Introduction to "Cellular Metal Homeostasis and Trafficking"

The vital role of metals in biology has been highlighted in two previous thematic issues of *Chemical Reviews*: Bioinorganic Enzymology (Vol. 96, No. 11, 1996) and Biomimetic Inorganic Chemistry (Vol. 104, No. 2, 2004), both of which were guest edited by Edward I. Solomon and Richard H. Holm. These compilations reviewed the rich diversity of metal active sites, the complexity and importance of the reactions they catalyze, and efforts to mimic the electronic structure, geometric structure, and reactivity of these fascinating metalloenzymes. In the Introduction of the 2004 issue, the editors note that incredible strides have been made in defining and mimicking the nature of metal active sites, but they comment that "Beyond site analog synthesis lies the vastly more difficult goal of defining the biosynthetic pathways to metal sites. At present there is no general agreement on the pathway leading to any metal site—mononuclear or polynuclear—in biology." It is perhaps no coincidence that, around this time, Dennis R. Winge initiated the first Cell Biology of Metals Gordon Conference (in 2005) to address the rapidly expanding subdiscipline of Metals in Biology, namely, the increasing influence of cell biology on bioinorganic chemistry and vice versa.

The field of metal homeostasis (i.e., how cells regulate their internal environment to maintain an optimal level of essential metals) emerged as a robust field in the 1980s when it became clear that metal availability directly regulates (at the transcriptional level) genes involved in metal ion resistance. The field continued to grow with the discovery of metal ion permeases and transporters as well as metallochaperones that directly insert metal ions into their target enzymes. These discoveries painted a complex and intricate picture in which cells tightly regulate metal accumulation, transport, distribution, recycling, and export. As the field grew, it became clear that the biology and chemistry were inextricably linked: bioavailability as well as coordination chemistry and protein−protein interactions could dictate what metal gets inserted into a given protein. This issue of *Chemical Reviews* is the first devoted to how cells acquire, distribute, and manage essential metal ions. This issue also addresses how cells (and organisms) manage nonessential but medically important metal ions and complexes. A number of articles highlight the power of chemistry and chemical tools to illuminate aspects of metal homeostasis, while others illustrate the essential role of genetic studies in model organisms for discovering key players in cellular metal regulation. As eloquently summarized by David Eide at the 2009 Cell Biology of Metals Gordon Conference, "The fundamental questions are simple, but the technical issues are not." How are metal ions transported into cells; how are they partitioned once they get there; how are cellular proteins and enzymes properly metalated; what processes are mediated by metal ions; how is metal availability regulated and what happens when it goes awry? This thematic issue of *Chemical Reviews* explores emerging themes in cellular metal homeostasis as experts highlight the dynamic chemistry and biology of cellular metal trafficking.

Iron is the most abundant transition metal in biology, and five articles in this issue are devoted to various aspects of its management. The article by **Kaplan and Kaplan** focuses on mechanisms of iron acquisition as well as transcriptional regulation of genes required for acquisition. Much of what

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we know about iron transport and regulation has been facilitated by the use of model organisms, and Kaplan and Kaplan detail how *S. cerevisiae* and *S. pombe* have been instrumental in identifying genes involved in iron acquisition, delineating how those genes are regulated under iron-replete and iron-deficient conditions, and elucidating how organisms store iron. Parallels are also drawn to higher organisms such as *C. elegans*, plants, and vertebrates. **Morrissey and Guerinot** dig further into the topic of iron uptake and transport in plants. Iron is absolutely required for plant growth, and this necessity imposes restrictions on environmental conditions that sustain plant life. Consequently, plants have evolved mechanisms for modulating iron availability in soil. This article also explores a common theme in metal acquisition: beneficial transporters are sometimes commandeered by toxic metals, nature's own Trojan horse. **Theil and Goss** provide a complementary perspective on iron homeostasis, as they focus on how complex, multicelled organisms acquire, distribute, and regulate iron. This article discusses how the bioavailability of iron is regulated both within cells and between cells to maintain optimal levels of iron in tissues and whole organisms. This review also highlights the intimate connection between iron and O_2 in regulating organismal iron homeostasis.

Microbes also require iron for survival, but bioavailable iron in their surrounding environments can be exceedingly low. To overcome this iron-acquisition challenge, several classes of microbes produce siderophores as high-affinity iron-binding scavengers. The review by **Sandy and Butler** highlights the unique chemical structures of siderophores used by marine microbes to extract iron from ocean waters, where the iron concentration is less than 1 nM. The article draws comparisons between marine siderophores and those produced by some pathogenic bacteria, where the quest for iron becomes a battleground between pathogen and host.

A significant portion of biological iron is incorporated into heme, an iron-containing porphyrin used as a prosthetic group in a number of metalloproteins. The transport and trafficking of heme exhibits many parallels to the transport and trafficking of biometals. Yet because the majority of organisms contain heme biosynthetic pathways, researchers have the additional challenge of dissecting and differentiating processes that influence biosynthesis vs transport. In this issue, **Severance and Hamza** provide a thought-provoking review of our current knowledge of heme trafficking. They discuss the power of using genetically tractable model organisms to identify important players and distinguish biosynthesis from transport.

Nickel is an essential trace element found in bacteria, archea, fungi, plants, and some invertebrates. The most famous nickel-containing enzyme is urease, which catalyzes the hydrolysis of urea. Urease was the first enzyme crystallized (in 1926), although it took nearly 50 more years for nickel to be recognized as an essential cofactor for the enzymatic activity. While urease is the most famous, there are a wealth of nickel-containing enzymes that catalyze essential and diverse reactions. **Li and Zamble** provide a comprehensive overview of nickel-dependent metalloenzymes, highlighting the important roles they play in both the environment and human health (due to the abundance of nickel-containing enzymes in bacterial pathogens). This article also reviews general features of nickel homeostasis and regulation including transporters involved in cellular uptake, nickel-specific efflux systems responsible for exporting nickel, and mechanisms of how nickel homeostasis is regulated.

A fundamental question in the field of metals in cell biology is how the right metal is transported, trafficked, and inserted into a given metalloprotein. **Ma, Jacobsen, and Giedroc** explore how nature uses metal coordination chemistry to fine-tune selection mechanisms. This article provides an overview of metal selectivity of transporters and metal sensors (also known as metalloregulatory proteins) to provide insight into bacterial metal homeostasis. The theme that coordination chemistry plays a central role in how metals are utilized and how they influence cellular processes is further extended in the article by **Maret and Li**, which focuses on how proteins and enzymes bind zinc, with emphasis on the physicochemical properties of zinc−ligand interactions. There is increasing recognition that the nature of these metal−ligand interactions plays a central role in modulating zinc availability, and there is now compelling evidence that zinc levels are dynamic.

The cell itself is also dynamic, with a very complex environment. While there are well-established mechanisms for how proteins are targeted to different locations and organelles, it is not clear how metals get partitioned and distributed within cells. How do metals get to where they need to go within cells? Several articles in this issue detail mechanisms and themes in intracellular metal transport and trafficking. The article by **Atkinson and Winge** focuses on the complexity of metal uptake and distribution in mitochondria. They review mitochondrial physiology, the metalloproteome of mitochondria, and how metals are transported into mitochondria. This article also highlights an emerging theme in metal regulation, namely, that intracellular compartmentalization plays a role in ensuring that proteins are properly metalated and homeostasis is maintained. This theme is extended in the review by **Reddi, Jensen, and Culotta** on manganese trafficking and homeostasis in *S. cerevisiae*. Their article provides an overview of transport mechanisms for manganese at the cell surface, Golgi apparatus, and vacuole, as well as the dynamic regulation of these transporters and the parallels between yeast and higher organisms. **Vangheluwe, Sepúlveda, Missiaen, Raeymaekers, Wuytack, and Vanoevelen** highlight an important theme that ion transporters are not always selective and there are connections between metal transport and the ubiquitous signaling ion, calcium. They compare and contrast Ca^{2+}-transporting ATPases found in the ER and Ca^{2+}/Mn^{2+}-transporting ATPases in the Golgi.

While the above articles explore the nature of transporters, how they were discovered, and how they are regulated, the review by **Boal and Rosenzweig** delves deeper into the molecular mechanisms of how metals are transferred between proteins. This article reviews structural characterization of proteins involved in copper trafficking, highlighting insights from multiple spectroscopic methods including X-ray crystallography, NMR, electron microscopy, and X-ray absorption spectroscopy. Such studies are essential for elucidating the details of how metals are bound and transferred from one protein to another.

Spectroscopic and analytical techniques are also fundamental tools used for identifying and quantifying metal ions in biological settings. **McRae, Bagchi, Sumalekshmy, and Fahrni** give a comprehensive and in-depth review of methods used for trace metal imaging, from histochemical

tissue staining to fluorescent probes to advanced X-ray beam techniques and everything in between. They provide an historical perspective and a balanced analysis of the advantages and disadvantages of various techniques, giving examples of how the methods have been applied to identify metal imbalance in several diseases.

The concept that new tools and methods can lead to new insight is further explored in the review by **Zhang and Gladyshev**. While many of the main players in metal transport and trafficking have been uncovered in genetic screens in model organisms, this review covers a new tool in the metals in biology toolbox: bioinformatics. This article discusses how comparative genomics can be used to explore trace element utilization across the three domains of life. The article reviews comparative genomics of 5 trace metals (molybdenum, nickel, copper, cobalt, and selenium) and discusses how such computational studies can be used to explore the evolution and functional consequences of trace metal utilization.

A recurrent theme in many of the articles in this issue is the dichotomy between metals as essential but also toxic, thereby requiring intricate mechanisms to control their uptake and bioavailability. In a specific example of metal toxicity, **Benedetto, Au, and Aschner** review the impact of manganese overload on human health by exploring the parallels between manganese-induced neurodegeneration and Parkinson's disease. Indeed, a growing list of human diseases are being linked to imbalances in metal homeostasis. In addition to understanding the biological ramifications of what happens when metal homeostasis goes awry, there is also intense interest in developing compounds to ameliorate diseases associated with metal overload. The review by **Scott and Orvig** explores chelating agents designed to redistribute or remove metal ions as a therapeutic intervention against diseases like Parkinson's, Alzheimer's, Friedreich's ataxia, and others. This review reprises themes that were highlighted in another previous thematic issue of *Chemical Reviews* that centered around metals in biology: Medicinal Inorganic Chemistry (Vol. 99, No. 9, 1999), edited by Chris Orvig and Michael J. Abrams. The parallel growth of the subdisciplines of Metals in Medicine and Metals in Cell Biology has obvious interconnectedness. Chelating agents are one way to intervene in metal trafficking and distribution pathways, but metal complexes themselves can also act as drugs, which begs the question: how do cells acquire and manage unnatural metal complexes? Cisplatin and related platinum drugs are widely used in the treatment of cancer, yet much still remains to be learned about the cellular processing of these inorganic complexes. **Klein and Hambley** highlight recent advances in how platinum drugs enter and exit cells, with a focus on ways of mapping the cellular distribution of platinum complexes in tumors.

Extending the theme of using coordination compounds for applications in medicine is the review by **Haas and Franz**, which explores the use of metal chelating agents, coordination compounds, and organometallic complexes as probes and tools to understand or control biological processes. This review examines how the principles of coordination chemistry can be applied to understand issues related to cellular trafficking and regulation, whether it be the trafficking of metals or some other molecule or process that is enabled or visualized by a metal complex.

We hope this issue provides a snapshot of the exciting developments in *Cellular Metal Homeostasis and Trafficking* and will serve to inspire deeper exploration of the cell biology of metals. Given both the breadth and depth of the articles in this issue, it is our hope that it can serve as a valuable resource for both research and teaching. We would like to thank all the authors for their outstanding contributions and the entire *Chemical Reviews* staff for assistance in putting together this issue.

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