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Invited Review Article

Mineral requirements for mitochondrial function: A connection to redox balance and cellular differentiation ☆

David W. Killilea [a], Alison N. Killilea [b]

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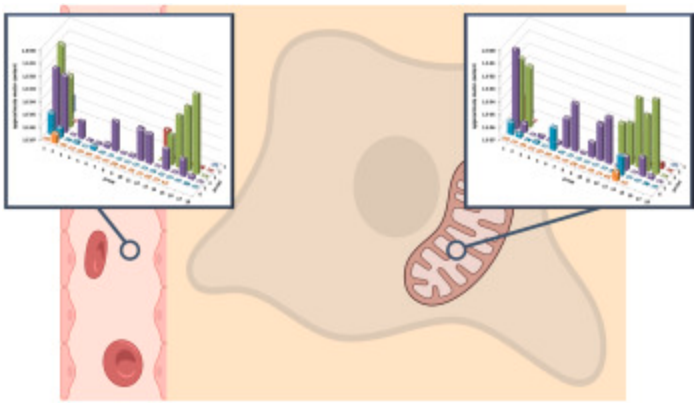
Highlights

- Eleven of the 12 minerals essential for human health have important roles within mitochondrial metabolism.
- Increased oxidative stress within the mitochondria is a common consequence of aberrant mineral homeostasis.
- Low oxidative stress is key for long-lived cell lineages, so optimizing mineral levels is important for cellular potency.
- Tuning up mineral metabolism should strengthen mitochondrial physiology, and thereby improve cellular health.

Abstract

Professor Bruce Ames demonstrated that nutritional recommendations should be adjusted in order to 'tune-up' metabolism and reduce mitochondria decay, a hallmark of aging and many disease processes. A major subset of tunable nutrients are the minerals, which despite being integral to every aspect of metabolism are often deficient in the typical Western diet. Mitochondria are particularly rich in minerals, where they function as essential cofactors for mitochondrial physiology and overall cellular health. Yet substantial knowledge gaps remain in our understanding of the form and function of these minerals needed for metabolic harmony. Some of the minerals have known activities in the mitochondria but with incomplete regulatory detail, whereas other minerals have no established mitochondrial function at all. A comprehensive metallome of the mitochondria is needed to fully understand the patterns and relationships of minerals within metabolic processes and cellular development. This brief overview serves to highlight the current progress towards understanding mineral homeostasis in the mitochondria and to encourage more research activity in key areas. Future work may likely reveal that adjusting the amounts of specific nutritional minerals has longevity benefits for human health.

Graphical abstract



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Keywords

Mitochondria; Minerals; Metals; Redox; Differentiation

Abbreviations

MFRN1, mitoferrin 1; MFRN2, mitoferrin 2; mitoBK$_{Ca}$, mitochondrial calcium-activated potassium channel; mitoK$_{ATP}$, mitochondrial ATP-regulated potassium channel; mitoKv1.3, mitochondrial voltage-gated Kv1.3 potassium channel; mitoTASK, mitochondrial TASK-3 potassium channel; Moco, molybdenum cofactor; MTM1, manganese trafficking factor for mitochondrial SOD2; NCE, mitochondrial sodium/calcium exchanger; NCX, cellular sodium/calcium exchange; NHE, mitochondrial sodium/proton exchanger; ROS, reactive oxygen species; TCA, tricarboxylic acid cycle

1. Introduction

In a series of papers beginning 20 years ago, Professor Bruce Ames proposed that the recommended intake for essential micronutrients should be reset to promote optimal health rather than just avoiding acute disease – a campaign he called 'tuning up metabolism' [[1], [2], [3]]. Central to this proposal is boosting the metabolism of the mitochondria [4], which Professor Ames and others postulated was the fulcrum for the pathological processes that drive aging and senescence [[5], [6], [7], [8]]. Of the 40–50 micronutrients required for human physiology, most can be found within the mitochondria and many have recognized functions within mitochondrial metabolism. There is strong evidence that deficiencies in many of these micronutrients can result in increased production of reactive oxygen species (ROS), redox imbalance, and mitochondrial decay [4,9]. Conversely, supplementation with micronutrients that are needed by the mitochondria has proven very successful in improving health and restoring vitality in many different models [[10], [11], [12], [13], [14]].

The nutritional minerals form a unique subset within the essential micronutrients, and they are integrated into all aspects of systemic metabolism. In the literature on mineral homeostasis, mitochondria are repeatedly referred to as 'hubs' for mineral processing – particularly for calcium and iron – given the many cellular pathways utilizing minerals that converge within this organelle. Yet a hub is a device that functions as a passive node within an existing network; instead, mitochondria actively manage, buffer, utilize, and route the minerals in order to maintain homeostatic balance and minimize stress levels throughout the cell. Interruptions in mitochondrial mineral handling are associated with metabolic dysfunction, which if prolonged results in increased cellular stress and consequential disease. Thus a more fitting metaphor for mitochondria is that they function as central

processing units for minerals within the cell. This active control of mineral balance by mitochondria is a key part of an optimized metabolism and cellular health.

The first step in optimizing mineral metabolism is to define all the substrates, reactions, and interactions of the minerals within the cell. It is also essential to understand how metabolic profiles change during development to match physiological needs. Professor Ames addressed this latter point in a more recent article in which he proposed the existence of longevity vitamins that support processes connected to long-term health instead of immediate survival or reproduction, and thus would not be under the same evolutionary pressure to preserve cofactor availability [15]. It is likely that some minerals also fit the definition of longevity micronutrients, but detailed examination of this topic has not yet been reported. In order to understand how some minerals may support long-term health functions during aging and development, it is necessary to characterize all the minerals and determine how they are interconnected, especially within the mitochondria.

Interest in mitochondrial mineral homeostasis continues to grow. There have been several excellent reviews that explore the metallome and the cognate metalloproteome of the mitochondria [[16], [17], [18], [19]], though to date our understanding of mitochondrial mineral homeostasis still remains incomplete. The purpose of this review is to illustrate specific knowledge gaps and highlight details about mitochondrial minerals that deserve more research attention. The minerals are divided into sections based on periodic table assignment that share chemical and physical properties. Mitochondrial regulation of the minerals will be addressed when known, as well as the impact on redox balance and cellular differentiation when mineral balance is altered. A central theme in mitochondrial mineral homeostasis is that imbalances often lead to increased ROS production and redox stress [4]. The term ROS refers to widely different molecular species, including lipid and nitrogenous radicals, that have distinct pharmacodynamic properties and chemical reactivities [20]. The terms redox or oxidative stress refer to conditions when the levels of ROS increase relative to the antioxidant or defense capacity within the biological system. Prolonged redox or oxidative stress can result in mitochondrial decay, altered metabolism, cellular dysfunction, and eventually systemic disease.

2. Mitochondrial metallome

Alkali Metals: The alkali metals are exclusively monovalent cations that exhibit only +1 oxidation state as ions under physiological conditions. These alkali metals do not have inherent redox capability and are mostly found free or in weakly labile complexes with

cellular macromolecules. These two common alkali metals sodium and potassium have major roles in mitochondrial physiology.

Sodium: Sodium is the most abundant cation in the extracellular space, and has a reciprocal relationship with potassium. Circulating levels of sodium in the serum/plasma are between 136 and 145 mM in healthy adults, while the intracellular levels are kept at 8–15 mM [21,22,23]. The potassium-sodium gradient between intracellular and extracellular spaces powers many cellular processes to maintain homeostasis of other metabolites. The concentration of sodium within the resting mitochondria has been reported between 5 and 50 mM [22,24,25]; this wide range likely reflects biological variability in different cell types with different excitation potentials. Excitation can cause substantial increases in mitochondria sodium levels, with 10-fold elevation observed during conditions such as ischemia [22,26,27]. Entry of sodium into the mitochondria mainly occurs through the mitochondrial sodium/calcium exchanger (NCE) in many cell types, with a supporting role from the sodium/proton exchanger (NHE), calcium uniporter, and cellular sodium/calcium exchange (NCX) in reverse mode. The regulation of these transporters is complex, coordinated by mitochondrial membrane potential, oxygen tension, pH, and concentrations of sodium, calcium, magnesium, and protons in the mitochondria and cytosol. The role of sodium within the mitochondria is similar to its role in the cytosol, namely the maintenance of volume, pH, membrane polarization, and macromolecular charge balance. However, mitochondrial sodium also has the unique role as a major driver of calcium currents into the mitochondria, thereby influencing the overall mitochondrial calcium content [23,28]. Additionally, mitochondrial sodium levels reciprocally influence the movement of protons across the inner mitochondrial membrane, thereby contributing to changes in mitochondrial energy charge and redox capacity [23].

Potassium: Potassium is the most abundant cation inside the cell, and has a reciprocal relationship with sodium. Circulating levels of potassium in the serum/plasma are 3.5–5.1 mM in healthy adults, while the intracellular concentration is approximately 100–150 mM [21,29]. The potassium-sodium gradient between intracellular and extracellular spaces powers many cellular processes that maintain homeostasis of other metabolites. The concentration of potassium within the mitochondria has been reported to range between 150 and 180 mM, which is higher than cytosolic potassium and indicates that potassium can be sequestered within the organelle [30,31]. Transport of potassium into the mitochondria occurs through multiple channels, including the ATP-regulated potassium channel (mitoK$_{ATP}$), calcium-activated potassium channel (mitoBK$_{Ca}$), voltage-gated Kv1.3 potassium channel (mitoKv1.3), and TASK-3 potassium channel (mitoTASK) [32]. The regulation of these channels is also complex, and driven by changes in mitochondrial membrane

potential, redox balance, oxygen tension, and concentrations of potassium and protons in the mitochondria and cytosol. Potassium has numerous roles in mitochondrial physiology, including maintenance volume, pH, membrane polarization, and macromolecular charge balance [33]. Many proteins require binding of monovalent cations like potassium for optimal function, including mitochondrial pyruvate kinase [34]. Mitochondrial potassium levels also are key to the regulation of mitochondrial volume, membrane potential, calcium homeostasis, and oxidative stress levels, especially through the mitoBK$_{Ca}$ channel that is functionally and structurally coupled to cytochrome c oxidase in the electron transport chain [32,33]. It seems clear that mitochondrial potassium balance is a major mechanism that controls mitochondrial energy charge and redox capacity. Evidence suggests that alterations in mitochondrial potassium currents can play important roles in the pathogenesis of cardiovascular and neurodegenerative diseases [32].

Other Alkali Metals: The other alkali metals are found at trace levels in the body, but have not been shown to be essential minerals for human health. *Lithium*: The average circulating lithium levels (not including lithium-treated patients) in the serum/plasma ranges from 1 to 4 μM in healthy adults [35]. Low levels of lithium in the diet are proposed to have health benefits. Studies specifically removing lithium from the diet of animals resulted in anemia and alterations in glucose, cholesterol, phospholipid, triglyceride, bile acid, and iron homeostasis [36]. Lithium has been shown to enter the mitochondria utilizing the sodium/calcium exchanger within the inner mitochondria membrane [37]. Once in the mitochondria matrix, lithium could inhibit various kinases and ion channels, including mitochondria glycogen synthase kinase [38] and Complex V of the electron transport chain [39]. Lithium may also indirectly promote mitochondrial energy charge by reducing the transcription factor LSD1 [40], which normally inhibits the expression of genes for mitochondrial oxidative phosphorylation [41]. *Rubidium:* The average circulating rubidium levels in the serum/plasma ranges from 0.5 to 7 μM in healthy adults [35]. Rubidium has been proposed to have health benefits, though it is difficult to discriminate specific activities of this metal given its similarity to potassium. Studies specifically removing rubidium from the diet of animal models resulted in decreased growth, fecundity, and life expectancy [36]. Yet while multiple investigations have shown that rubidium enters the mitochondria, this metal is usually studied as a tracer of potassium flux and not for determining any unique roles of rubidium per se [42,43]. Little information on the effects of rubidium on mitochondrial energy charge or redox capacity are known. The remaining members of this elemental group are too rare or unstable to have physiological relevance, so there is no information about content or function within the mitochondria.

Alkali Earth Metals: The alkali earth metals are exclusively divalent cations that exhibit only +2 oxidation state as ions under physiological conditions. These alkali earth metals do not have inherent redox capability and are found both free or in complexes with cellular macromolecules, including proteins, lipid membranes, and nucleic acid polymers. Two common alkali metals calcium and magnesium have major roles in mitochondrial physiology.

Calcium: Calcium is the most abundant metal in the human body, and has a reciprocal relationship with magnesium. Only 1% of whole-body calcium is found in the soft tissues and extracellular fluids, but the circulating levels in serum/plasma are still maintained at 2.1–2.6mM in healthy adults [21]. While the total intracellular concentration of calcium may be similar to circulating levels, the free/labile calcium in the cytosol is held to low nanomolar levels through a high-fidelity calcium sequestering system involving the mitochondria and endoplasmic reticulum [[44], [45], [46]]. Low cytosolic calcium is key to cellular function so that calcium oscillations can act as second messengers for stimuli ranging from proliferation to apoptosis. Calcium plays a critical role in mitochondrial physiology, and is arguably the most well studied of all the metals in this organelle. Resting concentrations for mitochondrial calcium are reported between 100 and 200nM [47], but these levels can quickly rise upon cellular excitation, with some microdomains peaking at 10–20 μM [45]. Transport of calcium into the mitochondria is complex and depends on coordinate systems including calcium-selective voltage-dependent anion channels across the outer mitochondrial membrane and a calcium uniporter across the inner mitochondrial membrane, with transport through mitochondria-associated membrane microdomains also playing a role [46]. The release of calcium from the mitochondria is also important to overall homeostasis and driven mainly by the sodium-calcium-lithium exchanger, and thus contributing to an entangled relationship between those ions. Calcium has a wide range of functions within the mitochondria. Several enzymes within the tricarboxylic acid cycle (TCA) cycle and electron transport chain require calcium ions for activity, including the rate-limiting isocitrate dehydrogenase [45,48,49]. Calcium also stimulates ATP synthesis and adenylate transport in mitochondria, with a corresponding increase in mitochondrial membrane potential [[50], [51], [52]]. Mitochondrial dynamics are altered by calcium transients in the mitochondria, including altered fission/fusion dynamics and distribution within the cell [[53], [54], [55]]. With sustained elevated calcium, the mitochondrial permeability transition pore is activated, triggering apoptosis [46]. There is extensive literature on the regulation of mitochondria bioenergetics and redox state by calcium [56,57].

Magnesium: Magnesium is the second-most abundant cation within the cell, and has a reciprocal relationship with calcium. Circulating levels in serum/plasma are buffered to 0.7–1.1 mM in healthy adults, with a higher total cell concentration reported between 15 and 25 mM and free/labile concentration in the cytosol estimated between 0.5 and 1 mM [21,58]. Free/labile concentration of magnesium within the mitochondria is estimated between 0.4 and 0.7 mM, but total concentration should be higher when including magnesium ions tightly bound to mitochondrial macromolecules [59,60]. Magnesium has many functions within the cell, but the most prominent is being bound to ATP, as the magnesium-ATP complex is the recognized form of the cofactor required for binding by hundreds of enzymes [61]. Binding of magnesium to membranes, proteins, nucleic acids, and other small organic molecules is also important for structural balance and charge neutralization considerations [62]. Deficiencies in magnesium lead to increased oxidative stress, accelerated senescence, and mitochondrial dysfunction in human cells [[62], [63], [64], [65]]. Magnesium plays a major role in mitochondrial function as well, with a third or more of the total magnesium in a cell being located in this organelle [66]. Mitochondria concentrate magnesium ions especially through Mrs2, a magnesium-selective transporter expressed in the mitochondrial inner membrane [67]. Several enzymes within the TCA cycle and electron transport chain require or are regulated by magnesium, including 2-oxoglutarate dehydrogenase (rate-limiting step of the TCA cycle), hexokinase, phosphofructokinase, pyruvate kinase, and several subunits of the electron transport chain including acting as a direct activator of the mitochondrial Complex V [68,69]. Consequently, disruption of magnesium homeostasis in the mitochondria decreases ATP production, disrupts mitochondrial membrane potential, and increases oxidative stress [70]. Several studies have added to a comprehensive understanding of how magnesium levels regulate mitochondrial transmembrane potential, bioenergetics, and redox state [70,71]. These authors suggest that magnesium may be a central regulator of mitochondrial function and metabolism in mammalian cells.

Other Alkali Earth Metals: The other alkali earth metals are found at trace levels in the body, but have not been shown to be essential minerals for human health. *Barium*: The average circulating barium levels in the serum/plasma ranges from 0.2 to 0.6 μM [35]. The mitochondria were found to be the principal site of barium accumulation when cells were exposed to barium salts [72], but the physiological relevance is unknown. *Strontium*: The average circulating strontium levels in the serum/plasma ranges from 0.3 to 0.5 μM [35]. Strontium is taken up by cells and mitochondria in a manner similar to calcium such that strontium is often used as a tracer to map calcium currents [73], but a unique role for strontium per se has not been reported. Little information on the effects of barium or strontium on mitochondrial energy charge or redox capacity are known. The remaining

members of this elemental group are too rare or unstable to have physiological relevance, so there is no information about content or function within the mitochondria.

Transition (d-block) Metals: Most of the transition metals located in the *d*-block section of the periodic table are redox-active and can have a range of oxidation states from +1 to +7 as ions under physiological conditions. The exceptions are the metals from Group 3 (scandium and yttrium) and Group 12 (zinc and cadmium), which only have a single oxidation state under physiological conditions. Group 12 metals have a complete *d* shell, but will still be included here since they are more commonly listed in this elementary category. The *d*-block transition metals are usually not found free, but instead in complexes with cellular macromolecules, especially proteins where the range of oxidation states provides catalytic power for enzymatic activities. Many of these metals have essential roles in mitochondrial physiology.

Iron: Iron is the most abundant transition metal within the body and has interconnected relationships with other trace metals, especially copper and zinc. Circulating iron levels in whole blood are as high as 10 mM due to erythrocyte content [35], but serum/plasma iron levels are normally between 9 and 31 μM in healthy adults [21]. The most common form of iron in mammalian biology is within porphyrin ligands collectively called heme, in which iron ions bind at a ratio of 1:1 (metal:porphyrin). The second-most common form of iron is within iron-sulfur clusters, in which iron ions bind to sulfur ions at different ratios ranging 2:2 to 4:4 (metal:sulfur). Systemically, iron is a component of hundreds of proteins involved in oxygen transport, oxygen sensing, energy production, stress defense, hormone production, and nucleic acid synthesis. In the mitochondria, the concentration of iron is substantial, with studies reporting levels between 0.5 and 1 mM [17,74]. Depending on the cell type, the mitochondria can contain up to 50% of all iron in the cell [75]. Iron enters the mitochondria through the iron-selective transporters known as mitoferrins, specifically MFRN1 (SLC25A37) and MFRN2 (SLC25A28), although there is evidence that other transporters may be involved [75,76]. Mitochondria are the starting and ending location for the heme biosynthetic pathway, and also the major site for iron-sulfur cluster synthesis, so maintaining adequate iron levels in the mitochondria is critical to match the iron cofactors requirements of the cell [77]. Iron cofactors are required by several subunits in the electron transport chain proteins, succinate dehydrogenase, ferrochetalase, and several other mitochondrial proteins. Mitochondrial iron that is not immediately needed for cofactor synthesis can be stored in proteins, including mitochondrial ferritin [78,79]. Other chaperone proteins can bind iron, including frataxin which plays an important role in oxidative phosphorylation and mitochondrial energy production [80]. If not stored properly, iron can interact with other molecules in the mitochondria to promote the formation of ROS

[81]. Extensive literature is available that describes the many roles of iron in mitochondria bioenergetics and redox state [79,82].

Zinc: Zinc is the second-most abundant transition metal within the body and has interconnected relationships with other trace metals, especially iron and copper. Circulating zinc levels in whole blood are approximately 100 μM due to erythrocyte content [35], but serum/plasma levels are normally between 11 and 18 μM in healthy adults [21]. Unlike most other essential transition metals, zinc is not redox-active and normally exhibits only one oxidation state [83]. Zinc is a cofactor in numerous proteins, providing catalytic, structural, and/or regulatory activity. In the human proteome, several hundred transcription factors require zinc for proper folding and over 50 enzymes utilize zinc for catalytic functions. Systemically, zinc is involved in immune function, neuronal function, vision, reproduction, bone health, growth, and development [84]. The transport of zinc into the mitochondria occurs mainly through ZnT2 (SLC30A2), a member of the zinc efflux transporter family that moves zinc out of the cytoplasm (and in this case into intracellular organelles) [85]. The mitochondrial concentration of zinc is substantial, with studies reporting levels between 167 and 300 μM, with some evidence of microdomains with elevated zinc content [17,74]. It is clear that mitochondria can sequester zinc, which serves as a zinc reserve for later cellular need [86]. Mitochondrial zinc that is not immediately needed as protein cofactors can be stored in the protein metallothionein, which although normally thought of in the cytoplasm has also been localized to the mitochondria [87]. Zinc is required as a cofactor for several mitochondrial enzymes and for multiple subunits of the electron transport chain [69]. Additionally, a fraction of zinc-containing superoxide dismutase 1 (normally found in the cytoplasm) localizes to the inner mitochondrial space and provides protection from oxidative stress [88]. Thus, low levels of mitochondrial zinc can promote increased sensitivity to oxidative stress [89]. On the other hand, high zinc levels in the mitochondria have been shown to cause toxicity by inducing loss of mitochondrial membrane potential, which is a known cause of increased ROS production [[90], [91], [92]]. There is additional literature describing the importance of mitochondrial zinc for control of mitochondria bioenergetics and redox state [87,91].

Copper: Copper is another important transition metal within the body and has interconnected relationships with trace metals, especially iron and zinc. Circulating copper in whole blood and serum/plasma are similar to iron with a range of 11–30 μM. Copper may be concentrated in the mitochondria, with studies reporting levels between 71 and 115 μM [17,74]. The transport of copper into the mitochondria occurs mainly through what was first known as the mitochondrial phosphate carrier protein (SLC25A3), but more recently shown to also transport copper and required for activity of mitochondrial copper proteins [93].

Copper is utilized as a cofactor in over 50 enzymes within the human proteome, including enzymes involved in energy production, connective tissue formation, iron homeostasis, neurotransmitter synthesis, and myelin formation [94]. Several of these enzymes are localized to the mitochondria, including subunits 1 & 2 of the cytochrome c oxidase and protein deglycase DJ-1, which functions as a sensor for oxidative stress and redox-sensitive chaperone proteins. Other important copper-containing chaperones and transporters include Cox11, Cox17, and cytochrome c oxidase assembly proteins SCO1 and SCO2, all of which have been identified in the mitochondria. Additionally, the copper proteins prion protein PrP and acetylcholinesterase-associated protein CutA have isoforms found in the mitochondria, but their function is unknown. Like other transition metals, excess copper can interact with other molecules in the mitochondria to promote the formation of ROS [95,96]. This is seen in Wilson disease, in which elevated increased mitochondrial copper levels leads directly to mitochondrial ultrastructure and function [97]. Thus maintaining balance in copper levels within the mitochondria is important for mitochondrial bioenergetics and redox balance [98,99].

Manganese: Manganese is a low abundant transition metal with circulating levels in serum/plasma at 8–18 nM in healthy adults [21]. Manganese may be concentrated in the mitochondria, with studies reporting levels between 3 and 16 μM [17,73]. The mechanisms for manganese entry into the mitochondria are not fully understood though, as both MTM1 (manganese trafficking factor for mitochondrial SOD2) and the mitochondrial calcium uniporter appear to be involved [18,100]. Manganese is required as a cofactor in a number of enzymes within the human proteome, including kinases, hydrolases, transferases, and decarboxylases [101]. Several of these enzymes are localized to the mitochondria, including arginase II, pyruvate carboxylase, and superoxide dismutase 2. Arginase is required for the urea cycle. Pyruvate carboxylase is essential for proper carbohydrate metabolism and anaplerotic reactions in the mitochondria. Superoxide dismutase 2 is critical to the protection of mitochondria from oxidative stress, and expression of this enzyme even correlates with lifespan in mammals [102]. Superoxide dismutase 2 and other enzymes systems in the mitochondria are also proposed to control the redox balance for the whole cell and to generate ROS transients that synchronize metabolism to changes in cellular physiology [103]. Like other transition metals, excess manganese can cause mitochondrial toxicity by inactivating oxidative phosphorylation, inducing the loss of mitochondrial membrane potential, and increasing ROS production [101,104,105]. Thus maintaining a balance in manganese levels within the mitochondria is also important for mitochondrial bioenergetics and redox balance [[101], [102], [103]].

Molybdenum: Molybdenum is another low abundant transition metal with circulating levels in serum/plasma at 1–31 nM in healthy adults [21]. The most common form of molybdenum in human biology is within pterin ligands collectively called molybdenum cofactors (Moco), in which molybdenum ions bind at a ratio of 1:1 (metal:pterin) [106]. Moco is required for at least 4 proteins in the human proteome, including xanthine oxidase, aldehyde oxidase, sulfite oxidase, and amidoxime reducing component [107]. The synthesis of Moco starts in the mitochondria, but finishes with metal addition to the pterin structure in the cytoplasm, however it is still unclear how the Moco cofactor is transported back into the mitochondria [18,108]. Mitochondria must take up molybdenum, with estimates of mitochondrial concentration between 1 and 6 μM[17]. Some of this molybdenum must be the Moco form, as isoforms of sulfite oxidase and amidoxime reducing component are localized in the mitochondria and require Moco for function. The mitochondrial amidoxime reducing component protein is involved with nitric oxide metabolism. Molybdenum can also form thiomolybdate compounds, including tetrathiomolybdate, that influence copper metabolism and handling. Both nitric oxide and copper levels are critical to mitochondrial redox balance and function, and disruption of Moco synthesis is known to cause loss of mitochondrial energy charge and oxidative stress [108]. Yet the degree to which molybdenum regulates mitochondrial function and redox state is still under investigation.

Cobalt: The only known form of cobalt in human biology is within corrin ligands collectively called cobalamins or vitamin B12, in which cobalt ions bind at ratio of 1:1 (metal:corrin). The circulating levels in serum/plasma for cobalt are reported as 2–8 nM; interestingly, this is higher than the circulating levels listed for vitamin B12 at 0.1–0.6 nM, suggesting either error in existing measurements or unknown other role for cobalt [21]. Estimates for the mitochondrial concentration of cobalt range from 50 to 90 nM, which if all corrin-bound would represent about 15% of the cellular vitamin B12 [17,109]. There are at least 2 proteins identified in the human proteome that require vitamin B12, including methionine synthase and L-methylmalonyl-coenzyme A mutase, with the latter localized in the mitochondria and required for synthesis of the key metabolite succinyl-CoA and the degradation of specific amino acids and fatty acids [110]. Vitamin B12 is also involved in the synthesis of glutathione, an important antioxidant in the cytosol and mitochondria [111]. It is unclear how the vitamin B12 cofactor is transported or regulated within the mitochondria, and little is known about the pathophysiology of vitamin B12 imbalances in the mitochondria. Yet cobalt as vitamin B12 clearly plays an important role in the mitochondrial metabolism and redox state, so further investigation is needed.

Chromium: The activity of chromium within the human body is not well understood. The best described physiological form of chromium is within an oligopeptide called

chromodulin, in which chromium ions bind at a ratio of 4:1 (metal:peptide) [112]. Circulating levels of chromium in serum/plasma are low and listed as 1–31 nM in healthy adults [21]. Chromodulin was shown to potentiate glucose responses, potentially by increasing the inherent kinase activity within the insulin receptor complex, though this mechanism is not fully elucidated [113,114]. To date, there seem to be no reports of chromodulin activity within the mitochondria. Other activities of chromium have also been proposed including attenuating oxidative stress and inflammatory tone [114]. The cellular regulation and localization of chromium and chromodulin pools are still under investigation, and the role of chromium in mitochondrial function and redox balance is not known.

Other Transition Metals: The other *d*-block transition metals are found at trace levels in the body, but have not been shown to be essential minerals for human health. *Nickel*: The normal circulating nickel levels in the serum/plasma ranges from 2 to 17 nM[21]. Studies removing nickel from the diet of animal models resulted in decreased growth and alterations in glucose, folic acid, vitamin B12, calcium, iron, and zinc homeostasis in multiple mammalian species [36]. Nickel has been directly detected within the mitochondria of human cells when treated with nickel salts [115,116], but specific roles in mitochondrial metabolism are unknown. *Titanium*: The average circulating titanium levels in the serum/plasma ranges from 1.1 to 2.5 μM [35]. Most reports on the biological activity of titanium focus on nanoparticle and not ionic species. One study in mice showed that labeled titanium nanoparticles were taken up by mitochondria in multiple tissues [117], although the physiological relevance is unknown. *Vanadium*: The normal circulating vanadium levels in the serum/plasma ranges from 0.3 to 9 nM[21]. Studies removing vanadium from the diet of animal models resulted in decreased lifespan and alterations in bone and thyroid development in multiple mammalian species [36]. Treatment of multiple animals models with vanadium compounds resulted in vanadium being localized within the mitochondria, indicating that mitochondria can take up this metal but a specific role in mitochondrial metabolism is not known [118,119]. Little information on the effects of nickel, titanium, or vanadium on mitochondrial energy charge or redox capacity are known. The remaining members of this elemental group are too rare or unstable to have physiological relevance, so there is no information about content or function within the mitochondria.

Post-Transition Metals & Metalloids: The post-transition metals and metalloids are a heterogenous grouping of elements in the periodic table that generally fill the *p*-block section of the periodic table, with some exceptions. These elements are often described as having partially non-metal character and exhibit a mix of single or multiple oxidation state potentials under physiologic conditions. Most of these elements are not often found free,

but instead exist in stable oxides or in complexes with cellular macromolecules. Only the element selenium in this group has been proven to have an essential role in human metabolism. However, two additional metalloids boron and silicon have strong evidence for beneficial roles in physiology.

Selenium: Selenium is the only metalloid with confirmed essentiality for humans. The normal circulating level of selenium in serum/plasma is between 0.6 and 1.8 μM in healthy adults [21]. The mitochondrial levels of selenium have been reported at 1.1–1.8 μg/g dry weight, representing about 25% of total cellular selenium in human liver tissue [120]. The major function of selenium in the cell is to be incorporated into the amino acids selenocysteine and selenomethionine, which are used to synthesize the 25 known selenoproteins in the human proteome [121]. These proteins have roles in redox regulation, protein folding, thyroid hormone function, calcium homeostasis, and antioxidant enzyme systems. Several of these selenoproteins affect or are located to the mitochondria, including thioredoxin reductase 2, selenoprotein O, and glutathione peroxidase 4 [122]. In particular, thioredoxin reductase and glutathione peroxidase play a key role in protecting mitochondria from the harmful effects of ROS, utilizing the endogenous antioxidants thioredoxin and glutathione [123]. Small molecular weight selenium compounds may also directly function as antioxidants and signaling molecules within the circulation and the cells, but little information is available for activity within the mitochondria [124]. It is clear that selenium plays an important role in supporting mitochondrial function and reduction of redox stress, but further investigation is needed to reveal the detail.

Boron: Boron is an essential metalloid for plants, but to date no biological role has been established for humans. Still, the evidence for boron as a beneficial mineral for humans is strong, and studies suggest that boron might have a role in hormonal regulation and in the metabolism of carbohydrates and lipids [[125], [126], [127]]. Additionally, boron deprivation in multiple animal models resulted in altered homeostasis of calcium, phosphorus, magnesium, potassium [36]. The circulating levels of boron in plasma/serum are reported between 3 and 11 μM [35,128]. Boron supplementation in human subjects decreased serum glucose, creatinine, and calcitonin, while it increased serum triglycerides, ceruloplasmin, and erythrocyte superoxide dismutase [36]. Boron administration had positive effects on mitochondrial membrane potential and function in multiple species, but entry into mitochondria was not confirmed [129,130]. The available evidence suggest that mitochondria may benefit from the availability of boron, which may promote metabolism and reduce redox stress.

Silicon: There is also growing evidence that the metalloid silicon may be beneficial for human physiology, especially for biomineralized tissue. The circulating levels of silicon in the serum/plasma are reported between 89 and 356 μM[35]. Studies removing silicon from the diet of multiple animal models resulted in altered bone structure, amino acid balance, and homeostasis of calcium, copper, magnesium, manganese, and phosphorus [36]. Possible roles for silicon include a direct structural presence within collagen or cartilage effects on expression and calcification of connective tissues. Multiple forms of silicon can enter the mitochondria [131], but the mechanisms of entry, concentrations, and effects are not resolved.

Other Post-Transition Metals & Metalloids: The other post-transition metals and metalloids are found at trace levels in the body, but have not been shown to be essential minerals for human health. *Aluminum*: The circulating aluminum levels in the serum/plasma range from 0.2 to 0.6 μM[21]. A few studies removing aluminum from the diet of animal models resulted in decreased growth and life expectancy [36]. Several studies show that high levels of aluminum can be toxic to mitochondria by increasing ROS production and decreasing mitochondrial membrane potential [132], but little work is available on any role for aluminum at normal exposure levels. *Antimony*: The circulating antimony levels in the serum/plasma range from 3 to 6 nM[21], but concentrations in the mitochondria are not known. Antimony intoxication in rats did result in mitochondria swelling, suggesting entry into the organelle [133]. *Arsenic*: The circulating arsenic levels in the serum/plasma range from 0.02 to 0.2 μM[21]. Arsenic is normally thought of as a toxic metalloid, but some reports claim that low levels of arsenic have health benefits. Studies removing arsenic from the diet of animal models resulted in decreased growth and changes in the balance of polyamines, taurine, glutathione, and zinc [36]. Prolonged arsenic deprivation in goats resulted in mitochondrial abnormalities in heart tissue, but mitochondrial concentrations were not measured [134]. Arsenic intoxication results in mitochondria depolarization and permeability transition, but entry into mitochondria was not confirmed [135]. *Bismuth*: The circulating bismuth levels in the serum/plasma range from 0.5 to 17 nM and is generally regarded as non-toxic despite being a heavy metal [35]. Humans consume bismuth in common antacids and other medicinal preparations. Treatment of cells with bismuth compounds resulted in localization of the metal within the mitochondria in one study [136]. *Germanium*: The circulating germanium levels in the serum/plasma are estimated to range within 2.6–4.0 μM [35,137]. A few reports have claimed that germanium stimulates the immune system [138], but corroborating evidence is needed. Germanium intoxication did result in mitochondria abnormalities including decreased cytochrome *c* oxidase activity, but entry into mitochondria was not confirmed [139]. *Indium*: The circulating indium levels in the serum/plasma are not widely known, but are estimated to range within 9–90 nM [140,

141]. Treatment of rats with indium compounds did result in indium uptake into cells and into the mitochondria [142,143]. *Lead*: Lead is normally thought of as a toxic metalloid, but some reports claim that low levels of lead have health benefits. Studies removing lead from the diet of animal models resulted in anemia and alterations in glucose, cholesterol, triglycerides, and iron homeostasis [36]. The circulating lead levels in the serum/plasma range from 0.06 to 0.9 μM[35], but no beneficial effects in humans are known. Lead intoxication inhibits the mitochondrial enzyme ferrochelatase and eventually causes mitophagy [144]. *Tin*: The circulating tin levels in the serum/plasma range from 3 to 5 nM[21]. Organic tin compounds are widely studied as anti-cancer compounds that promote mitochondria-dependent apoptosis [145], but the effects of physiological levels of tin on mitochondria are unknown. Little information on the effects of these other post-transition and metalloid elements on mitochondrial energy charge or redox capacity are known. The remaining members of this elemental group are too rare or unstable to have physiological relevance, so there is no information about content or function within the mitochondria.

3. Role of mitochondrial minerals in differentiation

Numerous studies have demonstrated how aberrant mineral handling in the mitochondria can cause metabolic imbalance and result in disease [23,46,75,82,146], but there are fewer reports on the roles that mitochondrial minerals have in the normal development of the cell. This is an important topic since mitochondria have been recognized as a key driver of cellular differentiation and programming [147,148]. Earlier studies revealed that mitochondria from pluripotent cells generally have reduced mass, immature ultrastructure, and low metabolic activity [149,150]. This intracellular configuration is now known to favor glycolysis and reduce ROS released during oxidative phosphorylation. Reductions in redox burden and oxidative stress are key to promoting cellular longevity required for long-lived pluripotent cell lineages. In addition to decreased ROS levels, stem cells have elevated antioxidant defenses, including increased superoxide dismutase, catalase, and glutathione peroxidase activity [151]. Also, the levels of the key antioxidant glutathione can be 3–4 fold higher in pluripotent cell types compared to differentiated somatic cells [152]. Once pluripotent cells are stimulated to differentiate, the up-regulation of mitochondrial bioenergetics and metabolism seems to be an early and necessary step. In fact, elevated ROS production by mitochondria is known to be a trigger stimulus for differentiation and reduced regenerative potential in human mesenchymal stem cells [153].

Given the changes to mitochondrial physiology during pluripotent cell maintenance or differentiation, it can be inferred that adjustments to the mitochondrial metallome are also needed. Calcium was reported to be reduced within the mitochondria of resting pluripotent

cells [154], which might be expected since calcium stimulates mitochondrial bioenergetics and increases ROS production. Other than calcium, only a few studies have evaluated mitochondrial mineral balance in the context of cellular differentiation. *Alkali Metals*: Sodium currents directly increase mitochondrial calcium content, so it is assumed that mitochondrial sodium levels are also low in pluripotent cells, but this has yet to be shown directly. Interestingly, lithium was shown to increase mitochondrial respiration in human neural precursor cells [155], yet the physiological relevance is not known. *Alkali Earth Metals*: Magnesium levels were shown to regulate neural stem cell proliferation *ex vivo*, although changes in mitochondrial magnesium content were not reported [156]. *Transition Metals*: Zinc levels were shown to regulate neural stem cell proliferation *ex vivo*, with increased ROS during zinc deficient conditions [[157], [158], [159]]. Also, exogenous zinc treatment of mouse embryonic stem cells resulted in increased expression of genes that maintain pluripotency and downregulated several genes involved in differentiation [160]. Another report showed that copper levels were low in resting hematopoietic stem cells, perhaps since copper can stimulate mitochondria metabolism [96,161]. Artificially increasing copper levels in hematopoietic progenitor cells resulted in accelerated differentiation [162]. Elevated manganese was shown to be toxic to neural stem cells [163], but that is true for most cell types; no specific role is known in pluripotent cells. *Post-Transition Metals & Metalloids*: Selenium content is known to influence cancer stem cell development due to its effects on mitochondrial redox balance [164], but we are unaware of studies investigating the role of selenium in maintenance of pluripotency or differentiation. Given the strong regulatory influence that minerals have on mitochondrial metabolism and redox balance, it is likely that other important relationships between minerals and cellular differentiation will be identified. A better understanding of the roles of mitochondrial metals will be important as we move closer to widespread application of pluripotent cells in clinical therapies.

4. Final comments

This brief survey reveals an incomplete understanding of content and function for the minerals within the mitochondria (Table 1). For essential minerals such as calcium and iron, there is a substantial amount of information on their metabolic roles and impact on mitochondrial physiology. But for other essential minerals such as chromium and selenium, the content and function of these minerals within the mitochondria is incomplete. For minerals such as boron and silicon, the details of their role with human metabolism are still not elucidated, so there is little to no information on mitochondrial context. Clearly there is much work to be done.

Table 1. Metals and metalloids known in the mammalian mitochondria.

Element	Serum/plasma concentration	Entry into in mitochondria	Mitochondrial concentration	Sequestration	Metabolic role(s)
Confirmed essential:					
Ca	2.1–2.6 mM	yes	0.1–20 μM	yes	yes
Co	2–8 nM	yes	50–90 nM	yes	yes
Cr	1–31 nM	–	–	–	–
Cu	11–30 μM	yes	71–115 μM	yes	yes
Fe	9–31 μM	yes	0.5–1.1 mM	yes	yes
K	3.5–5.1 mM	yes	150–180 mM	yes	yes
Mg	0.7–1.1 mM	yes	0.4–0.7 mM	yes	yes
Mn	8–18 nM	yes	3–16 μM	yes	yes
Mo	1–31 nM	yes	1–6 μM	yes	yes
Na	136–145 mM	yes	5–50 mM	yes	yes
Se	0.6–1.8 μM	yes	–	–	yes
Zn	11–18 μM	yes	167–300 μM	yes	yes
Possibly beneficial:					
Al	200–600 nM	yes	–	–	–
As	20–200 nM	–	–	–	–
B	3–11 μM	–	–	–	–
Ba	200–600 nM	yes	–	–	–
Bi	0.5–17 nM	yes	–	–	–
Ge	2.6–4.0 μM	–	–	–	–
In	9–90 nM	yes	–	–	–
Li	1–4 μM	yes	–	–	–
Ni	2–17 nM	yes	–	–	–

Element	Serum/plasma concentration	Entry into in mitochondria	Mitochondrial concentration	Sequestration	Metabolic role(s)
Pb	60–900nM	yes	–	–	–
Rb	0.5–7μM	yes	–	–	–
Sb	3–6nM	–	–	–	–
Si	89–356μM	yes	–	–	–
Sn	3–5nM	–	–	–	–
Sr	300–500nM	yes	–	–	–
Ti	1.1–2.5μM	yes	–	–	–
V	0.3–9nM	yes	–	–	–

Notes: See text for references. Many of the concentrations for mitochondria derive from disparate cell/tissue types and from limited number of references, so values are best viewed as estimates for mitochondrial metal and metalloid content. Table does not include data from reports listing elemental content per mitochondrial protein content or per dry weight. The symbol '–' indicates that a concentration or value could not be found in the available literature.

Many questions remain about mitochondrial mineral homeostasis. First, how are mitochondrial mineral pools sensed and maintained? Most proteins destined for the mitochondria are imported in as unfolded peptides, then assembled and metal-bound once inside the mitochondrial matrix. This presumes that an adequate amount of the required minerals are already maintained inside the mitochondrial matrix, although how that pool is maintained is not yet resolved[16,18,19.] Second, once the metal content of the mitochondria is fully identified, how will the binding proteins and cognate small molecules be determined? Development of new technologies to effectively measure labile metals and weak metal-protein binding dynamics is becoming more accessible [17,18]. Also, there has been progress in the development of new bioinformatics tools that can predict mineral binding sites in metalloproteins or metallochaperones [165]. Thirdly, mineral binding sites are never absolutely selective, so substitute minerals do sometimes replace primary minerals in binding sites, which could change the activity or behavior of the metalloproteins or metallochaperones. Determining this 'second dimension' of mineral complexes will be important to appreciate mineral activity during changing physiological conditions. Finally, how do the mineral profiles of the mitochondria change with differentiation and developmental stages? Many studies on mitochondrial minerals focus at a single timepoint,

but it is essential to monitor how mineral homeostasis in the mitochondria changes over time and during development to better optimize mineral requirements to metabolic need.

Once we have a complete catalog for the metallome of the mitochondria, more practical approaches to optimizing nutrition inputs become available. We can then better determine if there are longevity minerals that might provide countermeasures against the pathophysiologic processes of aging and senescence.

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