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Redox Regulation in Protein Folding and Chaperone Function

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1. Introduction: Protein Folding, Heat Shock Proteins, Molecular Chaperones

Chaperones are ubiquitous, highly conserved proteins, which utilize a cycle of ATP-driven conformational changes to refold their targets, and which probably played a major role in the molecular evolution of modern enzymes [1,2]. Environmental stress (a sudden change in the cellular environment, to which the cell is not prepared to respond, such as heat shock) leads to the expression of most chaperones, which therefore are called heat-shock, or stress proteins. Lacking a settled view about their action in the molecular level [3], chaperones are still best classified by their molecular weights (Table 1). Besides to promote the formation of the correct conformation of nascent or damaged proteins chaperones also assist in the formation of correct disulfide bridges offering the help protein disulfide isomerases (PDI-s) [4,5].

Higher levels of cellular organization also need a constant remodeling. Chaperones are obvious candidates to provide help in these processes. About twenty years ago based on high-voltage electron microscopy Keith A. Porter and co-workers suggested the existence of a cellular meshwork, called as "microtrabecular lattice" to organize cytoplasmic proteins and RNA-s [6]. Almost instantly a fierce debate arose considering the lattice as an artifact of the techniques used. However, as time passes more and more data provide indirect evidence for a high-order organization of the cytoplasm [7]. Chaperones are ideal candidates for being a major constituent of a cytoplasmic meshwork: they are highly abundant, form a loose and dynamic complex with all the elements of the cytoskeleton and each other, and also attach to a plethora of other proteins. Several lines of initial evidence shows that disruption of chaperone/protein complexes disturbs the organization of cytoplasmic traffic of several proteins, such as the steroid receptors, and accelerates cell lysis [8-10].

2. Redox Chaperones in the Endoplasmic Reticulum and in the Periplasm: Quality Control of Secreted Proteins

Secreted proteins have to prepared for the oxidative millieu of the extracellular space. A rapid oxidation would result in the formation of numerous incorrect disulfide bridges, which would lock the protein in a distorted conformation. Therefore folding of secreted/plasma membrane proteins is most probably accompanied by their *gradual* oxidation in the endoplasmic reticulum (ER). This would imply the existence of a redox gradient along the secretory