, the periodicity of 8 focuses attention on the lighter elements, and this is further emphasized by putting biologically less relevant heavy elements in smaller boxes on the periphery. Moreover, the current spiral depiction juxtaposes hydrogen with elements to which it is commonly bonded in biological systems: carbon, nitrogen, oxygen, phosphorus, and sulfur. The lighter elements that run through the spiral from the lower left to upper right are most abundant in biology. Those from the lower right (the noble elements) to the upper left (Al, Ga, and Ge) are not abundant in biological systems. While the transition metals are not shown individually in Fig. 1B due to the emphasis of the present review, the World Wide Web version

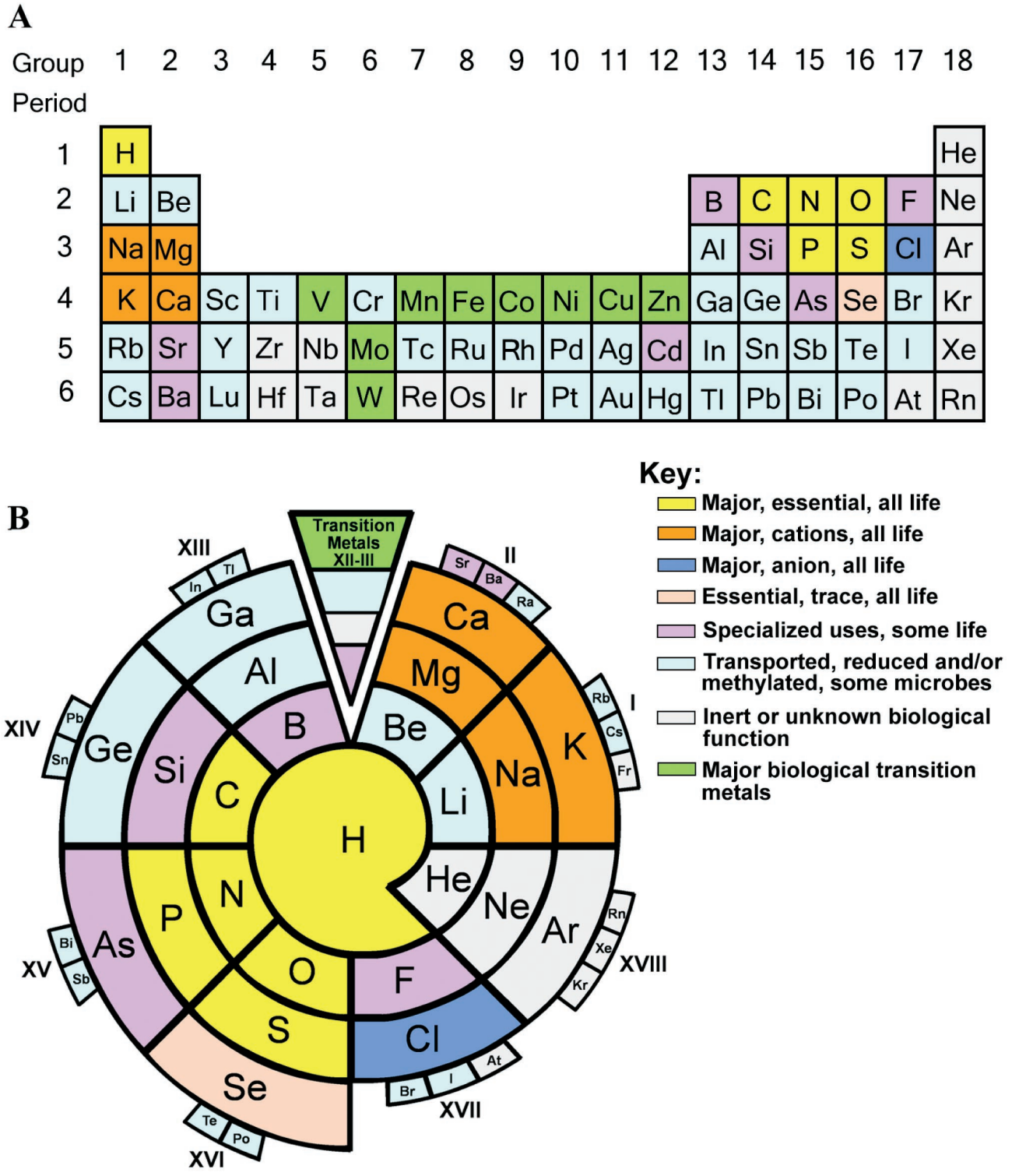

FIG. 1. Periodic representations of the elements. (A) Conventional table with linear columns and rows; the lanthanide and actinide elements, present in the on-line version, have been omitted for clarity of presentation. (B) Spiral representation of the elements which clusters elements that are prominent in biological systems. For on-line versions, see http://umbbd.ahc.umn.edu/periodic/.

provides a link to detailed information on transition metals in prokaryotes.

A key feature of the spiral elemental diagram depicted here (Fig. 1B) is the centrality of hydrogen, in sharp contrast to the isolation of hydrogen in the upper left corner of the standard periodic table (Fig. 1A). Hydrogen is central to microbiological systems because 60% of the cell mass is H_2O, most microbial enzymes effect H^+ transfer, H^+ gradients are widely used to

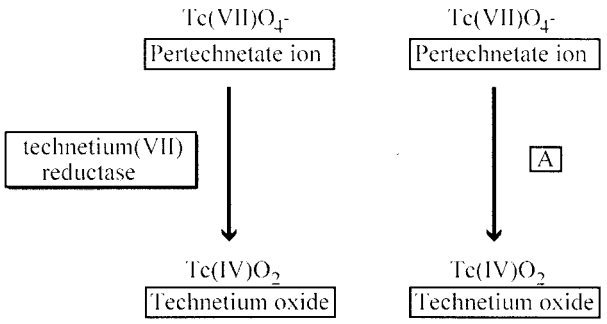

FIG. 2. Part of a pathway map for technetium (found at http://umbbd.ahc.umn.edu/tc/tc_map.html). Two reactions are shown. One is directly catalyzed by the enzyme technetium(VII) reductase, and the other is indirectly coupled to iron(III) reduction, and thus is labeled with an A to indicate nonspecificity.

generate ATP, H^- is a cellular two-electron transfer currency, and H bonding is crucial for the stability of major biomacromolecules. Until recently, hydrogenases (enzymes that carry out the equilibration of H^+ and H_2) were thought to be relegated largely to extremophilic prokaryotes and several mesophilic bacteria. Now, with broad scale genome sequencing, many prokaryotes are shown to contain hydrogenases, although the physiological importance of these enzymes is not always known (136).

The other major elements of the cell, C, O, N, S, and P, are clustered together with hydrogen in the spiral elemental diagram. These elements comprise approximately 97% of an *Escherichia coli* cell and are essential elements in all prokaryotes that have been analyzed. They are often bonded together in structural (lipids), catalytic (enzymes), and metabolic (intermediates in catabolism or biosynthesis) compounds. Thus, it is logical to have H, C, O, N, S, and P clustered in any elemental diagram where the focus is their biological relevance.

The spiral elemental diagram also clusters together the major elemental cations found in a microbial cell: Na^+, K^+, Mg^{2+}, and Ca^{2+}. While the abundance of these cations varies enormously inside prokaryotic cells, they are all important to cell function. Magnesium is typically the most abundant divalent cation inside prokaryotic cells (14). In addition to its previously mentioned role of coordinating to phosphoryl oxygen atoms, magnesium serves as a cofactor for numerous enzymes, in the maintenance of pH balance, and in iron transport and metabolism (22). The major magnesium transporter in *Salmonella*, CorA, has gene homologs that are widespread throughout the genomes of bacteria and archaea, suggesting that magnesium ion transport is important throughout prokaryotic systems (59). Moreover, *Salmonella* mutants defective in Mg^{2+}-dependent regulation and transport are hypersensitive to Fe^{2+}-mediated oxidative killing. Ca^{2+} is much less abundant in bacteria than Mg^{2+}, being present in only low-micromolar concentrations. As a result, the present understanding of calcium transport and metabolism is less developed, but genomics has added new information. Recent observations of bound Ca^{2+} ions in the X-ray structure of *E. coli* transmembrane transporter MthK initially led to the suggestion that this was a Ca^{2+}-gated K^+ channel (56), but since affinities of MthK for Ca^{2+} are in the millimolar range this conclusion is controversial (14). Historically, calcium has been considered a minor cation, largely involved in coordinating to some extracellular enzymes (66) and in specialized functions like sporulation (19). This perception has been changing. Analysis of sequences from a range of prokaryotes has revealed many putative EF-hand calcium-binding proteins that resemble an important class of calcium-binding proteins common in eukaryotes (83). In at least one example, a putative prokaryotic EF protein was demonstrated to coordinate calcium and have an important physiological role. *Rhizobium etli* produces the calcium protein calsymin. It contains six EF-hand motifs and is proposed to be important in the formation of nodules on plants.

Among monovalent cations, K^+ is the most prevalent species, being present at 300 mM in *E. coli* (14). The structure of a bacterial potassium transporter from *Streptomyces lividans* was resolved to a 3.2-Å resolution (32). This will allow a more accurate determination of the physiological function of prokaryotic genes identified as encoding transmembrane cation transporters. Sodium is often excluded from prokaryotic cells. However, sodium ions that do enter can participate with Na^+/H^+ antiporters to prevent overalkalinization of the cytoplasm under conditions of stress (14).

While major biological elements are generally the lighter elements, the lightest alkali metal and alkali earth elements, lithium and beryllium, are not generally used biologically by bacterial cells and, in fact, show some toxicity at moderate to high concentrations. Beryllium has been implicated in enzyme inactivation and malfunction (29, 74, 85, 99). Some of the toxic effects induced by beryllium may be due to spurious binding of Be^{2+} to sites normally occupied by Mg^{2+} and Fe^{3+} (75, 76). Lithium toxicity varies among microorganisms, and in this context media containing lithium have been used for the selective growth of bacteria such as *Bifidobacterium* spp. (68). In *E. coli*, lithium detoxification is at least partly mediated by Li^+ efflux via an Na^+/H^+ antiporter (51). Despite its toxicity, Li^+ can substitute for Na^+ in the cotransport of amino acids and some sugars in some bacteria (23, 71, 122, 129, 131, 132, 133). Li^+ can also replace Na^+ in driving the flagellar motor of *Vibrio alginolyticus* (69).

Heavier metals in the alkali metal and alkali earth family are generally not prominent biologically, and their reduced importance is indicated by a smaller wedge for these elements on the spiral elemental diagram (Fig. 1B). A major impetus for the study of these elements has been the microbiological sequestration of radionuclides produced in nuclear reactors, such as cesium-137 (4, 117, 130). In general, cesium is the most toxic of the alkali metal ions to microorganisms. Cs^+ influx usually occurs via monovalent cation transporters with various specificities, and the toxic effect of Cs^+ may result from subsequent reduced influx or increased efflux of K^+ or NH_4^+ (15, 57, 95, 116). Despite its toxicity, a low concentration of Cs^+ stimulated growth of a bacterium in the absence of K^+ (53), and Cs^+ replaced K^+ in the activation of some microbial enzymes (2, 50). Similarly, Sr^{2+} substituted for Ca^{2+} and Mg^{2+} without major cellular toxicity in processes such as spore formation (41), polysaccharide and flagellum biosynthesis (62, 104), stabilization of superficial layers (10), and enzyme activation (43, 111).

Rubidium and barium are not of concern as radioactive pollutants, but the ability of these elements to function as analogs to the lighter essential elements of their respective groups (or ions of similar valence) has been explored. No absolute requirement for rubidium in bacterial growth has been identified, but in the absence of K^+, Rb^+ restored normal or near-normal growth in several bacteria (17, 53, 77). Rb^+ effectively substituted for K^+ in the biosynthesis of a bacterial pigment (18) and for K^+ or NH_4^+ in the activation of some bacterial and fungal enzymes (11, 135, 141). Barium is the least studied of the heavier alkali and alkali earth metals in terms of functionally replacing the lighter elements of these groups in biological systems. Compared to Sr^{2+}, Ba^{2+} was a less effective substitute for Ca^{2+} or Mg^{2+} in the processes described above. However, barium sulfate does have a natural function in mechanoreceptor organelles found in members of the protozoan genus *Loxodes* (49), which is discussed later in this review.

Chloride, the major elemental anion in many microbes, is also the major halogen atom in biological systems. The element chlorine exists largely as chloride anion in soil and water, as well as in microbial cells. Chloride is required for the growth of at least some halophiles (105) and is thought to play an important role in osmoregulation and energy metabolism in other bacteria. As the result of human activities, chlorine oxyanions such as perchlorate, chlorate, and chlorite have increasingly appeared in the environment. Chlorine oxyanions are sometimes used as disinfectants to kill microorganisms, but some bacteria can use perchlorate as the final electron acceptor during anaerobic growth via a periplasmic perchlorate reductase and accessory enzymes (60). It has been proposed that perchlorate reductase is actually a nitrate reductase with broad specificity. However, some bacteria shown to reduce perchlorate do not use nitrate as a final electron acceptor (26).

In addition to chlorine, bacteria can incorporate other halogens (fluorine, bromine, and iodine) into metabolites, but these elements are not thought to be required for growth. These halogen atoms and chlorine are found in bactericidal halo-organic compounds and may be used by certain microorganisms in their native environments to kill competitors. For example, Hager (46) found a correlation between the antimicrobial activity of lipid extracts from 1,200 marine microorganisms and their halometabolite content. Chlorinated organics such as methyl chloride are mainly produced by soil bacteria; bromometabolites are predominantly formed by marine organisms (134). Chloro-, bromo-, and sometimes iodocompounds are formed by the action of haloperoxidases. Additionally, there are approximately one dozen fluorinated metabolites currently known to be produced by microorganisms. The mechanism by which biological fluoro-organic compounds are formed has only recently been revealed (93). The last element in the halogen series is astatine. Astatine has understandably received no biochemical attention; it is only found as a fleeting, unstable species during radioactive decay, and only 50 mg of it is estimated to exist on the Earth at any one instant (63).

The transition metals and zinc function largely as catalytic centers in enzyme catalysts. A typical bacterium will express several thousand proteins, of which approximately 30% are metalloproteins. Thus, while zinc and transition metals might comprise only 1 to 2% of the mass of a microbial cell, they are absolutely essential for cell functioning. The metallic elements are crucial catalytic centers for enzymes active in the cycling of the major elements H, O, C, N, and S (136). The major transition metals and zinc, in the general order of their prevalence in enzymes in *E. coli*, are Zn, Fe, Cu, Mo, Mn, Co, and Ni. The heaviest metal with well-documented functions in bacteria is tungsten (atomic number = 74; molecular weight = 183.9). Some anaerobic bacteria replace molybdenum with tungsten in some functions, probably because tungsten is much more bioavailable in certain anaerobic environments (64).

The heavy metals comprise the greatest number of elements. While they are generally not beneficial to bacterial cells, heavy metallic elements have been in the environment for billions of years, and so it is not surprising that microbes have evolved responses to their presence. A number of them are quite toxic to bacteria. Some of the most toxic elements modulate their effects by avidly binding to thiol groups inside a bacterial cell; for example, Hg^{2+} shows a K_d on the order of 10^{-52} for coordination with the thiolate anion (91). Silver, gold, and cadmium also bind avidly to thiols. Other metals show toxicity by mimicking essential elements and thus preventing normal functions mediated by those elements.

Because of this toxicity, microbes have evolved metabolic responses to the heavy, nonessential elements, but the responses differ with the element. Heavy metals often get into the cell via influx pumps for essential elements. The toxic metals then must be selectively pumped out. This mechanism comes into play with Cd, Ag, and Pb (102, 115). In some cases, heavy metals or metalloids are reduced in order to facilitate their efflux. For example, the metalloid oxyanion arsenate is reduced to arsenite to differentiate it from phosphate and allow its selective transport out of the cell (88, 114). Comparative genomic analysis has revealed the widespread occurrence of arsenate reductase in prokaryotes, suggesting that this is an ancient physiological function (88). Another widespread and relatively unique form of heavy metal detoxification is the well-studied mercuric ion operon, *mer* (126). This system is based on the enzymatic reduction of Hg^{2+} to elemental Hg. Elemental mercury has an unusually low boiling point for a metal, 357°C at atmospheric pressure, which allows it to be displaced from a microbial cell by simple volatilization.

Metal transformations are also important in microbial energy metabolism. The following metal ions or metal oxyanions are known to be or are potentially transformed when acting as a final electron acceptor during respiration by some microorganisms: Fe^{3+}, Mn^{4+}, vanadate, uranate, arsenate, rhodium sesquioxide, pertechnetate, chromate, molybdate, and tungstate. This has led to a conceptual appreciation that microbes "breathe" many elements and elemental oxyanions in addition to the more well-established anions such as nitrate and sulfate (72, 90). The ability to couple the concomitant oxidation and reduction of diverse organic or inorganic compounds underlies the prominent role of microbes in the geological cycles of Earth.

BIOALKYLATED ELEMENTS

Organometallic compounds are prominent intermediates in microbial metabolic pathways and include methyl-cobalamin (124) and methyl-Ni-F430 (36) for methyl group transfer and methanogenesis, respectively. Biologically common alkylated

TABLE 1. Elements known to exist in alkylated form within biological systems or produced by biological activity[a]

Element	Enzyme or system	Reference
Specific		
H	Methyl-*S*-coenzyme M reductase	54
C	Acetyl coenzyme A synthase	73
N	Phospholipid *N*-methyltransferase	139
O	*S*-Adenosylmethionine methyltransferase	30
F	*Streptomyces* sp.	93
P	Methylcobalamin	112
S	*S*-Adenosylmethionine methyltransferase	5
Cl	Various fungi and algae	48
Co	Methyl-B_{12}	98
Ni	Methyl-*S*-coenzyme M reductase	36
Nonspecific		
Cr	Cocorrinoids (in vitro only)	98
Cu	Cocorrinoids (in vitro only)	98
Ga	Cocorrinoids (in vitro only)	98
Ge	Methylgermanium in nature; source unknown	128
As	*S*-Adenosylmethionine methyltransferase	21
Se	*S*-Adenosylmethionine methyltransferase	100
Br	Marine phytoplankton	109
Rh	*Propionibacterium shermanii*	65
Pd	Methylcobalamin (in vitro only)	102
Cd	Polar marine bacteria	96
In	Cocorrinoids (in vitro only)	98
Sn	*Saccharomyces cerevisiae*	3
Sb	*Scopulariopsis brevicaulis*	55
Te	*Pseudomonas fluorescens* K27	7
I	*S*-Adenosylmethionine methyltransferase	1
Pt	Methylcobalamin (in vitro only)	37
Au	Methylcobalamin (in vitro only)	102
Hg	*Desulfovibrio desulfuricans* LS	25
Tl	Anaerobic bacteria from freshwater sediment	110
Pb	Bacteria from lake sediment	108
Bi	*Methanobacterium formicicum*	81
Po	Marine sediment	83

[a] Elements are listed in order of increasing atomic number. Specific reactions are carried out by enzymes that selectively catalyze the alkylation; others may be fortuitous.

elements include nitrogen, sulfur, oxygen, and the halogens (Table 1).

More recently, a large number of other elements have been shown to undergo bioalkylation; most or all of these are likely the result of nonspecific biochemical transformation (Table 1). The most dramatic example of a nonspecific alkylation is the formation of methylmercury and dimethylmercury by sulfate-reducing and other bacteria in anaerobic sediments, with potentially devastating effects on human health (126). The Minamata Bay disaster in Japan was perhaps most instrumental in demonstrating the neurotoxic effects of methylmercury species (47). Although nonspecifically produced, alkylmercury species are likely not of recent origin. Some bacterial mercury resistance operons contain an organomercurial lyase gene that encodes an enzyme cleaving the carbon-mercury bond of methylmercury species to produce methane and mercury(II); the latter can be then be detoxified by mercuric reductase. Microbially generated methyl selenium and methyl tellurium species are also toxic to humans but can be microbially decomposed (42). Recent reports (8, 38, 82) have documented a large number of methylated elements, including antimony, thallium, and bismuth, emanating from anaerobic environments such as landfills (Table 1). Biomethylation of less-well-studied elements has been recently reviewed (128).

"BIOLOGICALLY INDIFFERENT" ELEMENTS FOUND TO BE BIOLOGICALLY RELEVANT

In a recent review, Beveridge et al. (9) branded some members of the periodic table as "indifferent elements," meaning that biological systems may contain them at some low level but could very well do without them. For example, humans contain higher levels of strontium and ruthenium (two elements not known to have a physiological function) than cobalt, a known required element (35). But elements indifferent or toxic to some life forms may be critical components of others. Elements to be considered here in this context are boron, cadmium, strontium, barium, and bismuth. Molecular mechanisms by which those elements interact with biological systems are being revealed but are not broadly appreciated in the general biochemical literature.

For example, utilization of the element boron is poorly understood despite the knowledge that boron is required for proper biological function in microbes and plants. In 1934, boron was reported to be required for healthy plant growth (127). Lack of boron produces brittleness, and plants grown with excess boron have highly flexible tissues (12). These effects have only recently been explained; plant cell walls contain borate esters that cross-link pectin polysaccharides (94). With bacteria, boron salts have often been included in growth media (120). Certain *Streptomyces* (33) and *Sorangium* (52) species produce the boron-containing antibiotics boromycins and tartrolons, respectively. Cyanobacteria require boron to develop functional nitrogen-fixing heterocysts (13, 79). A compound mediating quorum sensing by bacteria has been isolated and shown to contain a furanosyl borate diester (24).

As discussed above, the heavier alkali earth metals strontium and barium are thought to be acquired by uptake systems for calcium and magnesium and to be largely indifferent in many biological systems, except for their toxicity. It is perhaps surprising that some organisms accumulate significant quantities of these elements for specific biological purposes. Protozoans of the subclass *Acantharia*, a sister subclass to the more well-known *Radiolaria*, have skeletons composed largely of strontium sulfate (103). Moreover, protozoan ciliates of the genus *Loxodes* have mechanoreceptor organelles composed mainly of barium sulfate (49). This suggests that these microorganisms have evolved specific mechanisms to accumulate and utilize these heavy elements.

In this context, cadmium is regarded as a toxic element, with microbial responses typically thought to be limited to detoxification via selective binding or efflux. However, it was recently discovered that growth of a marine alga is stimulated by cadmium addition to zinc-limited media (67). Under these conditions, the organism produces a cadmium-dependent carbonic anhydrase. It was proposed that the use of cadmium in this way is physiologically relevant in the native ocean environment, where competition is fierce for metals needed as enzyme cofactors (67).

Finally, bismuth is one of the heaviest naturally occurring elements and is found at a concentration of 0.1 to 0.2 mg/kg in the Earth's crust (39). While sharing chemical properties with arsenic and antimony, bismuth has more metallic character than the lighter group 15 elements (8, 39, 107). Bismuth compounds have been used medicinally for two centuries, and

about half of the bismuth used commercially today is for pharmaceuticals (16). Bismuth is relatively nontoxic to humans, but it is toxic to many bacteria, including *Helicobacter* (*Campylobacter*) *pylori*, the causative agent of peptic ulcers and gastroduodenal infections (78, 123), and enterotoxigenic *E. coli*, which causes traveler's diarrhea (45, 119). Yet, little has been published on the molecular interactions of microorganisms with bismuth compared to other heavy metals such as mercury and cadmium.

Bismuth sulfite agar medium has continued to be used successfully for the selective enrichment of *Salmonella* species from foods (142). Woolfolk and Whiteley (140) reported the reduction of bismuth compounds to elemental bismuth with a crude extract from *Micrococcus lactilyticus*, but analytical data were not presented; it was stated that a ". . .dark brown suspended material, probably elemental bismuth, accumulated." Moreover, at least two other groups have reported formation of "bismuth mirrors," also suggesting microbially mediated reduction of bismuth ions to metallic bismuth (31, 89). Novick and Roth reported bismuth resistance and sensitivity conferred by penicillinase plasmids in *Staphylococcus aureus* and mapped the general location of putative bismuth resistance genes on the plasmid (92). More recent research has shown that bismuth ions can induce the cadmium and arsenical-antimonial resistance operons (143, 144), but no evidence has been presented that this induction translates into bismuth resistance. Most recently, the CadC repressor that controls cadmium detoxification in *Staphylococcus* has been shown to bind near-stoichiometric quantities of bismuth (20). The physiological significance of bismuth binding is unclear.

CONCLUSIONS AND FUTURE PROSPECTS

Prokaryotes have existed on Earth for at least 3.6 billion years and are still the most successful life form based on total biomass and metabolic flux. During that time, how many elements might microbes have "learned" to interact with? There are 92 naturally occurring elements (6); the transuranic elements are largely created via anthropogenic nuclear reaction processes, and most have fleeting lifetimes. Currently, interactions with 77 elements, of which 74 are naturally occurring, are depicted on the UM-BBD. Of those not yet depicted on the UM-BBD, some are clearly not biologically relevant (e.g., astatine, as discussed earlier). Some elements, such as the noble gases, may be excluded from inquiry by some because of their chemical inertness. However, xenon has found use in the laboratory for doping the surfaces of proteins in X-ray crystallographic analysis (138). Might nature have found some use for noble gases? Moreover, it seems likely that we will find new biological requirements for specific elements, based on the relatively recent findings described above with the elements boron, strontium, barium, cadmium, and bismuth. In the context of microbial genomics, we need to be mindful that novel genes in newly sequenced microbes may do more than encode another kinase or phosphatase, but rather may be involved in interactions with the environment that are new and wonderful to us, but long "known" to prokaryotes.

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