

VACUOLAR COMPARTMENTATION PROTECTS *SACCHAROMYCES CEREVISIAE* AGAINST CADMIUM TOXICITY AND MUTAGENESIS

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Cadmium (CD) is one of the most toxic and mutagenic heavy metal, classified by IARC (International Agency for Research on Cancer) as human carcinogen. Its toxic effect seems to be related to an indirect oxidative stress that involves glutathione (GSH) mobilization. Using *Saccharomyces cerevisiae* as experimental model, we have investigated the mechanisms of Cd tolerance in eukaryotes. By measuring the level of intracellular oxidation, lipid peroxidation, and protein oxidation, we have identified the molecular markers of cell damage responsible for Cd sensitivity. We have used concentrations of metal similar to those found in the environment and accumulated in the human body; in yeast, these levels resulted in death, mutability and induction of apoptosis. According to the literature, one general mechanism for Cd detoxification is the chelation of the metal by GSH. In mammals, GSH complex is pumped out of the cell by the multidrug resistance-associated protein, MRP, while in *S. cerevisiae* GSH-Cd complex is transported to vacuole through Ycf1, homologous to MRP. According to ours results, vacuolar transport of Cd-GSH complex is necessary to allow Cd tolerance, probably, because once inside the vacuole, the complex can be decomposed, initially by gamma-glutamyl transferase and thereafter by Lap4, a dipeptidase, restoring the amino acids in the cytoplasm, which can be used to the synthesis *denovo* of GSH. Thus, the cytoplasmic GSH is recycled for the protection against metals, xenobiotics and oxidative stress. The presence of Cd-GSH complex in the cytoplasm increases the mutation rate, indicating that the compartmentation of Cd in the vacuole is crucial and determines the ability of the cells to survive metal toxicity.

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