Molecular mechanisms of copper homeostasis in yeast

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Abstract

Copper ions play critical roles as electron transfer intermediates in various redox reactions. The yeast *Saccharomyces cerevisiae* has served as a valuable model to study copper metabolism in eukaryotic cells. The systems for copper homeostasis; including the uptake, cytoplasmic trafficking, and metabolism in intracellular organelles, detoxification, and regulation of these systems have been characterized. Most of the molecular components for copper metabolism identified in yeast are functionally and structurally conserved in mammals. These findings have underscored the importance of evolving delicate mechanisms to utilize copper. Studies on copper metabolism in yeast certainly have opened up interesting and important research avenues that have shed light on the molecular details of copper metabolism and the physiological roles of copper.

1 Introduction

Copper (Cu) is a metal-ion abundantly found in the earth's crust. It easily accepts and donates electrons through redox reactions. Aerobic organisms have taken advantage of the chemical properties of Cu by incorporating it in various biological processes. Thus, organisms have developed mechanisms for acquiring Cu from the environment. Mechanisms for homeostatic Cu metabolism have been uncovered in prokaryotes, fungi, plants, and mammals. Among these organisms, the yeast *Saccharomyces cerevisiae* has served as a model organism to study Cu metabolism in eukaryotes. A number of experimental tools are available to understand the molecular mechanisms of Cu homeostasis. The sequencing of the yeast genome has provided an extremely valuable source of information. Deletion or expression control of yeast genes is much easier than in higher eukaryotes. Growth environments of yeast can be easily manipulated. Furthermore, most of the mechanisms and components in physiological and biochemical processes identified in yeast are conserved in higher eukaryotes.

Cu is required for at least three biological processes in yeast, (i) mitochondrial oxidative phosphorylation, (ii) superoxide anion detoxification, and (iii) iron metabolism. In the mitochondria cytochrome c oxidase subunits 1 and 2 contain Cu as an electron transport intermediate in oxidative phosphorylation (Tsukihara et al. 1995; Iwata et al. 1995). Thus, Cu is an essential micronutrient for yeast under

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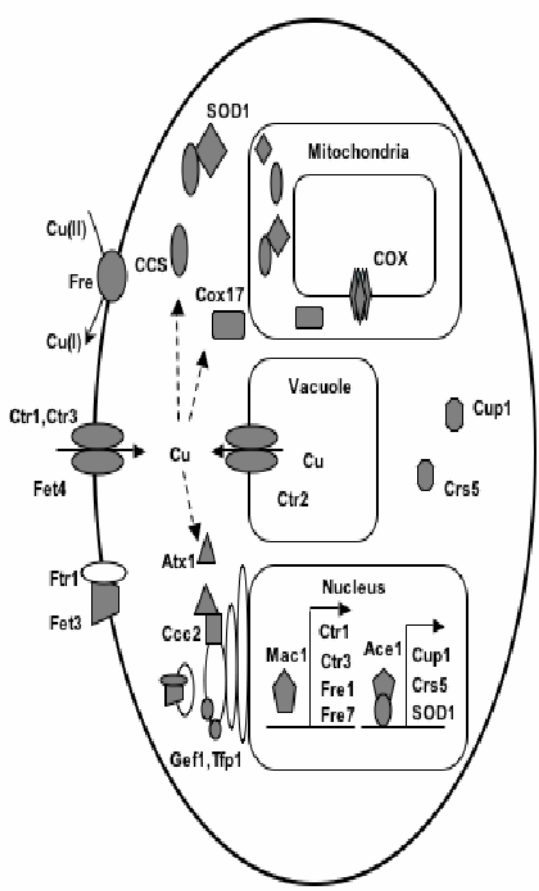

Fig. 1. Copper (Cu) homeostasis in yeast *S. cerevisiae.* Molecular mechanisms of Cu transport, distribution and detoxification have been characterized in yeast. Cu is reduced by cell surface reductases (Fre) prior to uptake by Ctr1 and Ctr3 Cu transporters. Fet4 serves as a low affinity Cu transporter. Ctr2 transports Cu form the vacuole. Cytosolic Cu chaperones Atx1, Cox17 and CCS deliver Cu to the secretory pathway, mitochondria and Cu, Zn superoxide dismutase (SOD1), respectively. At the post-Golgi vesicles Ccc2 accepts Cu from Atx1, followed by incorporation of Cu to Fet3, a multicopper ferroxidase. Gef1 and Tfp1 facilitate the transport and incorporation of Cu into Fet3. Fet3 forms a complex with the iron permease Ftr1 and both proteins are responsible for high affinity iron uptake at the plasma membrane. In mitochondria Cox17 plays essential roles in Cu incorporation into cytochrome c oxidase (COX) subunit 1 (Cox1) and subunit 2 (Cox2). CCS delivers Cu specifically to SOD1 in the cytosol. SOD1 and CCS also localize at the mitochondrial intermembrane space. Two metallothioneins, Cup1 and Crs5, are critical for Cu detoxification. Mac1 and Ace1, Cu-responsive transcription factors, regulate expression of genes involved in Cu metabolism. Mac1 and Ace1 directly bind to the *cis*-acting element of their target genes.