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Possible Links between Metabolism and Oxidative Protein Folding. Consequences of a Diabetes Study

Gábor NARDAI, Eszter PAPP, Tamás KORCSMÁROS, Krisztián STADLER*, Judit JAKUS* and Péter CSERMELY
Department of Medical Chemistry, Semmelweis University, P.O. Box 260, H-1444 Budapest 8, Hungary
[2]Chemical Research Center of the Hungarian Academy of Sciences, P.O. Box 17, H-1525 Budapest, Hungary

Abstract. The endoplasmic reticulum is a preferred compartment for several cellular processes (e.g.: glucose-6-phosphatase system, triglyceride and cholesterol synthesis, different steps of drug metabolism), its metabolic status and regulatory mechanisms are well characterized both in health and in several metabolic disorders. However, the regulation of oxidative protein folding, the chaperone-catalyzed formation and isomerization of protein disulfide bridges is rather poorly characterized. The influence of different metabolic pathways in disulfide bond formation and their changes under metabolic disorders are practically unknown in mammals. Recent studies uncovered a few connections between intermediate metabolism and oxidative protein folding. Here we summarize these data and our recent findings on changes of oxidative protein folding in diabetes. Our results suggest a possible role of small molecular redox systems in the regulation of oxidative protein folding, and can help us to map the metabolic links of the folding process.

Introduction

Subcellular compartmentalization was undoubtedly one of the major steps of evolution. Separation, besides many other consequences (e.g. enhanced effectiveness of enzyme reactions), helped the development of the more sophisticated regulation characteristic to complex organisms. Beyond the intra-compartmental regulation, the communication between the lumen of the compartment and the cytoplasm is also under tight control. In recent years a growing number of studies proved that there are direct structural and functional connections between the different subcellular compartments (e.g. between mitochondria and the endoplasmic reticulum (ER), phagosomes and the ER, as well as the nuclear membrane and the ER; see refs. 1-3). These interactions can also affect the different intra-compartmental pathways resulting in a more combined regulatory network of the metabolism and cellular homeostasis.

Taken into consideration the above complexity of regulatory pathways, it is not surprising that the regulation and the metabolic integration of some ER-specific processes are ill defined. One of them is protein disulfide bond formation, which is a redox process and requires the contribution of several proteins and small molecules [4]. Disulfide bond formation is integrated to other metabolic pathways, but the precise manner of these regulatory links is not yet uncovered.