Available online at www.sciencedirect.com

ScienceDirect

Journal of Nutritional Biochemistry xx (2015) xxx–xxx

Journal of Nutritional Biochemistry

Cellular sensing and transport of metal ions: implications in micronutrient homeostasis

Amanda J. Bird*

Department of Human Sciences, The Ohio State University, Columbus, OH, 43210
Department of Molecular Genetics, The Ohio State University, Columbus, OH, 43210
Center for RNA Biology, The Ohio State University, Columbus, OH, 43210

Received 7 May 2015; received in revised form 23 July 2015; accepted 4 August 2015

Abstract

Micronutrients include the transition metal ions zinc, copper and iron. These metals are essential for life as they serve as cofactors for many different proteins. On the other hand, they can also be toxic to cell growth when in excess. As a consequence, all organisms require mechanisms to tightly regulate the levels of these metal ions. In eukaryotes, one of the primary ways in which metal levels are regulated is through changes in expression of genes required for metal uptake, compartmentalization, storage and export. By tightly regulating the expression of these genes, each organism is able to balance metal levels despite fluctuations in the diet or extracellular environment. The goal of this review is to provide an overview of how gene expression can be controlled at a transcriptional, posttranscriptional and posttranslational level in response to metal ions in lower and higher eukaryotes. Specifically, I review what is known about how these metalloregulatory factors sense fluctuations in metal ion levels and how changes in gene expression maintain nutrient homeostasis.

Keywords: Zinc; Iron; Copper; Nutrient sensing; Gene expression

1. Introduction

A variety of transition metals including iron, copper, manganese molybdenum, cobalt, and zinc are essential for life [1,2]. When bound to protein, these metals facilitate catalytic reactions and stabilize structural domains. Metals also have more specialized functions, including being intracellular secondary messengers and modulators of synaptic transmissions [3–6]. Although required for life, redox active metals such as iron and copper can catalyze the production of toxic free radicals [7]. Metal overload can also result in the wrong metal ion being incorporated into metalloproteins, which in turn can disrupt their function [1,8–10]. To ensure that there are sufficient but nontoxic levels of metal ions for cellular metabolism, all organisms require mechanisms to tightly control metal levels and availability.

To be able to maintain an optimal level of a metal requires that an organism is able to sense and adapt to fluctuating metal levels. The ability of an organism to sense metal ions is largely dependent upon a class of metal-regulated factors that control the expression of genes involved in metal ion transport or storage. In eukaryotes, these types of factors control gene expression by regulating transcription, alternative splicing, translation, mRNA stability, protein activity or protein stability (Fig. 1). The goal of this review is to provide an overview of the mechanisms by which gene expression can be controlled at a transcriptional, posttranscriptional and posttranslational level in response to alterations in metal levels and to discuss how changes in gene expression can allow cell to control metal ion distribution, levels and expenditure.

2. Transcriptional control of metal homeostasis

Transcription is the basic process by which an RNA copy is made from a gene sequence. Regulating transcription in response to metal deficiency or overload allows dynamic increases or decreases in gene expression. Additional advantages of transcriptional control include that a single transcription factor can regulate the expression of multiple genes allowing for the coordinate control of gene expression, while multiple regulatory factors can regulate the transcription of a single gene allowing for combinatorial control in response to different physiological conditions [11]. Although transcriptional regulatory mechanisms can affect the rates of transcriptional elongation and termination, the majority of studies in eukaryotic systems have so far

Abbreviations: BMP, bone morphogenetic protein; CDF, cation diffusion facilitator; COMMD, COMM domain-containing protein; dsRNA, double stranded RNA; FRET, fluorescence resonance energy transfer; HAMP, hepcidin antimicrobial peptide; HFE, high iron (Fe); MMS, methyl methane sulfonate; siRNA, small interfering RNA; TfR, transferrin receptor; ZIP, Zrt1 Irt1-like protein.

* Department of Human Sciences and Department of Molecular Genetics, The Ohio State University, 1787 Neil Avenue, Columbus, OH, 43210. Tel.: +1 614 247 1559; fax: +1 614 292 8880.

E-mail address: bird.96@osu.edu.

http://dx.doi.org/10.1016/j.jnutbio.2015.08.002
0955-2863/

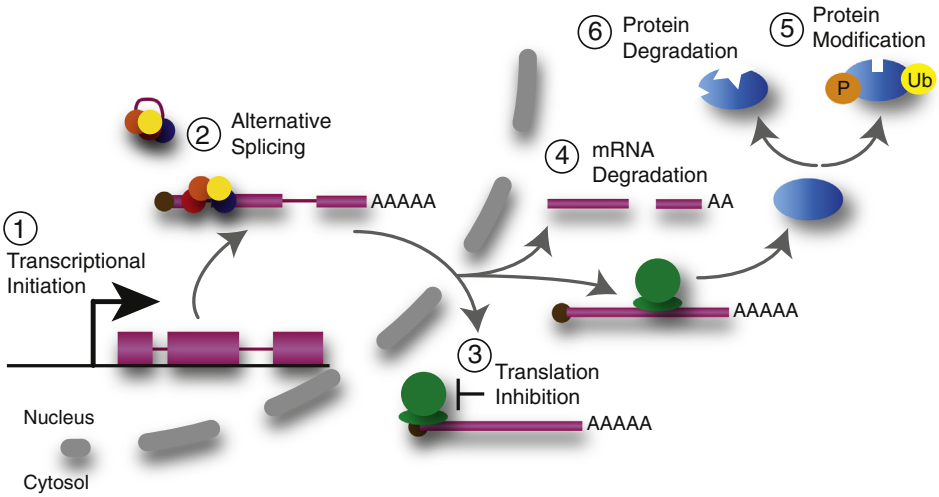

Fig. 1. Metal-dependent changes in gene expression in eukaryotes. In eukaryotes, metalloregulatory factors have been identified that control transcriptional initiation (1), alternative splicing (2), translation (3), mRNA stability (4), protein modifications (5) and protein stability (6).

focused on the regulation of transcriptional initiation by metal-responsive transcription factors.

2.1. Lessons from genetic model systems

Much of what we know about metal-dependent changes in transcription comes from studies of the unicellular organisms such as yeast and green algae. In these single-celled organisms, genes that are critical to metal ion homeostasis are robustly regulated at a transcriptional level in response to metal availability [9,12–14]. The large transcriptional changes that are observed in these organisms have greatly facilitated the identification of genes important for metal homeostasis and have expedited further studies to determine how changes in the levels of these genes can affect metal uptake, storage, usage and compartmentalization.

In lower eukaryotes, genes required for metal ion transport or metal ion storage are often tightly regulated at a transcriptional level (Fig. 2). In general, as intracellular metal levels begin to drop below an 'optimal' concentration, most unicellular organisms increase the transcription of genes required for metal uptake and/or its release from intracellular stores. In contrast, when metal levels become too high, genes required for metal storage or export from the cytosol are transcribed. Through these coordinated changes in transcription, cells are able to continuously adjust cytosolic metal levels to maintain a concentration that is sufficient for normal cellular metabolism but not inhibitory to cell growth.

Many unicellular organisms naturally live in 'feast or famine' environments. Studies of these organisms have therefore provided insight into how changes in gene expression can help cells to adapt and survive longer periods of metal ion starvation or exposure. Genes that are induced under these conditions include those that protect cells against the toxic conditions that may arise from metal excess or deficiency [15,16]. Transcriptional changes in response to metals can also remodel core metabolic pathways or metal-requiring processes to conserve or use metals. As an example, alcohol dehydrogenase 1 (Adh1) is one of the most abundant zinc-binding proteins in yeast. In both *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*, transcriptional mechanisms are present which reduce *adh1* gene

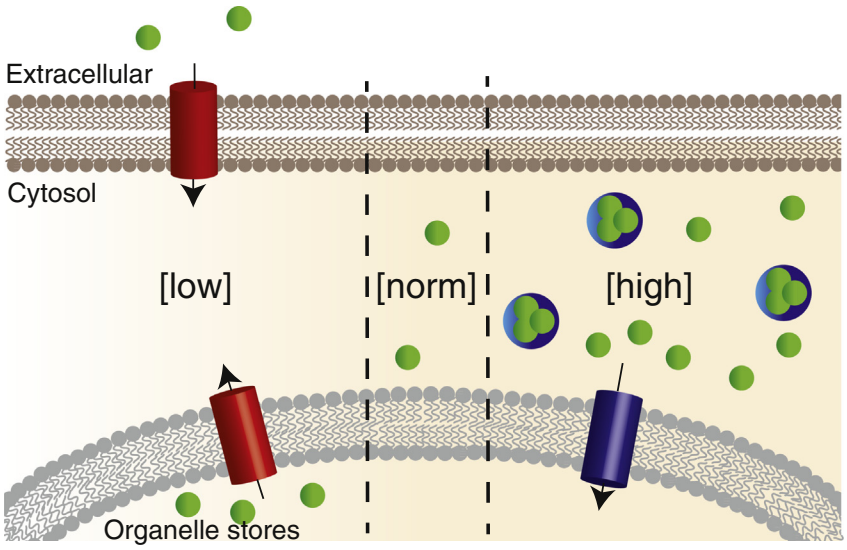

Fig. 2. Changes in the expression of genes encoding metal transporters affect intracellular metal ion levels. Metal transporters are shown as red and blue cylinders. Metal storage proteins and metal ions are represented by blue and green circles, respectively.