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# Metals in Biology 2016: Molecular Basis of Selection of Metals by Enzymes*

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**This ninth Metals in Biology Thematic Series deals with the fundamental issue of why certain enzymes prefer individual metals. Why do some prefer sodium and some prefer potassium? Is it just the size? Why does calcium have so many regulatory functions? Why do some proteins have an affinity for zinc? How is the homeostasis of calcium and zinc achieved? How do enzymes discriminate between the similar metals magnesium and manganese? Four Minireviews address these and related questions about metal ion preferences in biological systems.**

This is the ninth in the Metals in Biology Thematic Series of this Journal, a series that began in 2009 (1–8). The previous Thematic Series have covered a wide variety of topics related to the biological relevance of metals. Roughly 40% of all proteins crystallized to date have a metal bound somewhere and thought to be relevant to function (9). Thus, our knowledge of how enzymes work would be severely restricted without understanding what these metal ions do. In my own graduate course, I teach that metals can play structural roles in proteins, that many have oxidation-reduction capacity, and that they function in the active sites of enzymes by helping to position and activate substrates for reactions. Because of their positive charges, they act as "superacids," in that they are not inherently sensitive to pH changes.

Enzymes are highly selective in which metals they use, and even when an enzyme can use multiple metals, there is a difference in biological activity when a certain one is present, *e.g.* DNA polymerases (10). Replacement of one metal by another can be the basis of toxicity in some cases. Many enzymes use multiple metals at once, in different sites. This Thematic Series will explore the molecular basis for metal specificity in proteins.

The first Minireview, by Gohara and Di Cera (11), discusses monovalent cations and the selectivity for sodium *versus* potassium ions. As in other cases, new insights into protein structures have provided valuable information about metal preferences and function. Enzymes discussed in this Minireview include kinases, chaperones, phosphatases, aldolases, recombinases, dehydrogenases and ribokinase, dialkyl glycine decarboxylase, tryptophan synthase, thrombin, and Na/K-ATPase.

The second Minireview in the Thematic Series, by Carafoli and Krebs (12), deals with the divalent metal calcium and its prominence in biochemistry. Calcium may seem to be an enigma, at least at first glance. Many proteins are highly selective for calcium when compared with magnesium, which is in the same row in the periodic chart but smaller, although physiological concentrations of magnesium are generally much higher. Calcium is also highly compartmentalized in cells, and a breakdown of the pumps that maintain the gradients can lead to cell apoptosis and toxicity. Calcium sensor proteins, *e.g.* EF-hand proteins, are involved in the regulation of calcium homeostasis in cells. Calcium-binding proteins discussed here include EF-hand, calmodulin, and stromal interaction molecule-1 (STIM1), plus S-100 proteins and ATPases.

In the third Minireview in the Thematic Series, Capdevila, Wang, and Giedroc (13) discuss zinc selectivity in relation to host-pathogen warfare, a topic discussed in the seventh Metals in Biology series (7). Zinc, termed the foremost of nature's Lewis acids, has been reported to be present in 10% of all human proteins, and >200 enzymes use zinc for catalytic and structural function (13). Zinc homeostasis is highly regulated, in the context of protein affinity, transport, and storage proteins. These biological considerations are relevant to zinc in both the host and invading bacteria.

The fourth and final Minireview in this Thematic Series, written by Vashishtha, Konigsberg, and Wang (10), deals with DNA polymerases and their metal specificity. All DNA polymerases (and numerous other nucleic acid processing enzymes) require divalent metal ions. In general, this divalent metal is magnesium. However, manganese, cobalt, and calcium can support activity of some DNA polymerases under certain conditions, but the general pattern is that the alternate metals decrease fidelity. However, translesion DNA polymerase ι prefers manganese over magnesium (14, 15). The reasons for metal ion selectivity are structural, and details about the process are becoming available.

In summary, the selection of metals for biological tasks is not arbitrary. Proteins (and nucleic acids) can sense small differences among metals, in many cases even when a similar metal is present at a much higher concentration. As structural data and other insights become available, we will learn more about how this selectivity is achieved.

We hope that you will enjoy reading these four Minireviews and that you will learn something new about the roles of metals in biological systems. Finally, I welcome suggestions for the next Metals in Biology Thematic Series.

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