EDITORIAL
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Perspectives on *Metals in Microbiology*

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Reports of the requirement of metals for microbial growth and their toxicity feature amongst the earliest articles published in *Microbiology* (see for example [1, 2]. Now that we are celebrating 75 years of the journal, the importance of metals in biological systems and the need for microbes to precisely regulate the intracellular availability of these essential elements continue to be a theme of articles published in the journal and are at the core of the *Metals in Microbiology* collection, influencing, for example, microbial physiology, the outcome of host–microbe interactions, the production of biocatalysts, bioremediation and the biorecovery of metals.

Metals play key structural and catalytic roles in metalloproteins and metalloenzymes that participate in fundamental processes within a microbial cell, from transcription, translation, carbon metabolism, amino acid metabolism, respiration, energy production, and signal transduction. Metal availability can therefore directly regulate microbial physiology by influencing metalloprotein and metalloenzyme function. Metal availability can also indirectly regulate key pathways in a microbial cell. For example, key enzymes within glycolysis and the Krebs cycle are transcriptionally and differentially controlled in response to changes in iron availability. The known links between iron and central carbon metabolism in the pathogen *Mycobacterium tuberculosis* are summarized in a critical review by Serafini [3], providing insight as to how bacteria may metabolically adapt to metal-starvation and poisoning.

Given the requirement for metals as nutrients, microbes have evolved diverse systems to take up and subsequently distribute metals within the microbial cell. These systems typically involve transmembrane metal transporters and soluble metal-trafficking proteins. Such systems have been well described in bacteria and fungi, but less so in protists. The timely review by Sloan and colleagues [4] summarizes the current knowledge regarding iron, zinc, and copper uptake in Apicomplexa, including *Plasmodium* and *Toxoplasma*, and highlights key gaps for future investigations. In particular, how do metals move in and out of the unique organelle named apicoplast?

Many microbes can secrete metal chelators that scavenge metals from the extracellular environment and subsequently deliver these nutrients into the intracellular space. For example, the siderophores represent a superfamily of well-known iron scavengers, with enterobactin as the best characterized member. *Stenotrophomonas maltophilia*, a Gram-negative bacterium, possesses a putative enterobactin biosynthesis pathway but, interestingly, does not produce enterobactin or use iron-enterobactin complex as an iron source. In their research article, Hisatomi and colleagues [5] resolve this mystery and identifiy that the siderophore produced and used by this organism is a chemical derivative of enterobactin.

Some microbes have metal storage proteins that are loaded during conditions of metal sufficiency and unloaded during conditions of metal deficiency. The iron storage proteins named ferritins are perhaps the most familiar examples. Ferritins are large protein cages that can encapsulate up to several thousands of iron atoms. Under conditions of iron sufficiency, iron atoms enter as ferrous iron and become oxidized to form a mineral ferric oxy-hydroxide core. Under conditions of metal deficiency, the iron mineral is reduced back to ferrous iron and released into the cytoplasm. By studying the ferritin from cyanobacteria, Bradley and colleagues [6] provide evidence that the route of iron transit in and out of the ferritin core varies among prokaryotes. This variation may underpin the varying responses of different organisms to iron availability.

Beyond metal scavenging, metal uptake, and the discharge of metals from storage proteins, microbes have also evolved to respond to metal insufficiency *via* metal-sparing mechanisms. For example, certain zinc-dependent ribosomal proteins can be replaced by zinc-independent counterparts during conditions of zinc deficiency. The review by Li and colleagues [7], discusses how such ribosome remodelling in *M. tuberculosis* in response to zinc-starvation leads to ribosome hibernation, and could be a primary mechanism driving the development of nonreplicating persister bacteria that exhibit phenotypic tolerance to antibiotics. The above-mentioned review by Serafini [3] also highlights how the remodelling of carbon metabolism in iron-starved growth-arrested *M. tuberculosis,* via increased production of alternative iron-independent enzymes, allows carbon metabolism to proceed during the iron-starved dormant state. Such insight into the connection between metals and metabolic adaptation has the potential to inform the discovery of new anti-microbial strategies, including approaches to counteract antibiotic tolerance.

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There is also strong interest amongst researchers studying metals in microbiology to understand the microbial responses to metal insufficiency in the context of microbe–microbe and host–microbe interactions. Decreases in extracellular and, in turn, intracellular metal availability often signal potentially hostile environments, such as the presence of microbial competitors or a host. For example, Bhakat and co-workers describe how enterotoxigenic *Escherichia coli* use the environmental cue of iron-limitation to induce expression of the host colonization factor CS6 [8]. In response to infection, host organisms can suppress metal availability and starve invading microbes in a process known as 'nutritional immunity'. An understanding of host mechanisms that are involved in this process and microbial mechanisms that counter these host mechanisms can lead to new, metal-dependent strategies to control microbial growth in diverse environments, including in the management of infectious diseases. For example, in response to contact with the host, the fungal pathogen *Aspergillus fumigatus* secretes a secondary metabolite known as gliotoxin, which kills host cells. The biosynthesis and secretion of gliotoxin are transcriptionally upregulated in response to zinc insufficiency. In the host, this transcriptional upregulation can occur in response to host calprotectin, which limits zinc availability at the site of infection. Interestingly, a biosynthetic intermediate of gliotoxin, namely dithiol gliotoxin, is itself a zinc chelator. The research article by Traynor and colleagues [9] suggests that accumulation of this intermediate in the *A. fumigatus* cytoplasm can lead to intracellular zinc starvation. Thus, there is potential here to develop chemical inhibitors that stall gliotoxin biosynthesis at the dithiol gliotoxin intermediate step or those that inhibit secretion of gliotoxin from the cytoplasm as antifungal therapeutics.

As discussed above, too little of a metal impairs microbial physiology, but so does too much of a metal. An excess of any metal is toxic because it can promote insertion of the wrong metal into metalloproteins and metalloenzymes, leading to impaired protein and enzyme function. As described in the research article by Sarker and colleagues [10], exposure to excess zinc can inhibit growth of marine cyanobacteria, impair photosynthesis and damage bacterial membranes. An excess of a redox-active metal, such as copper and iron, can also catalyse undesirable redox reactions and the generation of toxic reactive oxygen and nitrogen species. To suppress metal toxicity, microbes have evolved systems that decrease metal availability within the cell, usually by scavenging and sequestration of excess intracellular metal or efflux of the excess metal out of intracellular compartments. Additional systems that repair or bypass the cellular damage have also been reported.

The toxicity of excess nutrient metal ions to microbes, especially copper, has been long exploited for the control of microbial growth in diverse settings. Copper has been used widely as an antibacterial agent and growth promoter in animal feed and as fungicides for crops. It is thus no surprise that highly copper-resistant bacteria have been isolated from the gut and faeces of livestock or from plants. As summarized in the review by Kaur and colleagues [11], these copper-resistant bacteria, including *Staphylococcus aureus* and *Listeria monocytogenes*, typically carry additional genes associated with copper scavenging and efflux in mobile genetic elements such as plasmids. These plasmids are likely exchanged between microbes that share common reservoirs, potentially increasing the spread of copper resistance in the environment. It is rather alarming that copper resistance genes in mobile genetic elements are frequently co-encoded and, therefore, co-selected with antibiotic resistance genes. Thus, high environmental copper availability may contribute to the problem of antibiotic resistance. This is also important in the context of host–microbe interactions, since as part of nutritional immunity, infected host organisms can also increase the availability of metals such as copper in a site- or tissue-specific manner.

The ability of microbes to uptake and transform metals is also of interest with respect to biotechnological applications, including environmental remediation and the recovery of waste metals, biomining, metal nanoparticle synthesis and biocatalyst production. Indeed, a wide range of metallic nanoscale minerals can be produced as a result of the interactions of microbes with metals and minerals that can be used for a range of environmental and biomanufacturing applications. This is highlighted in the research article from Liu and colleagues [12] that reports on the activity of copper carbonate nanoparticles, synthesized by the fungus *Neurospora crassa* using spent culture supernatant, with regard to methyl red degradation and chromate remediation. Such work not only demonstrates the important role microbes can play in the biorecovery of metals through the production of insoluble nanoparticles, but also how the catalytic properties of such products can be exploited.

The articles in this *Metals in Microbiology* collection showcase the breadth of research in this field and highlight many of the open questions. How do microbes sense and respond to changing metal availability? How do microbes scavenge, take up, transform, distribute, store, spare, sequester, or export metals? How do these mechanisms influence microbe–microbe and host–microbe interactions? How can fundamental knowledge regarding these mechanisms underpin biomedical and biotechnological advances that help solve contemporary global issues, especially those related to health and the environment? It is no doubt an exciting era in the field, and we cannot wait to see how it progresses.

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Conflicts of interest
The authors confirm that there is no conflict of interest.

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