Thiol Metabolism and Redox Regulation of Cellular Functions
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Reduction of the Endoplasmic Reticulum Accompanies the Oxidative Damage of Diabetes Mellitus

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1. Thiol Metabolism in the Endoplasmic Reticulum

The average redox potential of the endoplasmic reticulum (ER) is about –160 mV, but theoretical calculations and some experimental results suggest that redox potential gradients and redox potential inhomogenities are typical of the subcompartment. The ER redox potential was thought to be mantained mostly by the glutathione/glutathione-disulfide redox buffer (GSH:GSSG = 1 trough 3:1), and can be described by the thiol/disulfide ratio [1]. But there are many other systems, which are able to influence the thiol metabolism. The *in vitro* mechanism to alter the redox state includes sulfhydryl oxidase, a NADPH-dependent oxigenase and the vitamin-K redox cycle [2]. The direct role of hem, ubiquinone, Fe-S clusters and molecular oxygene was excluded recently in yeast models [3]. The possible involvement of flavin adenine dinucleotide (FAD) in the electron transport was also documented on yeast, where the addition of FAD accelerated the disulfide bridge formation by the ER-resident enzyme, ERO1p [3]. The yeast lumenal ER protein, ERV2 was also described as a flavoenzyme, and is able to accelerate O_2-dependent disulfide bridge formation [4]. Besides flavin adenine dinucleotide, increasing number of evidence supports the involvement of an other, well known redox system on ER redox state. Ascorbate/dehydroascorbate concentration is in milimolar range in the ER lumen, and asorbate is a very important cofactor of the enzymes catalyzing prolyl- and lysyl-hydroxylation. The characteristics of their transport was well described by G. Bánhegyi and co-workers [5]. Cytoplasmic ascorbic acid is first oxidized and dehydroascorbic acid is transported to the lumen by facilitated diffusion. Inside, the increasing concentration of oxidized form can help to mantain the transitional redox state, and take part in the GSH and protein thiol oxidation [6]. Moreover, protein disulfide isomerase itself has dehydroascorbate reductase activity [7]. The membrane-bound antioxidant agent, tocopherol was also mentioned as a possible contributor of the electron transport by ascorbic acid [8]. The importance of the glutathione/glutathione-disulfide redox buffer was recently described. The estimated redox potential of the ER (–160 mV) correlates with the current GSH/GSSG ratio, and its total concentration (1 to 2 mM) is high enough to affect redox environment and protein redox states [9]. But the processes setting the balance between GSH and GSSG have not yet been clearly identified. Glutathione synthetase, responsible for the *de novo* GSH generation, is located only in the cytoplasm, so GSH must enter to the ER lumen through transporters. A much faster GSSG transport was hypothesized to sustain the oxidative environment, but recent data are quite controversial