Expanding beyond canonical metabolism: Interfacing alternative elements, synthetic biology, and metabolic engineering

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ABSTRACT

Metabolic engineering offers an exquisite capacity to produce new molecules in a renewable manner. However, most industrial applications have focused on only a small subset of elements from the periodic table, centered around carbon biochemistry. This review aims to illustrate the expanse of chemical elements that can currently (and potentially) be integrated into useful products using cellular systems. Specifically, we describe recent advances in expanding the cellular scope to include the halogens, selenium and the metalloids, and a variety of metal incorporations. These examples range from small molecules, heteroatom-linked uncommon elements, and natural products to biominning and nanotechnology applications. Collectively, this review covers the promise of an expanded range of elemental incorporations and the future impacts it may have on biotechnology.

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1. Introduction

Metabolic engineering expands the chemical palate of cells to yield industrially-relevant products that compete with traditional chemical methods, especially with respect to product specificity and mild process conditions \cite{1-3}. These advances range from traditional examples of products such as alcohols, citric acid, and penicillin to more recent examples including artemisinin \cite{4}, lycopene \cite{5}, plant alkaloids \cite{6}, energy dense fatty acids \cite{7}, among others. However, the chemical space of cellular production has not yet been fully harnessed in most applications. In this regard, the field of metabolic engineering is currently accessing and competing with a subset of molecules accessed through traditional synthetic organic chemistry and primarily limited to combinations of only six common elements (carbon, hydrogen, oxygen, nitrogen, phosphorus and sulfur) comprising most compounds \cite{8}. Synthetic biology has begun to enable access to "unnatural" combinations of these common elements through composite pathways leading to molecules such as muconic acid, 1,4 butanediol, unnatural alcohols and amino acids, and rare heteroatom-heteroatom bonded compounds \cite{9-12}. However, new synthetic tools coupled with examination of native genetic diversity have uncovered unique chemistries that enable assimilation of uncommon elements. Such discoveries provide an exciting glimpse into how classic cellular biochemistry can transcend into cellular bioorganic and bioinorganic chemistry.

Indeed, there is a cellular advantage for incorporating uncommon elements. Inherently, each element has its own unique characteristics that have both biological and biotechnological advantages. Prevailing examples include halogenated molecules with enhanced biological activities used in pharmaceutics and agriculture \cite{13}, boronated antibiotics and signaling molecules \cite{14}, and transition metal nanoparticles used for optics and medical applications \cite{15}. Likewise, uncommon metals themselves may be inherent products in biomining applications where organisms can concentrate valuable metals, such as lithium and platinum. These applications begin to expand the subset of "bioreachable" products beyond the traditional six elements of canonical biochemistry.

In this review, we provide an up-to-date synopsis on the expanding "cellular periodic table" (Fig. 1). Specifically, we focus on compounds and structures containing halogens, other non-metals/metalloids (such as selenium and boron) and a collection of transition and rare earth metals. Through this overview, we aim to highlight previous and nascent engineering efforts aimed at incorporating uncommon elements into cellular metabolism to produce interesting products.

2. Cellular destinations for uncommon elements

For the sake of this review, we examine four major destinations for uncommon elements. These comprise: biological assemblies, precursors/feedstocks, biomining, and nanomaterials (Fig. 2). We briefly describe each of these four here with respect to product examples and industrial applications before discussing the types of uncommon elements in more depth.

2.1. Biological assemblies

A great deal of structural and biochemical diversity can be found in products stemming from biological assembly lines such as polyketides, non-ribosomal peptides, and proteins. Not surprisingly, engineering these components has led to therapeutically relevant natural products \cite{16}. Likewise, these compounds and proteins are targets for uncommon elements with several case studies leading to generation and incorporation of non-canoncal amino acids \cite{17-19} and molecules with improved biological function \cite{20}. Molecules like polyketides are both natural and synthetic substrates for halogenation \cite{21,22}. Precise incorporation of uncommon elements into these end-products is still an ongoing challenge assisted by advances in synthetic biology.

2.2. Precursors and feedstocks

As described above, metabolic engineering provides a unique opportunity for replacing traditional chemical synthesis of small molecules. However, many industrial compounds produced with toxic chemical syntheses also have biochemically uncommon elements. To this end, microorganisms capable of producing a variety of precursor molecules have the potential to be expanded in their use to include rare-element analogues which can be further utilized in downstream chemical applications \cite{3}. Such transformations include small molecules containing silicon and halogens, for example, that are suitable for reactions like cross-couplings \cite{23}, electrophilic cleavage \cite{24}, and polymerizations \cite{25}. These efforts involve both protein engineering and synthetic biology along with metabolic engineering to expand the chemical reach of cellular metabolism.

2.3. Biomining

Microorganisms adapt to challenging environments, especially through mechanisms of detoxification. In the case of biomining, organisms use both reductive and oxidative mechanisms to convert and sequester metals of potential interest. As an example, industrial biotechnology has utilized microorganisms for biomining of copper and other more common elements for decades and has begun to expand its elemental ambit to include transformations of rarer and more valuable metals including lithium, palladium, and platinum \cite{26}. This field shows great promise especially as we deplete rare-earth metals and generate substantial electronic waste.
2.4. Nanomaterials

As a final destination for uncommon elements, cellular systems are capable of serving biocatalytic roles in forming nanomaterials. The recent explosion of nanotechnology has yielded industrially-relevant products for a wide range of applications such as biosensing, drug delivery, catalysis, optics, and agriculture [27]. As with chemical production, microorganisms can provide precise nanoparticle functionalization and low-toxicity. Although not mutually exclusive from biomining, nanoparticle synthesis optimization requires distinct modifications of strain characteristics. Thus, the rewiring of biology’s native capacity to reduce metallic salts into nanostructures has resulted in many breakthroughs in this emerging field.

3. Halogenation

Among the many uncommon elements that can find their way into biological molecules, halogens are particularly interesting as halogenated organic compounds play a substantial role in the pharmaceutical, diagnostic, agricultural, and materials industries. While halogenation of organic compounds using synthetic chemistry is well-established, these procedures are often characterized by highly toxic chemicals and poor atom economy [28]. Additionally, these processes typically suffer from low yields due to difficulty of separation and purification of enantiomeric substances [29]. Thus, metabolic engineering can offer a more efficient and environmentally friendly method for producing halogenated molecules.
Both natural and engineered, are provided in order of their appearance. (*) Denotes completely unnatural products.

While fluorine is the most abundant halogen in the Earth’s crust, it is the rarest found in natural products and is only known to be incorporated into a handful of molecules. This reality can be attributed to a multitude of factors including fluorine’s high electronegativity, low bioavailability, and high heat of solvation [37]. Moreover, a major drawback of fluorinated natural products is the toxicity associated with certain metabolites, notably fluorooxetane and its downstream metabolite fluorocitrate, which inhibits aconitase in the citrate cycle. This toxicity is an issue since most known fluorinated metabolites are closely related to these compounds and originate from a single pathway, the well-studied fluorinase pathway, first discovered in the bacterium *Streptomyces cattleya* [38]. Recent studies by Ma et al. [39] found that pathway intermediate 5-fluoro-5-deoxy-D-ribose was converted into 5-fluoro-2,3,4-trihydroxypropionic acid, an undiscovered fluorinated metabolite. The reaction is catalyzed via the novel enzyme FdrC in the organism *Streptomyces* sp. MA37 and thus reveals new possibilities for the fluorinase pathway. Likewise, higher efficiency fluorinases (including one isolated from the marine bacterium *Streptomyces xinghaiensis*) can show specificity increases by over an order of a magnitude, thus opening the door to more efficient fluorination [40]. Beyond these initial pathways, a few slightly more complex fluorometabolites have been discovered, including ω-fluorooleic acids from the plant *Dickhapetalum toxicarium* and the antibiotic nucleocidin from *Streptomyces calvus* [41]. Nucleocidin is unique in that the fluorine is bonded at the C-4 position of a ribose ring, while every other recognized metabolite has originated from a fluorooracil molecule [42]. Further details of fluorinated natural products and the fluorinase enzyme have been published in other reviews [41].

Synthetic incorporation of fluorine has been achieved through precursor-directed incorporation aimed to mitigate the inherent toxicity of fluorinated anti-metabolites. This approach consists of determining desirable locations for incorporation and engineering promiscuity of existing enzymes and pathways to preferentially react with halogenated substrates. Several successful examples of...
incorporating pre-fluorinated precursors into metabolites can be found in the polyketide pathway. As examples, fluorine, along with the other halogens, have been incorporated into pacidamycin analogues via precursor directed biosynthesis [43]. Another group produced six fluorinated rapamycin analogues via precursor feeding in the bacterium S. hygroscopicus [44].

The Chang group has worked extensively to create fluorinated polyketides and has identified locations in the polyketide synthesis machinery that are amenable to fluorine incorporation through the addition of fluorinated precursors [45]. Through this work in E. coli, it was possible to convert fluoromalonate to fluoromalonyl-CoA and subsequently incorporate this molecule into novel fluorinated derivatives of tetraketide lactones. Further efforts have been made to enable loading of fluorinated extender units into this synthetic machinery, albeit at lower rates than native substrates [46].

Beyond small molecules, fluorinated precursors have been used to insert fluorine into amino acids and polypeptide chains, an approach that shows great promise for protein engineering and the production of bioactive peptide compounds [47,48]. Aromatic fluorinated amino acids are most commonly used for protein incorporation and biorthogonal fluorinated amino acids have utility as probes for molecular interactions [49]. More specifically, incorporation of fluorinated amino acids has shown great capacity for improving specific properties of proteins, such as refoldability, thermoactivity, and overall protein stability [50–52]. An excellent review on fluorinated amino acids and protein engineering was recently published for more details [Odar et al. [47]]. More recently, the biosynthesis of fluorinated peptaibols was enabled by using a site-direction building block incorporation approach in the fungus T. arundinaceum [53]. Overall, the incorporation of fluorine remains a challenge for synthetic biology primarily due to toxicity and low enzyme function and specificity.

3.2. Chlorine

Chlorine is the most prevalent halogen with respect to bioavailability, especially given the abundance of halogenating organisms in marine environments. As a result, natural chlorinated molecules are highly diverse particularly in bioactive natural products such as rebeccamycin, chloramphenicol, radicicol, and vancomycin [21]. Here, we highlight several notable examples of chlorine incorporation with a primary focus on synthetic approaches and promising routes for future metabolic engineering.

Based on their bioactivity, the first major contributions in the field were natural products such as the in vivo combinatorial synthesis efforts by Sanchez et al. [54]. In this work, the authors reconstituted the pathway for the chlorinated bioactive molecule rebeccamycin and created novel pathway derivatives by co-expressing the tryptophan halogenases PyrH and Thal in Streptomyces albus. These two enzymes uniquely bind the chlorine atom to tryptophan’s aromatic ring with different regioselectivities. The resulting chlorinated derivatives have potential applications as antibiotics and antitumor agents. A similar approach was taken by Okada et al. to produce chlorinated derivatives of daurichromenic acid with higher antibacterial activity via the halogenase AscD [55]. Introducing a similar tryptophan halogenase into the plant C. roseus yielded novel chlorinated alkaloids, which have potential as powerful bioactive pharmaceuticals [56]. Likewise, PrnA was introduced into Streptomyces coeruleorubidus to yield chlorinated pacidamycin [55], a molecule that can be modified via cross-coupling reactions to produce further unnatural pacidamycin derivatives. As can be assumed from these efforts, halogenated tryptophan plays a central role for halogenation pathways. Likewise, most engineering efforts on halogenases have been performed on tryptophan halogenases, notably RebH [57,58], and demonstrate the potential to switch regioselectivity [59].

Chlorine incorporation has also been seen in pathways related to phenolics and flavonoids. For example, introduction of fungal flavin-dependent halogenase Rdc2 can be used to drive radical biosynthesis in S. cerevisiae leading to a new halogenated analogue, 6-chloro, 7,8-dehydrozearalenol [60]. Production of 2-chlororesveratrol in E. coli was also accomplished by incorporating Rdc2, which is known to have broad substrate specificity, into a heterologously expressed resveratrol pathway at an initial titer of 7.0 mg/ L [61]. The same Rdc2 gene can also be used to convert fed hydroxyquinolines into a chlorinated derivative in vivo [62,63]. The RadH enzyme, an ortholog of Rdc2, has been investigated in E. coli for the production of a novel chlorometabolite, 8-chloro–7-hydroxycurcin [64]. To accomplish this feat, site-saturated mutagenesis coupled with a fluorescence screening assay was employed to isolate a RadH variant with an improved affinity for 7-hydroxycurcin.

Beyond aromatics, chlorine can be incorporated into different chemical scaffolds. As an example, enzymes such as WelOS [65], AmbO5 [66], and AioQ [67] have been well characterized for their ability to charge a chlorine atom to an aliphatic, non-activated carbon atom – a conversion that cannot currently be performed through chemical means. Among these enzymes, AmbO5 is an especially promising candidate for enzyme engineering approaches due to its promiscuous nature. Regarding substrate diversity, the recent discovery of the enzyme CyIC displays the potential for chlorination of fatty acid residues [68].

Metabolic engineering strategies have been coupled with some of these incorporation approaches to increase titers of chlorinated biomolecules. For example, chlorotetracycline biosynthesis in Streptomyces aureofaciens was increased nearly 2-fold in titer to 25.9 g/L [69]. In another example, the entire gene cluster for chloramphenicol was imported into the industrial microorganism Streptomyces avermitilis [70]. Resulting chloramphenicol titers were initially 6-fold higher than the original host (S. venezuelae) and further shikimate pathway modifications increased titers over 12-fold, reaching a titer of 250 mg/L. These initial metabolic efforts coupled with chlorine’s moderate properties and biological accessibility are quite impactful for further expanding bioprocesses for chlorinated molecule generation.

3.3. Bromine

Bromine and chlorine are nearly identical in both mechanism of incorporation and possible bonding locations. More often than not, chlorinase enzymes also incorporate bromine. However, brominases have a more difficult time accepting chlorine due to differences in the oxidation potentials of intermediates and dehydration penalties, i.e. addition of chlorine requires more energy and enzymatic effectiveness [71]. As a result, brominated natural metabolites are more common and are found in a greater variety of molecular positions. Despite its prominence, the biological activity modulation imparted by bromine is not easily predictable and varies by the molecule [30].

In contrast to chlorinated molecules, brominated molecules and pathways have not been as extensively engineered. Initial efforts involved simply replacing chloride with bromide in solution. In doing so, Sanchez et al. were also able to produce brominated indolocarbazole derivatives through combinatorial biosynthesis in a similar fashion to how they produced chlorinated derivatives [54]. Using a transformation-associated recombination strategy, Ross et al. heterologously expressed an entire alterochromide lipopeptide pathway from Pseudoalteromonas piscicida in E. coli and obtained unusual brominated lipopeptides, originating from
tyrosine, where bromine is added early during the NRPS assembly via the enzyme AltN [72].

Additional brominated small molecules have been explored in heterologous hosts as well. As examples, Agarwal and Moore engineered genes from the bmp gene locus of a marine γ-proteobacterium to produce a variety of brominated phenolic molecules in E. coli [73]. A very recent effort produced 7-bromo-tryptophan in E. coli and subsequently modified downstream peptide molecules in vivo using Suzuki-Miyaura cross-coupling reactions [74]. Beyond these initial efforts, there is great potential for expanding cellular bromination pathways into structures such as terpenoids, non-terpenoid C15-acetogenins (ACGs), indoles, and phenols/aromatics [75]. Thus, future bioprospecting and engineering efforts will continue to expand this unnatural element incorporation.

3.5. Halogenation outlook

Collectively, these examples demonstrate the capacity for halogen atoms to be integrated into a wide variety of metabolic destinations in vivo in both native and nonnative hosts. Through rational protein design, directed evolution, and metabolic engineering, the underlying reaction mechanisms and associated pathways can be altered and improved, thereby enabling further advancements. Although promising, notable challenges exist for halogen biochemistry including off-target effects of toxic products, advancements. Although promising, notable challenges exist for halogen biochemistry including off-target effects of toxic products, metabolism including off-target effects of toxic products, and the lack of information on related pathways and enzymes compared to halogenated natural product discoveries. Continued efforts have been made to improve substrate recognition [82], turnover rates [57], and often necessary carrier proteins [83] to expand the scope and yield of halogenated metabolites. To address the low-throughput nature of analytical analyses for these metabolites (NMR, HPLC, or LC-MS), high-throughput screening techniques for halogenated molecules are continually being developed that accelerate the process of protein and metabolic engineering [64,84–87]. Nevertheless, halogenated metabolites remain a fertile and promising area of expansion for metabolic engineering, especially for the case of natural products and secondary metabolites. Advances in large-scale genome mining and further discovery and engineering of halogenases will continue to unlock new reaction possibilities, moving us one step closer to highly robust cellular factories.

4. Selenium and the metalloids

Various non-metals and metalloids can be incorporated into cells both through covalent bonds to metabolites (as in the case with halogens described above) and as nanoparticle assemblies. We highlight here advances in the incorporation of selenium, boron, silicon, and tellurium as examples of the expanding periodic table for cells (Fig. 1, Table 1).

4.1. Selenium

Perhaps the most ubiquitous and well-characterized unnatural incorporation in biology is selenium in the form of the 21st proteinogenic amino acid — selenocysteine [88]. Beyond selenocysteine, selenium metabolism [89] can also lead to bioactive natural products [90] and potentially complex pharmaceuticals including the synthetic drug Esbelen that is being investigated as a treatment for hearing loss and many mental disorders [91]. Additionally, simple metabolites such as Se-methyl-selenocysteine and methylseleninic acid have been shown to be potent chemopreventative compounds [92]. Finally, given the trace element dietary requirement of selenium, enriched yeast provide an economical means to supplement selenium for human nutrition and cancer prevention [93]. The selenium metabolic pathway in yeast and bacteria has been mapped to identify key selenium metabolites with selenomethionine being the most dominant and accounting for 60–85% of selenium in yeast [94]. Further selenium incorporation beyond this local pathway has not yet been fully explored, but various microorganisms and plants contain compounds like 3-Butenyl isooselenocyanate, selenobiotin, and selenosinigrins [95]. Additionally, the volatile selenium compounds dimethylselenide and dimethylselenide were produced in both bacteria and yeast as part of selenium metabolism; however these compounds have limited known applications [96,97]. Overall incorporation of selenium from selenite in strains was increased by Pusztaheleyi et al. through increased in glutathione concentration and glutathione reductase activity [98].

Current research in the field focuses on examining the interplay between sulfur and selenium metabolism [99]. For example, replacing the sulfur with a selenium atom in biologically active molecules like the plant alkaloid camalexin, could potentially improve functionality [100]. Enzymes also exist that can selectively exchange sulfur for selenium, including a selenouridine synthase that converts 2-thiouridine to 2-selenouridine, found in the wobble position of certain bacterial tRNAs [101]. Further investigation into similar enzymes could potentially open new doors for selenium incorporation.

Beyond metabolite compounds, a common destination for selenium in a variety of microorganisms are selenium nanoparticles [102]. Cellular systems can provide an advantage to the field with better control of size, polydispersity, and morphology of these nanoparticles. For example, Dobias et al. investigated the role of different proteins in controlling nanoparticle size in E. coli [103]. Specifically, four proteins were identified that bound tightly to SeNPs resulting in narrower size distributions and more spherical nanoparticles with further investigations also being reported recently [104,105]. Expression of a metal-resistant variant of reductase enzyme cytochrome b5 in Pichia pastoris led to selenium nanoparticles that were far less cytotoxic to human cells than...
conventional nanoparticles [106]. With regard to applications, selenium nanospheres have the ability to sequester elemental mercury for bioremediation applications [107]. Selenium metabolism and pathways within cells can be expanded both with respect to metabolites and nanomaterials, but will require fine tailoring to balance toxicity and selenium incorporation. Future metabolic engineering opportunities exist to balance two competing pathways: selenium metabolite incorporation vs. selenium reduction into nanoparticles. Once realized, selenium metabolism could establish a new path for bioactive molecules and materials.

4.2. Boron

Despite being an essential micronutrient, boron is rarely found in natural products and instead is commonly found in the cell walls of plants in complexes with polysaccharides and other structural features. A small handful of boronated natural products exist, all of which share the similar structure of a tetracordinate boron-oxygen complex. These molecules include borophycin, boromycin, aplasmomycin, the tartrolons, autoinducer AI-2, and the recently discovered but extinct borolithochromes [108,109]. Evidence from Chen et al. [16] suggests that the majority of the naturally-occurring molecules is incorporated into the macrocyclic ring in the final synthesis step without enzymatic catalysis required [110]. The bacteria-produced Autoinducer AI-2 is a quorum sensing compound produced from the reaction of naturally occurring boric acid with 1-deoxy-3-dehydro-D-ribulose [111]. Other non-natural boron-containing molecules can be altered using promiscuous enzymes, however a heteroatom boronating enzyme is yet to be found [108].

Although not yet a mature field, boron chemistry has carved a space in modern medicinal chemistry and drug discovery. A recent review on the versatility of boron's bioactivity provides mechanistic and structural insights into the development of primarily synthetic boron molecules designed to be bioactive [112]. Yet, the recent discovery of a complex boronated polyketide compound in a prehistoric fossil displays the potential for boronated complexes to act as bridges between complex backbones to create larger scale unique molecules [109]. Future efforts in the field may enhance the ability to form functional boronated molecules using microorganisms.

4.3. Silicon

Silicon makes up nearly 28% of the Earth’s crust and plays a vital role in modern chemistry as well as in elastomer production, microelectronics, and in many biotechnology applications. Standard chemical production of many enantioselective silicon molecules relies on multi-step chemical syntheses and separations, but biocatalysis has seen a slow yet steady adoption in the industry for certain reactions [113]. In this regard, silicon biotechnology is still a fairly new field. While not discussed here, additional applications in the area of nanotechnology are possible with the formation of complex silica structures [114,115].

Until recently, the only known silicon-related bond formations that occurred in biological systems were silicon-oxygen bonds (such as the elaborate silica structures formed by diatoms [114]). Research performed in the yeast Kloeckera cortices demonstrated that enzymes can promiscuously react with silicon-bearing analogues of their native substrates, a form of precursor directed biosynthesis [116]. This method has been applied to other microorganisms as well to produce a handful of enantioselective silanes, with the oxidoreductase systems thought to serve as the catalytic machinery. Notably, Saccharomyces cerevisiae could reduce a variety of acylsilane substrates with high efficiency, but had trouble reducing phenyl-functionalized silicon molecules [117]. Other organisms, including Pichia pipipet, have shown to be more efficient at reducing these and expression of toluene dioxygenase in E. coli results in the dioxygenation of several phenyl silanes [118]. Free enzymes in non-aqueous solvents can perform more complex reactions such as polymerizations and generation of siloxane-phospholipids, but these conditions are not immediately compatible with in vivo use [24].

Silicon’s chemical similarity to carbon has always hinted that microorganisms and biocatalysts may have a greater capacity for novel silicon-heteroatom bonds than what has been discovered previously. To this end, the first instance of an enzyme directly catalyzing the formation of a carbon-silicon bond was shown very recently in the Arnold lab using an engineered cytochrome C [119]. This evolved system was capable of catalyzing multiple substrates to siliconated products with high enantioselectivity and in vivo experiments demonstrated the feasibility for in vivo carbon-silicon bond formations. This example demonstrates the potential for broadening the production scope of enantiomerically pure, complex heteroatom organosilicon compounds.

4.4. Tellurium

Tellurium is most often found in various metal ores with below detectable limits in seawater [95]. Tellurium is assimilated by microorganisms and reduced into forms similar to that of sulfur and selenium. The tellurium-containing amino acids, telluro-cysteine and telluro-methionine can be detected in microorganisms when sulfur is replaced with tellurium, and much like selenium, can be incorporated into proteins where it has some benefits for crystallographic structure determination and other applications [120]. Analogous to selenium, engineering efforts with tellurium have enabled E. coli to produce volatile organotellurium compounds through the expression of a gene cluster from the organism Geo-bacillus steaothermophilus V [121]. These molecules include dimethyl telluride, dimethyl ditelluride, methanetellurol, and dimethyl tellurenyl sulfide, but have yet to be found useful for downstream applications. Much like selenium, certain tellurium compounds possess chemopreventative, anticancer, and antibiotic properties but extensive research is needed due to the toxicity of tellurium compounds, especially relative to human health [122,123].

A potentially more promising aspect of tellurium metabolism is the reduction of tellurium salts into nanostructures. Mechanistically similar to selenium, microorganisms can produce elemental tellurium nanoparticles in various shapes, including spheres and rods [124–126]. These nanoparticles showed efficacious antimicrobial activity, especially in biofilm eradication [127]. Tellurium also plays a promising role in semiconductor nanoparticle composites (as discussed below for other metals). As with certain other elements described above, tellurium metabolism is rather rare and limited by toxicity, but holds promise in certain product applications.

4.5. Selenium and the metalloids outlook

The profound biological function of molecules containing selenium and the metalloids discussed give rise to a variety of unique biotechnological applications. Moreover, microbial-based synthesis of metalloid compounds can produce highly enantioselective products that are unable to be easily synthesized using conventional methods. Further investigation into the design of heteroatom-forming enzymes and the identification of promising metabolic routes will provide insight into the production of novel metabolites and nanomaterials with more fascinating properties.
5. Metals

Microorganisms have been exposed to trace elements and minerals for billions of years and have evolved uses for these as both critical catalytic components and important co-factors as is the case with elements like cobalt, copper, iron, magne-
sium, manganese, molybdenum, potassium, sodium, and zinc [128]. Likewise, disparate organisms show the potential to assimilate and reduce nearly every metal in bioremediation applications [129].

Many extensive reviews cover the fundamentals of biomining, bioremediation, and nanomaterial structure synthesis for these metals [26,130,131]. Instead, this review will focus primarily on biologically-uncommon metals that possess value for modern applications in biomining and nanomaterials (Tables 2 and 3).

The foundation of bionanotechnology as a field is still young, but many proteins and other biomolecules have been discovered that interact with an assortment of metals. There are two major industrial outcomes of this field with two distinct modes of production. For nanoparticle formation, extracellular formation is desired, whereas with biomining applications, it is advantageous for the metal to accumulate within the cells to facilitate facile downstream separations. Biomining may also be used to solubilize insoluble forms of a metal to enable simpler extraction, a process called bioremediation. Favorable aspects of these bioconversions include lower capital expenditures, simpler operation, and a lower overall carbon footprint than traditional reaction-based processes.

Metabolic engineering approaches are beginning to improve upon the relatively slow reaction rates inherent in metal conversion processes [132]. Beyond these applications, another area where biological systems are interacting with uncommon elements is metalloenzyme engineering. In one instance, the iron in heme proteins was replaced with iridium to catalyze novel reactions [133]. Another study achieved artificial ring-closing metathesis in vivo using a biotin-ruthenium (Biot-Ru) catalyst complex localized in the periplasmic space to improve activity [134]. Thus, the chemical palette has expanded beyond metabolism into biocatalysis, a topic of significant interest [135]. The sections that follow outline advances in prevalent biological metal incorporations while other elements that are not discussed in depth are highlighted in Tables 2 and 3.

Table 2

| Element | Description | Application | Organism(s) | References |
|---------|-------------|-------------|-------------|------------|
| Cobalt  | Recovery from laterite tailings | Bioleaching | Acidithiobacillus thiooxidans and Acidithiobacillus ferrooxidans | Marrero et al. [172] |
| Copper  | Intracellular, 550 nm average, flakes | Biomining and nanomaterials | Pseudomonas aeruginosa | Srivastava and Constanti [173] |
|        | Copper bioleaching performed industrially | Biomining | Consortium of bacteria, archaea, mesophiles, and thermophiles. | Gentini and Acevedo [174] |
| Dysprosium | Extracellular nanoparticles, 3–10 mm, spherical | Biomining and bioremediation | Sternum hirsutum | Cuevas et al. [175] |
| Europium | Intracellular accumulation of Dy | Biomining | Penidiella sp. T9. | Horike and Yamashita [176] |
| Gold   | Accumulation on cell surface | Biomining | Chlorrella vulgaris | Ozaki et al. [177] |
| Lithium | Ultra-efficient recovery from acidic leachate obtained from jewelry waste | Nanomaterials – catalytic and medicinal | Shewanella halotoleris | Zhu et al. [153] |
| Iron   | Recovery of iron from iron-containing minerals | Biomining | Acidithiobacillus thiooxidans | Marrero et al. [178] |
| Lithium | Lithium solubilization from various ores | Nanomaterials – catalytic and medicinal | Acidithiobacillus thiooxidans | Srivastava and Constanti [173] |
| Palladium | Extracellular, 3 nm average, dense pyramids | Biomining | Pseudomonas aeruginosa | Srivastava and Constanti [173] |
|         | Monodisperse, small (4–5 nm) nanoparticles were observed | Nanomaterials - catalytic | E. coli | Zhi et al. [149] |
| Platinum | Extracellular nanoparticles, 5–30 mm | Biomining | Desulfovibrio desulfuricans, Bacillus benzoacetica | Omajali et al. [150] |
|          | Intracellular accumulation of palladium nanoparticles | Nanomaterials - catalytic | Fusarium oxysporum | Syed and Ahmad [145] |
| Rhodium | Extracellular, 10 nm average, spherical | Biomining | Acinetobacter calcoaceticus | Gaidhani et al. [147] |
| Ruthenium | Extracellular, 3 nm average, dense pyrogens | Nanomaterials – catalytic | Pseudomonas aeruginosa | Srivastava and Constanti [173] |
| Selenium | Extracellular, rod-shaped Se nanoparticles, average size 17 nm | Nanomaterials | Pseudomonas aeruginosa | Srivastava and Constanti [173] |
| Silver  | Extracellular nanoparticles, 10–100 nm, protein functionalized | Nanomaterials – catalytic and medicinal | Streptomyces biminiensis | Ahmad et al. [179] |
|        | Silver uptake capabilities of up to 153 mg/L were observed | Biomining | Cladosporium cladosporioides | Balaji et al. [180] |
| Technetium | Reduction of Tr(VII) to Tr(IV) via various reducing agents | Biomining and bioremediation | Fe(II)-reducing, sulfate-reducing, fermentative, aerobic, and anaerobic bacteria | Chernyh et al. [182] |
| Tellurium | Intracellular, rod-shaped Te nanoparticles, 20 × 180 nm | Nanomaterials and biomining | Bacillus sp. | Zare et al. [124] |
| Uranium | Uranium bioprecipitation engineered for different cellular loci | Biomining | Deinococcus radiodurans, E. coli | Kulkarni et al. [142] |
| Ytterbium | Accumulation on cell surface | Biomining and bioremediation | S. cerevisiae | Jiang et al. [183] |
| Zinc   | A 75% Zn extraction was obtained from Zn-plant leach residues under optimized conditions | Biomining | Acidithiobacillus thiooxidans | Sethurajan et al. [184] |
Lithium has become pervasive in our modern-day society primarily for its use in materials and batteries. As a result, lithium mining operations have continued to expand and although the global availability is currently stable, sustainable recycling and extraction are major concerns of the future due to a growing global market [136]. Unsurprisingly, traditional lithium extractions are energy and reagent intensive and incur high capital expenditures. In this regard, biomining via microorganisms may be an attractive avenue for lithium extraction and recycling.

Lithium is present in many minerals with varying degrees of resistance to traditional chemical leaching. Among these minerals, the best studied are spodumene (6.9% Li2O) and lepidolite (3.8% Li2O). Lithium extraction from spodumene has been investigated using *Penicillium purpurogenum*, *Aspergillus niger*, and *Rhodotorula rubra* [137]. Similarly, *A. niger* and *R. rubra* were also shown to extract lithium from lepidolite [138, 139]. Although the maximum lithium yield was 413 μg/g biomass, these processes show potential as ecofriendly methods for lithium extraction. Lithium accumulation in these systems occurs via two mechanisms: (1) adherence to the outer surface of the cell via exopolymer interactions and (2) uptake of lithium into the cytoplasm through an unknown transport mechanism. The initial step of the bioleaching process, the solubilization of lithium from the ore, occurs via a reaction with biogenic organic acids. Thus, organic acid overproducing strains could lead to improved lithium extraction in the future. While still in its early stages, cellular systems along with metabolic engineering can lead to a more sustainable recycling of lithium from batteries and traditional mining-resistant minerals.

### 5.1. Lithium

The biogenic organic acids produced by microorganisms have the potential to sequester and convert uranium into a useable source. Accordingly, uranium biomining through bioleaching has been industrially used for nearly 6 decades, beginning in the 1960s [140]. Several efforts to understand this process have been conducted including modeling bioleaching efficiency [141] and evaluating the influence of phosphatase enzymes localization in the cell for *Deinococcus radiodurans* and *E. coli* [142]. A further report discovered that non-crystalline U(IV) from biogenic sources is the predominant form of uranium in characterized ore deposits [143]. This report supports the idea that biogenic processes are very important to uranium ore genesis and further characterization of ore and microorganism composition could guide future research involving biomining efforts.

### 5.3. Platinum

Platinum's intrinsic low reactivity allows it to perform as an excellent catalyst and surface coating material, especially when formulated into nanoparticles [144]. This area has been investigated with cellular systems through the secretion of proteins by the fungus *F. oxysporum* that can stabilize and organize platinum nanoparticles [145]. Likewise, sulfate-reducing bacteria are a platform for studying the bioreductive mechanism behind platinum nanoparticle formation [146]. This process likely involves a two-step reduction, each with separate enzymes, reducing the initial Pt(IV) to Pt(II) and then to Pt(0) before the metal precipitates into nanocrystals. Finally, intracellular precipitation and formation of smaller nanocrystals has been observed, opening the future door to biomining [147].

### 5.4. Palladium

Palladium, a widely-used platinum group transition metal, is also highly sought after for its catalytic capabilities. Biological reductions and particle formation is possible in cells fed with palladium sources. For example, using *E. coli* mutant strains, Deplanche et al. determined that [NiFe] hydrogenases are responsible for accelerating the reduction of Pd(II) to Pd(0) [148]. *E. coli* could also be used as a vehicle to make biogenic Pd nanoparticle catalysts [149]. These catalysts provided lower cis-trans isomerization during hydrogenation of alkynes and alkenes, an advantage over conventionally produced Pd-NPs. Similar Pd-NPs were also produced in the sulfate-reducing bacteria *Desulfovibrio desulfuricans*, which created smaller and thus more effective Pd catalyst particles. Biomining efforts can also be envisioned based on observations of intracellular accumulation of palladium in *Desulfovibrio desulfuricans*, *Bacillus benzeivorans*, and other microorganisms [150].

| Composition | Description | Application | Organism(s) | Reference |
|-------------|-------------|-------------|-------------|-----------|
| AuPd        | Intracellular, 2–4 nm, gold-palladium core-shell particles | Nanomaterials | *E. coli* | Deplanche et al. [185] |
| BaTiO3      | Extracellular, 4–5 nm | Nanomaterials - ferroelectric | *Fusarium oxysporum* | Bansal et al. [161] |
| CdSe        | Intracellular, 7–13 nm, uniform size | Nanomaterials - semiconductor | *E. coli* | Yan et al. [166] |
| CdSe@ZnTe, AuCdSeZn, SrCd₃P₃Gd | Various sizes and shapes | Nanomaterials | *E. coli* | Park et al. [163] |
| CdTe        | Extracellular, 2–4 nm, uniform size | Nanomaterials - semiconductor | *S. cerevisiae* | Bao et al. [187] |
| Cerium oxides | Extracellular formation of Ce₂O³ nanoparticles containing Ce (III) and Ce (IV) mixed oxidation states | Nanomaterials - semiconducting | *Humicola sp.* | Khan and Ahmad [188] |
| CoFe₂O₄     | Extracellular, 3–15 nm, spherical | Nanomaterials - magnetic | *S. cerevisiae* | Jha and Prasad [189] |
| Copper oxides | Extracellular, various size and shape, mechanism investigated | Nanomaterials | *E. coli* | Singh et al. [190] |
| NiO         | Hollow Cylinder NiO Nanostructured Material | Nanomaterials | *Sporosarcina pasteurii* | Vaidyanathan et al. [191] |
| PbS         | Intracellular, 2–5 nm, cubic structure | Nanomaterials - semiconductor | *Rhodospirillum diobovatum* | Seshadri et al. [192] |
| SiO₂        | Extracellular, 15 nm average size, spherical | Nanomaterials | Thermophic bacterium (BKH1) | Show et al. [193] |
| TiO₂        | Extracellular, 50–100 nm, spherical | Nanomaterials | *Bacillus subtilis* | Kirthi et al. [194] |
| Zircon sand (Zirconia and silica) | Selective leaching of silica to form SiO₂ nanoparticles, and enrich zirconia content | Nanomaterials and bioleaching | *Fusarium oxysporum* | Bansal et al. [195] |
| Zirconia    | Extracellular, quasi-spherical, 3–11 nm | Nanomaterials | *Fusarium oxysporum* | Bansal et al. [196] |
5.5. Gold

Gold has historically been one of the most valuable elements, especially given its inherent oxidation resistance, malleability, and medicinal properties. Biorecovery of gold has been studied in both *Escherichia coli* and *Desulfovibrio desulfuricans* as an alternative to conventional reclaiming methods [151]. Gold nanoparticle synthesis using the fungus *Penicillium brevicompactum* has been explored and tested for cytotoxicity effects on mouse mastoeytoma cancer cells [152]. More recently, a 99% biorecovery efficiency of gold into small, spherical nanoparticles and subsequent catalytic reduction activity was shown in *Sheewanella haliotis* [153]. As with other metals, several other organisms have been explored to both sequester gold and to produce nanostructures with exquisite size and shape control [154].

5.6. Silver

As the most conductive of all elements, silver has a multitude of applications, especially in the fields of catalysis and material coatings. Once again, cellular systems provide an excellent platform for both nanoparticle synthesis and biomining applications. As an example, *Fusarium oxysporum* is capable of efficiently producing size-controlled silver nanoparticles [155]. The industrially-relevant yeast *Yarrowia lipolytica* and fungus *Neurospora intermedia* can also mediate the synthesis of Ag nanoparticles [156]. Given the antimicrobial properties of silver nanoparticles, each of these studies demonstrated significant activity with biogenically created structures. Regarding silver nanoparticles, biological synthesis has been shown to proceed faster than chemical or physical processes, providing a potential advantage. To this end, monodispersed silver nanoparticles (5–25 nm) were produced extracellularly by the fungus *Aspergillus fumigatus* in only 10 min [157].

5.7. Nanoparticle composites

Nanotechnology has demonstrated the importance of nanoparticle composites for functionality, especially in the areas of magnetic nanoparticles, semiconductor materials, and quantum dots. Among the biologically-produced quantum dot and semiconductor materials are PbSe, CdSe, CdTe, and PbS [158–160]. Ferroelectric materials are also capable of being produced within microorganisms, evidenced by the synthesis of barium titanate in *Fusarium oxysporum* [161]. In addition, Au-Ag alloy nanoparticles were produced by *S. cerevisiae* and displayed anti-microbial properties [162]. These efforts were taken further by Park et al., who used recombinant *E. coli* for the in vivo biosynthesis of a wide variety of nanoparticle composites [163]. Their results show that cellular reduction mechanisms can reduce a wide range of metallic elements (Table 3). Moreover, this system can produce nanoassemblies which have not yet been possible through chemical means, such as CdSe/ZnTe and AuCdSe2N. Further applications of coupling microfluidic devices to optimize process conditions resulted in homogeneous nanocluster production by *E. coli* [164].

5.8. Metalloid and metal metabolism outlook

As described in the sections above, nanoparticle synthesis in cells is an interesting interaction between metabolism, protein expression, and cell capacity. Mechanisms for formation are beginning to be elucidated, paving the way for the tailoring of size, shape, and other properties [165]. Certainly, there are newfound possibilities to interface nanomaterials with synthetic biology and metabolic engineering. Although not mutually exclusive from nanoparticle synthesis, biomining developments will also require disparate optimization of strain characteristics and processes specifically. In this regard, motivated by organisms naturally capable of metal reduction and oxidation, model organisms and microbial functional communities can be engineered to selectively capture an assortment of valuable metals [166]. Ideally, advances in these areas will parallel those of metabolic engineering, where elucidation of mechanisms and subsequent process optimization will enable microorganisms to perform desired traits beyond the levels currently seen in Nature.

6. Conclusions and future prospects

Metabolic engineering and cellular rewiring have the capability of greatly expanding the chemical diversity within cells (Fig. 1). Through this review, we seek to demonstrate this premise and provide insight into the various avenues of further innovation to incorporate uncommon elemental groups. Products containing heteroatom-bonded, conjugated, and nanoparticle-sequestered uncommon elements are important in all fields and industries. Although many challenges exist in the field of alternative element incorporation, especially with regard to toxicity, insight gained from the remarkable chemical feats of nonconventional organisms can be used to engineer more capable model organisms. Thus, the expanding array of synthetic tools will play an important role in future developments. Ultimately, enabling novel elemental chemistries within cellular systems will be a major contribution of the biotechnology era that expands the scope of renewable chemistries performed by microorganisms.

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