REVIEW ARTICLE

HEAT SHOCK AND THE HEAT SHOCK PROTEINS: AN OVERVIEW

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ABSTRACT

Organisms are exposed to a variety of stressful condition that damage important cellular structures and interfere with essential functions. In response to heat and other insults, cells activate an ancient signalling pathway leading to the transient expression of heat shock or heat stress proteins (HSPs). HSPs exhibit sophisticated protection mechanisms that protect the damaged cells. HSPs assist in protein folding, translocation and assembly of newly synthesized polypeptides. They also stabilize proteins during heat shock and other stresses, thus contributing to cell survival after injury. The elevated expression of stress proteins is considered to be a universal response to adverse conditions. In this Review we summarize the concepts of the HSPs protective mechanism.

KEY-WORDS: Heat Shock; Polypeptides; Cellular Structures; Heat Stress Proteins

Introduction

Natural and farming environments can be variable and unpredictable. Environmental stresses influence a plethora of physiological activities in living organisms. In some habitats, a stress from daily or seasonal fluctuation of environmental temperature causes an organism to respond by inducing sets of proteins including heat shock proteins (HSPs) and this process is known as a heat shock response or stress response In addition to heat stress, HSPs respond to other factors such as pathogen infection, oxidative stress, heavy metals and xenobiotic stresses. The name of these proteins however was derived from the first trigger i.e. heat that was identified as increasing their synthesis. These HSPs, are commonly referred to as "molecular chaperones".[1-3]

One of the most amazing aspects of heat shock response is that it is triggered by a temperature increase of just a few degrees. This is even true for organisms living at extreme temperatures. This is because of the dynamic character of proteins. Proteins have to compromise on the requirements for structural stability and functional flexibility. Therefore the energy of stabilization of a folded protein is relatively low (30-65 KJ/mol) and a slight increase in temperature may cause labile proteins to lose their distinct native conformation. A small increase in temperature can cause protein unfolding, entanglement and unspecific aggregation.[4,5] Many of the morphological and phenotypic effects of heat stress can be explained by the aggregation of proteins and an imbalance of protein homeostasis. Thus the deleterious accumulation of unfolding proteins is a signal to start counter measures. Heat shock has deleterious effects on the internal organization of cell beyond the unfolding of individual proteins. Structure and function of important organelles like golgi system, ER, mitochondria cytoskeleton is also affected in response to any kind of stress.[6-8]

HSP70 Family: A Multi-Gene Family with Overlapping & Distinct Functions

Heat shock protein 70 (HSP70) are the molecular chaperones that assist in folding of newly synthesized polypeptides, refolding of misfolded proteins and translocation of proteins through biological membranes, and in addition have regulatory functions in signal transduction, cell cycle and apoptosis. Molecular chaperones of HSP70 family are also essential for the cell to survive environmental stress including heat shock. HSP70 family is structurally and

functionally conserved in evolution. Proteins of this class of chaperones have been found in nearly all organisms. E. coli contains at least two different HSP70 proteins, Dnak and HSC66 and 14 different genes encoding HSP70 have been found in the genome of Saccharomyces cereviseae. The human HSP70 family comprises of at least eight unique gene products that differ from each other by amino acid sequence, expression level and sub cellular localization. The prokaryotic version shares about 80% sequence identity with the eukaryotic HSP70 protein which is found in the cytosol and in the organelles such as ER, mitochondria and chloroplast.[9-11]

Structure of HSP70

Prototypical HSP70 proteins contain a nucleotide binding domain (NBD) and a peptide-binding domain (PBD) that are connected by a flexible linker region that contributes to allosteric regulation of NBD and PBD activity. The HSP70 NBD has two structurally similar lobes (I and II) that comprise four sub units (IA, IB, IIA and IIB). Tight nucleotide binding occurs when domains of lobes I and II collapse around an ATP molecule. The peptide binding unit comprises of β sandwich subdomain (β-PBD) and an extended α-helical subdomain (α-PBD). Using a groove formed by the β subdomain in the PBD, HSP70 binds to protein that have exposed hydrophobic regions with an extended conformation and the α-helical part serves as a lid on the peptide binding unit without direct contact to the substrate. An ATP hydrolysis cycle regulates polypeptide binding and release by HSP70. In the ATP bound state (T state) the HSP70 PBD binds to substrate with low affinity as the NBD and PBD make extensive contacts with one another. However ATP hydrolysis to ADP drives a conformational change in the NBD-PBD interface in which the α-PBD closes over the β-PBD (R- State). T state is characterized by low affinity for substrates and fast rates of binding and release, whereas the ADP-liganded R state shows high affinity for substrates and slow kinetics. The conformational change results in high affinity substrate binding by HSP70. Subsequent nucleotide exchange to regenerate HSP70-ATP promotes the conformational change in the PBD that drives the substrate release. It is this cycle of HSP70 substrate binding and release that prevents substrate aggregation, fosters proper folding and facilitates the engagement of newly synthesized proteins with their assembly partners.[12-14]

The crystal structure of the Dnak peptide binding domain has confirmed that hydrophobic polypeptide of at least seven residues are optimal binding partners. The central residue of the heptamer is of particular importance for high affinity binding. It protrudes into a relatively large hydrophobic pocket on the floor of binding channel. The best fit is achieved by large hydrophobic amino acids. For high affinity binding, a bound peptide should not contain negatively charged residues, and positive charges can be present at the ends of the heptamer. The α-helical lid of the peptide binding domain can adapt two different states, open and closed. The interaction of the peptide binding domain with the N-terminal ATPase domain is of central importance. With ATP bound state, peptide can easily bind and dissociate, in an ADP state, the complex with the peptide is more stable. Both stages can be correlated with opening (ATP bound state) and closing (ADP bound state) of the α-helical lid.[15-17]

The HSP70 system comprises of two cochaperones, an activating protein and a nucleotide exchange factor (NEF). The activating protein is the group of HSP40/J-domain containing proteins. They bind the non-native protein and deliver it to the HSP70. The J-domain of these proteins interacts with the ATPase domain of HSP70 and stimulates the hydrolysis of bound ATP.[18-21] Exchange of nucleotide is facilitated by binding of the regulatory protein GrpE to the ATPase domain. GrpE is a protein of 22KDa that is thought to function mainly in initiating the release of bound peptides by causing the exchange of ADP for ATP. GrpE has been found to undergo a reversible thermal transition within the physiologically relevant temperature range while in DnaK and DnaJ no conformational transitions have been observed in this temperature range .Consistent with the structural data, the rate of the DnaJ-triggered T→R conversion follows an Arrhenius temperature dependence, whereas the rate of the GrpE-dependent R → T conversion increases less and

less with increasing temperature and even decreases above 40° C. Stabilizing the long NH_2-terminal helix pair of GrpE by an engineered disulfide bond abolishes the thermal transition in GrpE and reduces the deviation of the ADP/ATP exchange activity of GrpE from an Arrhenius temperature dependence, indicating that the long helix pair acts as the primary thermosensor of the chaperone system. The thermal responsiveness of GrpE is of functional significance. A mere increase in temperature results in a shift of DnaK from its low-affinity T state toward its high-affinity R state and thus in a higher fraction of substrate being sequestered by DnaK. Four unrelated groups of eukaryotic NEFs have been identified: homologs of the protein GrpE from the bacteria Escherichia coli; homologs of the human HSP70 binding proteins (HSPBP1), BAG (Bcl-2 associated athanogene) domain proteins and HSP110/HSP170 family members.[18-20]

HSP90: An Essential Chaperone Machine

Although many types of cellular activity have been identified for the HSP70 proteins, the general roles of HSP90 and its many co-chaperones in vivo (e.g. p23, CDC37, AHA1, and SGT1) remain elusive, despite their conservation within eukaryotes. The HSP90 chaperone was identified originally in stable association with signalling proteins i.e. kinases and steroid receptors. Based on evolutionary considerations, cellular reliance on the Hsp90 chaperone system has increased significantly. Prokaryotes typically contain a single non-essential HSP90 gene (e.g. HtpG in Escherichia coli), yet eukaryotes often have multiple HSP90 genes that are essential and have acquired a collection of co-chaperone partner proteins that do not appear in prokaryotes. HSP90 defines a family of molecular chaperones that are highly conserved from prokaryotes to eukaryotes. This chaperone is peculiar in several ways. First, it does not seem as promiscuous in its substrate spectrum as GroEL/ES or HSP70. Second it does not bind unfolded proteins, but native like proteins. Third it appears to have evolved from a single component in prokaryotes to the most sophisticated chaperone machinery known in eukaryotes working together with a large cohort of cochaperones that associate in a defined order during the chaperone cycle. More specifically, HSP90 is one of the most abundant proteins (1-2%) in the cytoplasm of unstressed cells where it performs housekeeping functions, controlling the stability, maturation, activation, intracellular disposition and proteolytic turn-over of a plethora of proteins generally termed as 'client proteins'.[21-23]

HSP90 Architecture

Three highly conserved domains comprise the structure of HSP90. These include the N-terminal domain responsible for ATP binding, a proteolytically resistant and the C- terminal core domain that facilitates homodimerization (Terasawa K. et al 2005). In eukaryotes, a more variable charged region links the N-terminal domain to the core domain. The length and composition of this linker region is highly divergent among organisms. Structural analysis of the N-terminal domain of HSP90 revealed that this domain contains an ATP binding site. Additionally biochemical studies suggest that transitory interaction between two N-terminal domains of the HSP90 homodimer occurs in an ATP dependent manner, and this provides the mechanistic basis for the ATPase driven molecular clamp. Mutations in this region that impairs the ability of HSP90 to either bind or hydrolyze ATP eliminate its chaperone activity. HSP90 exerts its molecular chaperone activity by conformational cycles of binding and release which are dependent upon its ATPase activity. This ATP-driven conformational cycle is regulated by specific co-chaperones, such as HSP70, Hop, immunophilins, cdc37 and p23, that complex with HSP90 and assembles into the HSP90 chaperone machinery, in order to assist the loading and release of client proteins.[24-26]

GroEL/ES: Essential for Folding in a Sequestrated Folding Compartment

In contrast to members of the HSP70 family, which appears to bind and stabilize unfolded proteins, the GroEL/ ES family seem to actually promote or catalyze protein folding and/or assembly events This family of proteins first described in E. Coli consists of a larger 60 Kd subunit GroEL and a smaller but related 10 Kd

polypeptide GroES. In eukaryotic cells the homologs of both GroEL and GroES have been described and at least the larger molecular weight subunit is regulated in cells subjected to stress. This protein is often referred to as HSP58 or HSP60. So far HSP60 has only been described within either chloroplast or mitochondria. The HSP60 or GroEL related proteins exist as large oligomeric complexes, consisting of 14 subunits arranged as two rings, often referred to as a double donut. Similarly the smaller GroES subunit, atleast in bacteria, also exists as a ring of seven identical subunits. In E. Coli GroEL/ES were shown to facilitate the orderly assembly of bacteriophage head complex in infected bacteria. Subsequent studies also implicated a role for GroEL/ES in a number of other bacterial processes, including DNA replication cell division and protein secretion. A GroEL related proteins have been isolated from plant chloroplast and shown to be equivalent to the so called rubisco binding protein. GroEL/ES purified from E. coli, can substitute for the related rubisco binding protein in facilitating the assembly of the rubisco complex in vivo. In yeast GroEL related proteins (HSP60) have been described and again appear to be an integral in facilitating higher ordered protein assembly events. For example via both genetic and biochemical studies, yeast HSP60 has been shown to interact with a variety of newly synthesized mitochondrial proteins, catalyzing their assembly into final oligomeric and enzymatically active form Such processes appear to be dependent on ATP and probably require the assistance of additional component, one possibility being a eukaryotic homolog of GroES On the basis of all these studies it has been suggested that GroEL provides a surface or workbench which binds to unfolded proteins, and through a series of ATP hydrolysis events, result in the proper folding of target polypeptide.[27-29]

Small Heat Shock Proteins (sHSP): Structure and Chaperone Function

The super family of small heat shock proteins (sHSP) combines a large number of proteins having subunit molecular mass in the range of 12-43 KDa. All proteins belonging to this family contain α-crystallin domain that consists of 80-100 residues and is flanked on both sides by variable N and C terminal ends. The small heat shock proteins are ubiquitous proteins that are expressed in all organisms except in some bacteria. Higher eukaryotes contain several genes encoding different forms of the small heat shock proteins. sHSP tend to form oligomers containing different number of monomers. The large oligomers of sHSP seem to be in rapid dissociation /association equilibrium with smaller oligomers and the dimer seem to be the preferential exchange subunit. In the vast majority of sHSPs structural changes by the assembly or disassembly or their oligomerization are prerequisite for their chaperone activity. While most chaperones machines such as DnaK-Dnaj-GrpE or GroEL-GroES consume energy, sHSPs are generally believed to be ATP independent. sHSP substrate have very diverse complex sizes since sHSP form a large multicomplex structures. As a consequence, sHSPs lack the folding and refolding capacities of the major chaperones, because the unfolding and release of folding intermediates cannot be triggered. Nevertheless, sHSPs have been added to the catalogue of molecular chaperones because they bind to denatured proteins as holding chaperones and thereby suppress the unintended interactions that may lead to the precipitation of aggregates.[30-33]

All small heat shock possess chaperone like activity and prevent aggregation of denatured proteins. However, in addition to this common feature each sHSP has its unique properties. For instance HSPB6 plays important role in cardioprotection and phosphorylation of HSPB6 by cyclic nucleotide dependent protein kinase is associated with relaxation of smooth muscles. HSPB1 counteracts apoptosis, protects cytoskeleton and after phophorylation is supposed to prevent relaxation of smooth muscles. Thus each of the sHSPs possesses unique properties that can be modified upon formation of oligomeric complexes.[34-37]

Regulation of the Heat Shock Response

Heat shock response requires a specific transcription factor and in eukaryotes the critical regulator is heat shock factor, HSF1. Its binding to the heat shock element (HSE) on DNA initiates the assembly of the transcription machinery. In E. coli,

the regulatory protein σ32 is responsible for HSP over expression. σ32 is an alternative subunit of the bacterial RNA polymerase, which replaces the normal regulatory σ 70 protein under heat stress. HSF1 and σ 32 are not related in terms of structure or sequence, but they share basic mechanistic properties. It is believed that the disturbance of protein homeostasis leads to the activation of HSF1 and σ 32. A model for the regulation of HSF1 by chaperones has been proposed and subsequently refined .The chaperones HSP70, HSP90 (in eukaryotes), and HSP40 have the potential to inhibit Hsf1 and σ 32. Under permissive conditions, σ 32 is present in a complex with the HSP70 protein DnaK and its cofactor DnaJ. It is primed for degradation by these chaperones, thereby reducing its cellular level and keeping the heat shock genes untranscribed. According to the widely accepted chaperone titration model, the presence of increasing numbers of unfolded proteins upon heat shock releases σ32 from these chaperone complexes, as chaperones are required to bind unfolded proteins. A similar model is suggested for the eukaryotic transcription factor HSF1. HSF1 is kept in an inactive complex together with components of the HSP90 chaperone system. The HSP70/ HSP40 system also binds HSF1 or acts as loading helper for the HSP90 system. Hsf1 regulation is more complex than that of σ32, as phosphorylation, other post translational modifications, and oligomerization regulate HSF1 activity. In complex with chaperones, HSF1 is a monomer. Its release leads to homotrimerization and transport into the nucleus. Here HSF1 is hyperphosphorylated by several kinases. Further modification events, like sumoylation, regulate the activity of the final transcription factor complex. The chaperone titration model elegantly explains the inactivation of heat shock transcription factors in the presence of unemployed chaperones, and their dramatic activation if chaperones are busy due to the presence of unfolded proteins. Once the cell returns to normal function, the excess of free chaperones leads again to the down regulation of the transcriptional regulator.[38-40]

Conclusion

The regulatory feedback system of the heat shock response is a protein based, very sensitive and integrative thermometer itself, as it "measures" all deviations from physiological conditions based on their cumulative effects on cellular protein homeostasis. In this article, we have discussed the structure and function of different HSPs. Many questions on the structure of HSPs, function of HSPs and the heat shock response in general have been answered in the last decades. Substantial effort has gone into the mechanistic analysis of HSPs by a variety of biochemical and biophysical in vitro approaches, and this effort is expected to continue until an exhaustive understanding is achieved. It will also be important to understand the function of HSP networks not only in the context of heat shock and other stresses, but also, and may be more importantly, in the context of disease and aging.

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