Family matters: gene regulation by metal-dependent transcription factors

Harm van Bakel and Cisca Wijmenga

Abstract

All organisms require trace amounts of metal ions, such as copper, iron, and zinc, since they form an essential component of a number of enzymes. In the past few years many metal-responsive transcriptional regulators have been identified in both prokaryotes and eukaryotes, which can be grouped in distinct families, based on their evolutionary and structural relationships. By regulating systems involved in metal uptake as well as metal efflux and sequestering, these transcription factors help to maintain a delicate balance between necessity and toxicity. Despite the structural similarities within the transcription factor families, individual members can have an affinity for different, and sometimes multiple, metal substrates. The recent availability of crystal structures for key members has led to a detailed understanding of the origins of metal specificity and the mechanisms of transcriptional activation for most of these transcription factor families.

1 Introduction

A number of metals are essential for life because they function as redox-active cofactors in enzymes (Table 1). However, the same properties that make these metals useful to cells can also lead to toxicity, since they can participate in reactions that generate highly reactive free radicals. In addition, some metal ions do not have a known physiological role and are toxic to cells at all concentrations; these include cadmium, lead, mercury, aluminium, and arsenic. Specialized systems have therefore evolved in prokaryotes and eukaryotes to ensure delivery of essential metals to their target sites, while minimizing exposure of sensitive cellular components to metal toxicity. These systems include transporters to import metal ions from the environment and protein chaperones to guide them to their destination. When metal-ion concentrations reach toxic levels, organisms can express a multitude of specialized detoxification systems. These include metal-specific efflux transporters; cytoplasmic or periplasmic carrier proteins and metal-sequestering systems such as glutathione, phytochelatins, and metallothioneins that bind multiple metal ions. An alternative mechanism for protection against metal toxicity in some prokaryotes uses reductases to convert toxic mercury ions to the metallic form, which subsequently leave the cell by diffusion (Schiering et al. 1991).

Topics in Current Genetics, Vol. 14
M.J. Tamás, E. Martinoia (Eds.): Molecular Biology of Metal Homeostasis and Detoxification
DOI 10.1007/4735_104 / Published online: 15 September 2005

Table 1. Essential metal requirements.

Element	Symbol	Described in	Examples of use
Copper	Cu	Archaea	Respiratory chain
		Bacteria	Iron metabolism; multicopper oxidases
		Eukaryotes	Cu/Zn Superoxide dismutase
Iron	Fe	Archaea	Respiratory chain
		Bacteria	Iron-sulfur cluster proteins
		Eukaryotes	Fe Superoxide dismutase
			Hemoglobin
			Methane monooxygenase
Zinc	Zn	Archaea	Zinc finger proteins
		Bacteria	Zinc hydrolases
		Eukaryotes	Cu/Zn Superoxide dismutase
			Alcolhol dehydrogenases
			Angiotensin-converting enzyme
Manganese	Mn	Bacteria	Serine-Tyrosine-Threonine phosphatases
		Eukaryotes	Mg Superoxide dismutase
Chromium	Cr	Eukaryotes (Human)	Insulin metabolism: chromodulin
Molybdenum	Mb	Bacteria	Sulfite oxidases
		Eukaryotes	Aldehyde oxidases
			Xantine dehydrogynases
			Bacterial nitrogenases
Selenium	Se	Eukaryotes	Glutathione peroxidase
			Thioredoxin reductase
			Formate dehydrogenase
			Selenophosphate synthase
Vanadium	V	Bacteria	Bacterial nitrogenases
		Fungi	Chloroperoxidases
Cobalt	Co	Bacteria	Vitamin B12
		Fungi	Electron carriers
			Hydrolysis enzymes
Nickel	Ni	Bacteria	Ureases
			NiFe hydrogenases
			CO dehydrogenases
			Acetyl-CoA decarboxylase/synthase
			methyl coenzyme M reductase
			Glyoxalases
			aci-reductone dioxygenase
			Ni-dependent superoxide dismutases
			Methylene diurease
Boron	Bo	Bacteria	Cell wall
		Eukaryotes	AI-2 cell communication

Homeostatic balance of metal metabolism is regulated at the protein level, for example, through rapid internalization and degradation of uptake proteins and re-localization of exporters to the plasma membrane upon metal exposure (Petris et al. 1996, 2003; Kim et al. 2004), and at the transcriptional level by controlling expression of genes involved in metal uptake or detoxification. Post-transcriptional