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Editorial overview: Bioinorganic chemistry: Metals in biology: approaching the big picture

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In this special 'Bioinorganic Chemistry' issue of *Current Opinion in Chemical Biology*, we present a series of review articles that encompass and bridge fundamental bioinorganic principles and 'systems level' views of metals in biology. The reviews are divided into three general areas: '*Frontiers in the Homeostasis of Metals and Sulfur in Biology,*' '*Inorganic Tools to Modulate Biology,*' and '*Advances in Systems Level Metals in Biology.*' From these reviews, we learn about the metabolism of inorganic species in simple to complex organisms (bacteria to humans), novel approaches to perturb metal homeostasis and the latest ways to image metals in cells to answer fundamental questions regarding metal regulation.

In the '*Frontiers in the Homeostasis of Metals and Sulfur in Biology*' section, we start with bacteria. Here, Lauren Waters (https://www.sciencedirect.com/science/article/pii/S1367593120300041) teaches us about manganese homeostasis, describes new manganese transporters that serve as gateways to manganese uptake and their regulators, including metal-binding riboswitches, and provides novel insights into modulation of manganese homeostasis in virulence, as well as symbiosis. The reviews then expand to eukaryotes and begin with two stories in yeast that focus on deciphering fundamental principles of zinc and iron homeostasis. In Amanda Bird's review (https://www.sciencedirect.com/science/article/pii/S1367593120300120), she lays out the current understanding of how zinc is distributed among organelles and proteins under conditions of zinc starvation and zinc overload, updates us on the roles of zinc transporters in zinc speciation, and provides ideas for how cells prioritize the proteins that bind zinc under zinc starvation, and how cells buffer excess zinc during zinc overload. In Caryn Outten's review (https://www.sciencedirect.com/science/article/pii/S1367593120300247), mechanisms of iron metabolism in nonpathogenic and pathogenic yeast are presented. Outten describes the ensemble of proteins that work together to regulate iron uptake, use and storage, and we learn that Fe-S clusters play a central role as sensors of iron bioavailability. We also learn that the regulation pathways for different yeast species involve unique combinations of proteins that reflect the species' adaptations to their environmental niches.

Tracey Rouault (https://www.sciencedirect.com/science/article/pii/S1367593119301425) brings us up to mammalian cells in her review,

which focuses on iron–sulfur cluster biogenesis. We learn about the exciting cryo-EM structure of the ISCU core complex which provides clues to the mechanism of Fe-S cluster assembly. We also learn about the roles of Fe-S cluster chaperones in assembly and the new discovery that Fe-S clusters can be assembled in the cytoplasm, in addition to the mitochondria. Finally, Jon Fukuto (https://www.sciencedirect.com/science/article/pii/S1367593119301401) reviews the role of H_2S in regulating biological pathways via reactivity with metalloproteins, offering another layer of regulation. Fukuto describes how H_2S can target heme proteins, iron–sulfur proteins, and zinc finger proteins via the post-translational modification of persulfidation. We learn that we are just beginning to unravel the chemical biology of H_2S vis-à-vis metal homeostasis, and exciting advances are anticipated.

Using Inorganic Tools to Modulate Biology: One fascinating, creative area of bioinorganic chemistry is developing reagents that report on and/or control biological processes. Here, the 'bioinorganic' assignment can be in the reagent, the target, or both. Although some areas of bioinorganic chemistry direct organic molecules as reporters on bioinorganic processes, others use the properties of metal coordination complexes to create new functions. In this issue, we feature two examples from the latter class that further contrast in their exploitation of the unique attributes of late transition metals to create compounds that are functional in mammalian cells. In one example, Woods and Wilson (https://www.sciencedirect.com/science/article/pii/S1367593119301279) review the importance of mitochondrial Ca^{2+} uptake in biology and disease and in particular how inhibition of the mitochondrial calcium uniporter protein may mitigate disregulation associated with stress and disease. They describe current known inhibitors of the mitochondrial calcium uniporter, both organic and inorganic, and then focus on the promise of dinuclear Ru compounds, wherein seemingly small changes in bridging and terminal ligands have large influence on on- and off-target effects. An attractive attribute of these Ru and other inorganic compounds is that they are relatively nonreactive, achieving their function without undergoing major in vivo alterations. By contrast, Thomas and Casini (https://www.sciencedirect.com/science/article/pii/S1367593119301279) present an alternative aspiration with a review of reactive transition metal compounds that are designed to mediate chemical transformations inside of cells. They review specifically the field of Au chemistry, including examples of intracellular Au sensing through Au(III)-specific activation of turn-on fluorophores. Another fascinating arena is development of new Au(III) reagents capable of metal-mediated protein modification, including cysteine arylation. In combination, these two reviews highlight the unique promise of transition metal compounds of a spectrum of attributes ranging from inert scaffolding to active chemistry, all of which can be harnessed in service of understanding biological processes.

The aforementioned advances made in unraveling metal homeostasis in biological systems, via a range of approaches from clever genetics approaches to application of chemical tools that perturb homeostasis, are further complemented by a series of reviews that zoom out to the 'systems' level to provide a global perspective of metal ion distribution in cells, tissues, and whole organisms.

Advances in Systems-Level Metals in Biology. Farrer and Griffith (https://www.sciencedirect.com/science/article/pii/S1367593119301413) bridge into this arena in their review of approaches using azide–alkyne cycloaddition 'click' reactions in pursuit of understanding Pt chemistry in cells. This robust cycloaddition reaction can be used with modified Pt compounds for pretreatment or post-treatment conjugation. In pretreatment approaches, click chemistry is a powerful tool for modular syntheses yielding desired multifunctional Pt compounds. Alternatively, the azide or alkyne modification provides a post-treatment handle for visualizing or isolating Pt-bound biomolecules following cellular treatments. With this ability for comprehensive target identification, this review acts as a bridge between chemical tools and 'systems' approaches.

Continuing into cell-wide metal-biomolecule identification, Sun Hongzhe et al. (https://www.sciencedirect.com/science/article/pii/S1367593120300223) provide a very comprehensive review of integrating techniques, such as linking metalloproteomics with metabolomics, to provide a broad view of both biomolecular binding sites, as well as cellular responses to metal ions. Examples from Bi and Ag chemistry provide the impressive full circle of '-omics' applications back to distinct target identification, validation, and even structural biology.

Zooming out from metals in cells toward the complexity of larger organisms, the final two reviews focus on the application of cutting-edge imaging approaches to capture the spatial distribution of metals in tissues and model organisms.

Leary and Ralle (https://www.sciencedirect.com/science/article/pii/S1367593119301437) bring us up to date on the latest advances in synchrotron-based X-ray fluorescence microscopy (XFM) to image metals in cells, organs, and tissues, with a review that focuses on copper in the brain. We learn about how XFM imaging is helping us understand the connections between copper and aging. In one story, we learn about how copper localizes to small puncta called CSVs in the astrocytes in an age-dependent manner, with the CSV's hypothesized to function as copper 'filters' regulating copper

availability to neurons. In a second story, we learn how XFM imaging of plaques from the brains of Alzheimer's animal models is providing spatial distribution of copper (and zinc and iron) and contributing to the amyloid plaque hypotheses.

Skaar et al. (https://www.sciencedirect.com/science/article/pii/S1367593120300090) expand metal imaging to review the emerging new area of multimodal imaging. Here, 2D and 3D images from tissues and model organisms are generated by combining data from two or more distinct imaging methods and using machine learning (called data-driven image fusion) to obtain the image. To image metals, at least one of the methods used must be selective for metals, whereas the second can be selective for another biomolecule of interest (e.g. MALDI-imaging mass spectrometry (IMS) to image lipids). Skaar et al describe several exciting studies, including one that combines LA-ICP-MS with MALDI-IMS to correlate the distribution of Pt drugs with lipids in tissues and another that uses LA-ICP-MS and nano-SIMS with microscopy to image copper in a Menkes disease zebrafish model. In addition, a study using LA-ICP-MS, absorption microcomputed tomography and 3D confocal μXFI that produced a stunning 3D image of metal distribution in the water flea, *Ceriodaphnia dubia* is presented. These multimodal imaging approaches are technically challenging, but these early images offer the promise that as this approach advances, we will be able to routinely monitor metal homeostasis at the systems level.