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Inactivation of Homocitrate Synthase Causes Lysine Auxotrophy in CuZnSOD-deficient Fission Yeast *Schizosaccharomyces pombe*

Eun-Soo Kwon* and Jung-Hye Roe

Laboratory of Molecular Microbiology, School of Biological Sciences and Institute of Microbiology, Seoul National University

The fission yeast *Schizosaccharomyces pombe* lacking Cu, Zn-containing superoxide dismutase (CuZnSOD) is auxotrophic for lysine and cysteine on aerobic plate culture. A multi-copy suppressor gene (*phx1*$^+$) that resumes growth of CuZnSOD-deficient cell on minimal medium was isolated. It encodes a putative DNA-binding protein with a conserved homeobox domain. Overproduction of Phx1 increased synthesis of several proteins, and one of those turned out to be homocitrate synthase encoded by the *lys4*$^+$ gene in *S. pombe*, as judged by mass spectrometric analysis. Consistent with this observation, overexpression of the *lys4*$^+$ gene increased homocitrate synthase enzyme activity and was sufficient to suppress the lysine requirement of CuZnSOD-deficient cell. Estimation of enzyme activity and Western analysis revealed that the activity and the amount of homocitrate synthase were severely reduced upon depletion of CuZnSOD. These results lead us to propose that homocitrate synthase, the first enzyme in α-aminoadipate-mediated pathway for lysine synthesis common in fungi and some bacteria, is a labile target of oxidative stress caused by CuZnSOD depletion, and its synthesis is positively regulated by a putative transcriptional regulator Phx1.