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Understanding How Cells Allocate Metals

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Abstract Life depends upon multiple metals. It is estimated that approximately one-third of all gene products require a metal for folding and/or catalysis. How does the correct metal locate to the correct protein? Provision of sufficient atoms of each of the

metals required by protein metal-binding sites is a challenge for cell biology. This is often especially true for iron, which is poorly soluble under aerobic conditions. Protein metal-binding sites follow universal affinity series. Under such a regime, exclusion of the wrong metals from metalloproteins is arguably an even greater challenge. High-fidelity homeostasis must match the number of some metal cations to the number of bonafide metal-binding sites. Selective protein–protein interactions also limit access of some atoms to the required subsets of proteins. Here we provide an overview of the contributions of metal sensors, metallochaperones, metal transporters and metal-storage proteins to the allocation of metals in cells. In this chapter an emphasis is placed on studies of the cell biology of metals in cyanobacteria.

1 The Irving–Williams Series and the Challenge for Homeostasis

The principles that govern the chemical speciation of metals in cells are clearly laid out in "*The Biological Chemistry of the Elements*" by Fraústo da Silva and Williams (2001) to which readers are directed. The underlying issue is that the metal sites of individual proteins are not sufficiently selective to solely bind the correct metal and exclude all others. Multiple partitioning events are required. Viewed as systems, cells monitor and modulate the number of atoms of each metal ion and the respective number of ligands. The homeostasis of different metal ions is also somehow integrated to avoid a surplus or deficiency of one element interfering with the speciation of another.

The Irving–Williams series was initially based upon empirical observations of the divalent transition metal-binding properties of model complexes and has been extended to include monovalent copper (Fraústo da Silva and Williams 2001). It specifies that the binding constants of proteins for essential metals will approximately follow a standard global order:

$$Mg^{2+} < Mn^{2+} < Fe^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+}(Cu^{+}) > Zn^{2+} .$$

In a simple cell model, where all metal ions are equally available and in surplus to proteins, all metallo-proteins would become copper proteins. From this binding affinity series it follows that concepts of all nascent metalloproteins plucking the correct metal ions from free solution as they emerge from the ribosome, and of all transporters releasing metal ions to a cytosol that contains some concentration of the free ions, are grossly naive. The full suite of protein ligand chemistries, coordination geometries, and other physico-chemical properties, is inadequate for such a simplistic model, and therefore cells must have evolved to manage metal-protein speciation (Tottey et al. 2005).

From the perspective of bioinorganic chemistry, a series of pseudo-equilibria between the number of atoms of each metal ion and the number of ligands for each metal ion in any compartment can substantially resolve metal ion selectivity by becoming a function of relative affinity between dif-