Mechanisms of toxic metal tolerance in yeast

Markus J. Tamás, Jean Labarre, Michel B. Toledano, and Robert Wysocki

Abstract

Toxic metals are an integral part of our environment and all organisms possess systems to evade toxicity and acquire tolerance. Studies in yeast have revealed a number of important tolerance systems encompassing metal uptake and export pathways, metal binding and sequestration systems as well as the regulatory mechanisms that the cell utilizes to control these systems. The study of the physiological, molecular, and genetic details of the function of these systems has significantly contributed to our understanding of toxic metal tolerance acquisition. This review will focus on tolerance mechanisms to toxic metals including cadmium, arsenic, antimony, mercury, and selenium in the model eukaryote *Saccharomyces cerevisiae* (bakers' yeast) and other fungi.

1 Introduction

All living organisms are exposed to metals through natural geological as well as anthropogenic sources. Many metals serve as essential nutrients, while others are either toxic or harmful in excessive quantities. Deposition of nonessential toxic metals in the environment has dramatically increased during the last century. Cadmium, arsenic, mercury, and lead are extensively distributed in nature and can reach relatively high concentrations in some locations. These metals are highly toxic and pose a considerable threat to the environment and to human health. Metal intoxication often occurs through occupational exposure or through ingestion of contaminated food and water. In fact, organisms have been exposed to toxic metals since the origin of life and have therefore developed various tolerance mechanisms early during evolution. Currently, metal pollution leads to the spread of plasmids containing resistance genes among prokaryota.

Metal tolerance mechanisms in bacteria are relatively well-described where plasmids containing specific operons account for this phenomenon (Silver 1998, 2003; Nies 1999; Rosen 2002). Similarly, there has been a tremendous advance in the understanding of nutrient metal homeostasis and detoxification in many organisms. These mechanisms are extensively reviewed in other chapters in this volume and will not be considered here. However, the mechanisms of tolerance to various nonessential metals in eukaryotic organisms have remained poorly explored. The increasing use of toxic metals in medical therapy, *e.g.*, the use of arsenic for the treatment of certain forms of cancer and of diseases caused by protozoan parasites,

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as well as the need to develop systems for phytoremediation of contaminated sites, has spurred research in this field and led to a significant progress in understanding metal responses and tolerance acquisition mechanisms in eukaryotic organisms (Tamás and Wysocki 2001; Alkorta et al. 2004; Desoize 2004; Macek et al. 2004). In particular, the use of the yeast *Saccharomyces cerevisiae* (bakers' yeast) as a eukaryotic model organism has proved very useful to unravel the molecular mechanism of many cellular metal tolerance systems. Here, we review the current knowledge about tolerance mechanisms to cadmium, arsenic, antimony, mercury, and selenium in *S. cerevisiae*.

1.1 Metal abundance, distribution, and usage

Arsenic is a semimetal or metalloid and as such, it has intermediate properties between those of metals and nonmetals. Arsenic compounds, in the form of sulphides and oxides as well as in the form of calcium, sodium, and potassium salts, are naturally occurring and ubiquitous in the environment. Arsenic contamination of drinking water is a serious problem worldwide: Bangladesh, West Bengal, Vietnam, and Taiwan are the most affected areas where global epidemic of arsenic poisoning is observed (Frisbie et al. 2002; Nordstrom 2002). The sources of arsenic in underground water supplies in these areas are geologically deposited sediments. Elevated concentrations of arsenic in soil and surface water are also associated with the use of arsenic compounds as pesticides, fungicides, insecticides, and wood preservatives (Mukhopadhyay and Rosen 2002). Nonferrous ore smelting, semiconductor, and glass manufacturing as well as power generation by the burning of arsenic-contaminated coal further contributes to arsenic pollution (Hei and Filipic 2004).

Arsenic has a long and well-documented history of usage in medicine since ancient times (Waxman and Anderson 2001; Ravandi 2004). In the 18th century, potassium arsenite in the form of Fowler's solution was used to treat a number of ailments. The use of arsenic in treating leukaemia was first described in the 19th century and its efficacy was confirmed in the 1930s (Evens et al. 2004). At the beginning of the 20th century, Paul Ehrlich and his co-worker Sahachiro Hata developed the arsenic-containing 'compound 606' (Salvarsan) and introduced this drug for the treatment of syphilis and trypanosomiasis (Sorgel 2004). This was the first example of modern chemotherapy; in fact, Paul Ehrlich coined the term 'chemotherapy'. However, arsenic was often overdosed producing severe side effects. With the introduction of penicillin and other less toxic drugs, arsenic was no longer in use. Recently, arsenic trioxide was re-introduced in the treatment of acute promyelocytic leukaemia (APL) and multiple myeloma (Zhu et al. 2002; Ravandi 2004). Arsenic trioxide exerts its effect by inducing differentiation of leukaemia cells (by promoting degradation of the leukemogenic PML-RARα fusion protein) and/or by inducing apoptosis (Hu et al. 2005).

The metalloid antimony is related to arsenic. Antimony is not abundant but is found in more than 100 mineral species. Antimony, in the form of sulphide called stibnite, has been known since Biblical times as a medicine and as a cos-