Zinc in yeast: mechanisms involved in homeostasis

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Abstract

The first eukaryotic zinc uptake transporter was discovered in the yeast, *Saccharomyces cerevisiae*. Since then, this organism has been an invaluable tool for the discovery of genes involved in zinc homeostasis. Genomic and proteomic studies have revealed an abundance of Zn^{2+}-regulated genes and Zn^{2+}-binding proteins. The large number of essential functions of Zn^{2+} necessitates a complex homeostatic mechanism involving the transport and storage of Zn^{2+} as well as its allocation to essential sites. Studies in yeast have elucidated the opposing roles of the ZIP and CDF Zn^{2+} transporter families and uncovered additional transport systems. The transcription factor, Zap1p, functions as the central Zn^{2+} sensor by regulating genes involved in Zn^{2+} uptake and adaptation to Zn^{2+}-deficiency. The investigation of the role of Zn^{2+} in the regulation of signaling pathways is becoming a primary research direction, and yeast will undoubtedly play a major role in any discoveries in this field as well.

1 Introduction

Cellular organisms are constrained by an absolute requirement for ionic Zn^{2+} (Vallee and Falchuk 1993). The relatively high bioavailability and useful chemical properties of Zn^{2+} allow its extensive use in three general biochemical capacities. Zn^{2+} is primarily used as a structural component of proteins, serving to stabilize a wide variety of architectures. The Lewis acidity of Zn^{2+} also makes it an excellent cofactor for catalysis and many enzymes require Zn^{2+} for full catalytic potential. Finally, Zn^{2+}, like Ca^{2+}, is highly labile and capable of forming transient, yet robust, associations with proteins (Bertini and Luchinat 1994). It is this property that allows zinc to function as a signaling molecule.

The versatility and abundance of Zn^{2+} have made it indispensable. As a consequence, cells must maintain optimal levels of cellular Zn^{2+}, regardless of supply, via a complex process known as homeostasis (Eide 2003). Under conditions of low nutritional Zn^{2+}, cells must ensure that adequate quantities are acquired from the environment. This entails the activation of specific transporters that scavenge Zn^{2+} from the surroundings and transport it across the plasma membrane. Furthermore, the various intracellular uses of Zn^{2+} must be prioritized so that growth can be optimized during periods of limitation. When cells encounter nutritional

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can be optimized during periods of limitation. When cells encounter nutritional surplus, one general strategy is to exclude excess Zn^{2+} from the interior of the cell by downregulating the plasma membrane transporters. Another strategy involves the continuous acquisition of Zn^{2+} so that it can be stockpiled for leaner times. In the latter case, cells require both a means of storing large quantities of zinc in a manner that does not upset homeostasis and a controlled way to release these stores at the appropriate times.

A proper understanding of Zn^{2+} homeostasis requires the identification of all the players in the game. It is, therefore, beneficial to study an organism for which the most information is known. The yeast, *Saccharomyces cerevisiae*, has proven to be an invaluable model system for this purpose. The genome sequence is complete and decades of research have allowed an in-depth analysis of almost every biochemical system. More importantly, the proteins involved in metal metabolism are remarkably conserved from *S. cerevisiae* to humans. This review will summarize what is known about zinc metabolism in *S. cerevisiae* and the mechanism by which homeostasis is sustained. Appropriate consideration will be given to the discussion of zinc metabolism in other yeast species.

2 Zap1p: The zinc sensor

Any discussion of Zn^{2+} in *S. cerevisiae* should begin with Zap1p (Zinc-regulated Activator Protein). Zap1p is an 880 amino acid transcription factor that functions as the central sensor and regulator of zinc homeostasis (Bird et al. 2003). In response to Zn^{2+}-deficiency, Zap1p becomes active and binds to Zinc Response Elements (ZREs) in the promoters of genes involved in Zn^{2+} uptake. The ZRE is an 11 base pair palindrome that has the consensus sequence ACCTTNAAGGT. Zap1p is comprised of a C-terminal DNA binding domain and two distinct activation domains (AD1 and AD2) that recruit RNA polymerase II to the promoter (Fig. 1). Close homologues of Zap1p are found in fungi alone and only the DNA binding domain is fully conserved. [PSI-BLAST and homology searches were performed on the NCBI website (Altschul et al. 1997) or the Saccharomyces Genome Database (Christie et al. 2004).]

2.1 Regulation of Zap1p activity

Zap1p is constitutively located in the nucleus; therefore, its translocation from the cytosol to the nucleus does not seem to be a primary determinant of its transcriptional activity. In addition, there is no evidence to suggest that Zap1p activity is regulated by any type of posttranslational modification. The current state of understanding is that nuclear localized Zap1p generally binds to ZREs during Zn^{2+}-deficiency, but not during Zn^{2+}-repletion and that a direct interaction with Zn^{2+} is responsible for this phenomenon (Bird et al. 2000).