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Metalloregulators: Arbiters of Metal Sufficiency

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Abstract Metal homeostasis relies on the ability of metalloregulatory proteins to coordinate the expression of transport and storage functions. Metalloregulatory proteins can be divided into two major groups: those that regulate the uptake of essential metals (the Fur, DtxR/MntR, and NikR families) and those that regulate metal efflux and detoxification mechanisms (the ArsR/SmtB and MerR families). Within each metalloregulator protein family, there is a tremendous diversity in metal selectivity and the corresponding biological responses. The availability of at least one protein structure from each family is beginning to provide insights into the origins of metal selectivity. Biochemical measurements of metal ion selectivity and affinity provide a window into the ambient metal ion conditions within the cytosol: metalloregulators that sense nutrient metals must be poised to bind the metal ion once the essential functional sites are saturated, but before adventitious associations begin to interfere with cellular function. Similarly, sensors of metal ion excess, whether for non-essential toxic metals or nutrient metals, must respond to metals, at levels below those that will inhibit or prevent cell growth, to activate appropriate defensive measures. Recent insights highlight the global nature of stress responses elicited by metal ion deficiency. In addition to the expected derepression of high affinity

uptake systems, metal ion starvation leads to a large-scale remodeling of the proteome that includes: (i) metal-sparing, (ii) metal-substitution, and (iii) metal-mobilization responses.

1 Introduction: Metalloregulation and its Guises

Metal ions are essential cofactors for perhaps one-third of all enzymes and are essential for life (Holm et al. 1996). To facilitate the acquisition of essential metal ions from the environment, bacteria have evolved a suite of high affinity transport systems. Typically, these uptake systems are induced when a particular metal ion is limiting for growth. Conversely, when metal ions are in excess, bacteria respond by the induction of efflux pumps or sequestration proteins to mitigate the toxic effects of metal ion overload. The regulation of metal transport and storage proteins is tightly controlled, most often at the transcriptional level. Here, we present an overview of the major families of metalloregulatory proteins operative in bacteria, with an emphasis on those regulating the uptake of nutrient metal ions. We then draw some general conclusions regarding the biological roles of metalloregulators and their remarkable ability to discriminate against chemically similar metal ions in the complex milieu of the cytoplasm.

Metalloregulation refers to the regulation of gene expression in direct response to metal ion availability (O'Halloran 1993). Metalloregulation, as defined here, does not include systems that sense metal ion complexes, changes in metal ion valence state or coordination chemistry, or indirect effects of perturbed metal homeostasis. In contrast with the complex regulatory cascades that abound in eukaryotic cells, metalloregulation is often remarkably simple. For example, many genes involved in metal ion uptake are repressed by a protein that directly binds the cognate metal ion as a co-repressor (Fur /DtxR/ NikR families), thereby providing a direct "read" on the level of available metal ion in the cell. In other cases, metal ion resistance, efflux, or detoxification genes are induced when the cognate metal ion triggers derepression of a repressor (ArsR/SmtB family) or activates an activator protein (MerR family). Naturally, there are numerous variations on these common themes and, in some cases, proteins can function as both transcriptional repressors and activators in response to metal-ion binding.

Not all metalloregulation involves transcription factors. Regulation may also be exerted at the level of translation or mRNA stability. One of the best characterized examples of such a post-transcriptional control mechanism is the iron-responsive element (IRE)-binding protein in eukaryotes (Hentze et al. 2004). IRE-BP is an enzyme (aconitase) containing a 4Fe-4S cluster whose integrity is sensitive to iron availability. When iron is limiting, the IRE-BP is inactive as an enzyme, but binds with high affinity to RNA stem loop