Metals in biology: past, present, and future

Barry P. Rosen

"For now we see through a glass, darkly; but then face to face: now I know in part; but then shall I know even as also I am known."
I Cor. 13:12.

Abstract

This chapter reviews basic concepts in metal biology and suggests a vision for the future of metals in medicine. Important developments in the field include the discovery of metallochaperones that prevent free metals from reeking havoc inside of cells. These intracellular metal ion carriers may work in conjunction with scaffold proteins or may deliver their cargo directly to metalloenzymes or metal transport proteins. Another area reviewed is the mechanism of metalloid uptake and detoxification. This leads into the future of metals in medicine, using examples from past and recent history.

1 Introduction

This chapter will review recent concepts and developments in the field of metal biology. With scientific knowledge accumulating at an accelerating pace, we have learned so much over the past decade that only the highlights can be presented here. Fortunately, the details of many of these concepts have been recounted in previous chapters, allowing this chapter to focus on a limited number of important developments.

2 Concepts and developments

2.1 Chaperones and scaffolds

Over the last decade, it has become clear that most transition and heavy metal ions do not exist as free ions in the cytosol but are instead sequestered by a variety of proteins variously called metal ion chaperones, scaffolds, or intracellular carriers (Field et al. 2002). There may be fine distinctions between these terms, but, for the purposes of this review, they will be considered in the group of metal chaperones.

Topics in Current Genetics, Vol. 14
M.J. Tamás, E. Martinoia (Eds.): Molecular Biology of Metal Homeostasis and Detoxification
DOI 10.1007/4735_94 / Published online: 26 July 2005

2.1.1 Copper chaperones

The biology and chemistry of these metal chaperones have been described in detail in Chapters 2 and 5. The first copper chaperone, *Saccharomyces cerevisiae* Atx1p (for antioxidant protein), was identified nearly a decade ago (Culotta et al. 1995). Although the 73-residue Atx1p was originally identified as a suppressor of SOD1 (superoxide dismutase) mutants, its physiological role is as an intracellular Cu(I) chaperone for Ccc2p, a golgi-related Cu(I)-translocating ATPase. Ccc2p delivers copper to the multicopper oxidase Fet3p, which is involved in high affinity iron uptake (Lin et al. 1997). As a result, mutations in Atx1p have an iron deficiency phenotype that can be rescued by increased medium copper. Similarly, its human homologue ATOX1 (HAH1) is a chaperone for the Menkes protein (ATP7A), which is an intestinal copper uptake pump, and for the Wilson protein (ATP7B), which is a liver copper pump for extrusion of excess copper into bile.

A second copper chaperone, the 69-residue yeast protein Cox17p (63-residue COX17 in humans) was identified as the copper delivery protein for mitochondrial cytochrome oxidase (Glerum et al. 1996). A third copper chaperone for superoxide dismutase was subsequently identified as the *LYS7* gene product, the 249-residue Ccs1p (Culotta et al. 1997). The *lys7Δ* strain cannot insert copper into SOD, but otherwise the phenotype is relatively mild, with a requirement for lysine and methionine during aerobic growth. Thus, the copper chaperone is not essential for aerobic growth of yeast. In humans, genetic defects in SOD result in some forms of familial amyotrophic lateral sclerosis (ALS), so the physiological role of the mammalian homologue, CCS, is of considerable interest. A mouse knockout is more sensitive to paraquat and has reduced levels of active SOD (Wong et al. 2000), but the involvement of CCS in ALS is unclear and controversial.

One concept that comes out of these studies is that copper chaperones are ubiquitous, but another concept is that they are not essential for growth, especially for unicellular organisms. In higher organisms such as humans, their biological roles may become apparent during development or later in life. A third concept, and perhaps the most important, is the physical complementarity between the copper chaperones and their partner proteins. This is best illustrated by the interaction of Ccs1p and Sod1p. The structures of Ccs1p and the interacting domain of Sod1p are so similar that they interact with each other as if they were two subunits of a homodimer (Lamb et al. 1999). Atx1p is likewise a structural homologue of the N-terminal metal binding domain of its partner, the Ccc2p copper pump (Rosenzweig et al. 1999). This metal binding domain is widespread and has evolved the ability to bind other metals such as mercury and nickel, as described below.

2.1.2 MerP and MerA, mercury binding proteins

Mercury resistance (*mer*) operons are widespread (Barkay et al. 2003). MerP is a 72-residue periplasmic protein of uncertain function. The structure of MerP has been determined and has the βαββαβ fold characteristic of copper chaperones but binds Hg(II) rather than Cu(I) (Serre et al. 2004). Central to resistance is MerA, an