Editorial

The Biology of Molecular Chaperones — Very Complex Activities for Quite Simple Proteins

From a social perspective, the term chaperone refers to a person, usually a matron, who used to accompany young ladies in public and supervise young people at a social gathering to ensure proper behavior. By analogy, proteins that assist others in their proper folding and biological functions are also referred to as chaperones. From the historical perspective, the first recorded use of the term *chaperone* for a biological phenomenon was in 1976 for α-taipoxin associated proteins [1]. Taipoxin is a potent presynaptic toxin isolated from the venom of an Australian snake named taipan. It is a ternary complex whose subunits (α, β and γ) must be properly assembled to potentiate the intrinsic neurotoxic action of the α subunit. In that study, it was postulated that the function of β and γ subunits is to sharpening the specificity of action and increasing the stability of the toxic α subunit, like if they were *chaperones* able to minimize the functional distraction and degradation of the active component.

A couple of years later, the term '*molecular chaperone*' was coined to make reference to the ability of nucleoplasmin to prevent the aggregation of histones with DNA during the assembly of nucleosomes [2]. After this, the name was extended to those proteins that mediate the post-translational assembly of protein complexes. In this regard, it is accepted that some newly translated proteins can fold spontaneously following thermodynamic principles. Nevertheless, most of the proteins are not entirely efficient at folding by following the thermodynamic laws only, and become consequently vulnerable to misfolding processes, a problem which is exacerbated by a highly crowded cellular environment [3]. Although the primarily concept of molecular chaperone was related to its ability to assist the proper folding of newly synthesized peptides in the cytoplasm and refolding of stress-denatured proteins, it should be emphasized that they are also related to a very essential and more sophisticated function, i.e. promoting the correct assembly of oligomeric complexes [4]. Perhaps one the most representative examples for this special feature is the ability of a particular set of molecular chaperones, the *heat-shock proteins*, to assist the proper assembly of steroid receptor heterocomplexes. In turn, this allows hormone binding to activate the receptor, a ligand-dependent transcription factor [5]. In this sense, the heat-shock protein of 90-kDa, Hsp90, is one of the best examples since its principal role in the cell is to provide biological activity to properly folded client proteins with a preserved tertiary structure acting as a delicate and refined sensor of protein function rather than a gross folding factor. In the above-mentioned example, Hsp90 behaves as a *sine qua non* factor of the receptor to bind steroid.

The term heat-shock protein stems from the original observation that heat-stress greatly enhances the production of this particular class of molecular chaperones. In other words, all heat-shock proteins show properties of molecular chaperones, but not all molecular chaperones must necessarily be heat-shock proteins. However temperature is not the only stimulus able to induce heat-shock proteins. Upon the onset of several environmental types of stress or due to the exposure to damaging and extreme insults, the cells increase dramatically the production of molecular chaperones, which play prominent roles in many of the most basic cellular processes by stabilizing unfolded or misfolded peptides, giving the cell time to repair or re-synthesize damaged proteins. In addition of commanding the proper folding of a factor exposed to an environmental injury, many chaperones are also related to other key functions such as enzyme activity, cytoskeletal architecture, nuclear organization, protein trafficking, transcriptional regulation, epigenetic alterations of gene expression and, even more intriguingly, heritable alterations in chromatin state [6].

The biological relevance of molecular chaperones during the modern times should be traced to the early 1960s when the Italian scientist Ferruccio Ritossa was studying nucleic acid synthesis in puffs of *Drosophila* salivary glands [7]. The story tells us that a colleague accidentally changed the temperature of the cell incubator and something unexpected was noticed —an incredible transcriptional activity of new chromosomal puffs. New RNAs were detected as soon as to 2-3 min after increasing the temperature. The importance of this fortuitous observation was immediately grasped —cells react through the synthesis of some unknown factors in response to high temperatures. Today we know that these factors are the heat-shock proteins, their induction being one of the clearest demonstrations of environmentally induced changes in gene expression to date. As it often happens, this concept was very difficult to accept during those times and Ritossa's fortuitous but clever observation was systematically rejected form highly prestigious journals with the argument that the finding 'lacked of biological significance'. Paradoxically, the study of molecular chaperones became itself an entire field of the biological sciences from that moment onwards and the experimental evidence showed that, thanks to molecular chaperones, cells adapt to changes in the environment and become resistant to harmful conditions. Accordingly, large increases in temperature or smaller increases for a prolonged period of time leads to cell death due to a number of changes in cells such as protein denaturation, transient cell cycle arrest, changes in membrane fluidity, increased turnover of plasma membrane proteins, etc. Actually, there is a plethora of stresses beyond the heat-shock that trigger similar responses— metabolic toxics, ultraviolet light, oxidations, heavy metals, ethanol, irradiation, glucose deprivation, disturbance of calcium homeostasis, osmotic or nutritional variations of the cellular milieu, etc.

One of the major and earlier damages observed in response to most of these stressing conditions are defects of the cytoskeleton [8]. Accordingly, mild heat-stress leads to the reorganization of actin filaments into stress fibers, while severe heat-stress results in the aggregation of vimentin or other filament-forming proteins, leading to the collapse of intermediary, actin, and tubulin networks. Along with the disruption of the cytoskeleton, the loss of the correct localization of organelles and a breakdown of intracellular transport processes are also observed. However molecular chaperones also play key roles under non-

stressful conditions by monitoring the proteins of the cell or switching on and off client proteins to regulate their actions, or targeting them to proteosomal degradation. The proper balance of these activities is a cardinal part of the cell own repair and functional systems.

The whole proteome of the cell is successfully maintained thanks to the assistance of molecular chaperones. In addition, the subcellular localization, local concentration, and biological activity of each protein must be strictly regulated in response to both intrinsic and environmental stimuli. The recently coined portmanteau word *proteostasis* describes this equilibrated state of the healthy proteome balance, whereas the term *proteostasis network* refers to the group of cellular events and factors involved in proteostasis maintenance. Failures of proteostasis regulation are responsible for a number of diseases as well as for the deleterious consequences of physiologic processes such as ageing. Since molecular chaperones play a key role in the maintenance of this proteostasis network, they became potential pharmacological targets to preserve that proteostatic function and to improve the biology of the cells by enhancing certain activities (or preventing others). In this regard, several endeavors are currently focused in targeting Hsp90 and some of its cochaperones such as high molecular weight immunophilins and p23. Currently, this is being tested as an exciting alternative for molecular-based therapies, particularly in both malignant and neurodegenerative diseases.

In this special issue of Current Protein & Peptide Science, several aspects of the biology of molecular chaperones have been addressed with the purpose of providing an updated overview of the field. I wish to acknowledge the valuable viewpoint of all contributing authors and hope that this assemblage of perspectives will be a valuable resource for researchers in this and other related fields. Also, I hope that the high enthusiasm showed by all our contributors to make this endeavor possible will be appreciated by the readers. Finally, I must express my greatest thanks to Dr. Ben M. Dunn, Editor-in Chief of the journal, for his kind invitation to edit this special thematic issue, and also to Ms. Nadia Razzaque, Assistant Manager of Bentham Science Publications, for her excel assistance during this project.

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