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Zinc, Cadmium, and Lead Resistance and Homeostasis

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Abstract Metals such as zinc are required for life but can be toxic in excess. Other metals such as cadmium and lead have almost no known biological function, and can lead to cell damage and death even at low concentrations. Interestingly, all three metals are often recognized by the same gene regulators and membrane transporters. Therefore, an examination of the inherent chemical properties of these three metal ions is essential in understanding the basis of metal specificity displayed by target proteins responsible for metal homeostasis and resistance. The relationship between the chemical properties of these metals and similarities in structural responses they may elicit are discussed. The core elements regulating uptake, efflux, and sequestration of these metals are described and interpreted both biologically and chemically. Additional mechanisms aiding cell survival, such as precipitation of metal salts on the cell surface, are also mentioned.

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Introduction

Divalent cation "micronutrients" include cobalt, copper, zinc, manganese, nickel, and the macronutrient iron. Zinc is an essential metal for all organisms and has many biological roles. In contrast, a biological function for cadmium has only been suggested in a few instances, such as carbonic anhydrase from a marine diatom (Lane et al. 2005). Though lead can substitute zinc in carboxypeptidase resulting in a still functioning enzyme, it does not occur naturally as a required element in biology. Thus in most organisms, cadmium, lead, and mercury have no known beneficial role, making resistance mechanisms necessary. The mercury resistance mechanisms are described in the chapter by Silver and Hobman (this volume). Zinc levels have to be carefully regulated to ensure sufficient supply of zinc while avoiding toxicity. This process is often referred to as metal homeostasis as opposed to resistance, which only applies to metals with no biological role in a specific organism. However, in the course of this chapter it will become evident that often the transporters responsible for zinc uptake and efflux are also responsible for transport of other metal ions, such as Cd(II), Pb(II), and Hg(II).

All organisms need to maintain homeostasis of different essential metals, such as zinc, iron, manganese, and copper. In order to do this, mechanisms had to evolve to differentiate between closely related metals. The initial expectation was that regulatory proteins or transporters would have domains that allow them to bind only specific metals with high affinity. The basis for how metal specificity is achieved is only now beginning to be understood. In recent work, it has become clear that metal specificity is not just dependent on differences in metal binding affinity. Other important factors include the chemical properties of different metals, such as their coordination geometry preference and softness according to the Lewis acid–base concept. As we will later see, these distinct properties can lead to different conformational changes that are transmitted through a protein domain and affect function. The softness of a metal ion determines its affinity for thiolate ligands and is another factor that determines specificity (Lippard and Berg 1994). Size and charge of the metal ion are other important factors that play a role in determining specificity. Therefore, in order to understand how zinc homeostasis and resistance to cadmium and lead is achieved without negatively affecting the concentration of other essential metals, we have to review some basic inorganic principles and coordination preferences of these metals.