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REVIEW ARTICLE

HEAT SHOCK PROTEINS A DEFENSIVE SYSTEM FOR CORRECTING IRREGULAR BIOLOGICAL SYSTEMIC EXPRESSION

Moula ali S* Mohammad rizwan B[1], Sunil Kumar Y[1], Bhuvaneswara Rao C[2]

1. Mahathi College of pharmacy, C. T. M. Cross Roads, Madanapalle-517 319, Andhra Pradesh, India.
2. Department of Pharmacology, Seshachala College of Pharmacy, Tirupathi - Chennai High way, Puttur-517 583, Chittoor (dist), Andhra Pradesh, India.

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Email: moulabpharms14@gmail.com

Abstract: HSP regulate the response to any detrimental factors, including temperature, radiation, hypoxia, toxins or infectious agents, by controlling the three-dimensional structure of the newly synthesized proteins, preventing their misfolding or degradation. Stress response may evoke the release of HSP outside the cell, as an effect of an active transport or cell disintegration due to the infection, damage, or necrosis. Heat shock proteins or HSP are a class of proteins with related functions. Their expression increases when cells are exposed to elevated temperatures or other stress. Heat shock proteins help protect other proteins from heat stress. Chaperones regulate changes in the protein arrangement through membranes during transport. They regulate conformation - arrangement of proteins at the slight damage. Later studies demonstrated the presence of molecular chaperones in the folding of new synthesized proteins they participate in their transport across membranes, as well as their integration into various organelles. The experimental tools for examining Hsps and the standards for such examinations have both advanced considerably. As a result, much either of the earlier work on evolutionary and ecological physiology of Hsps regrettably does not withstand current scrutiny or contributes little to issues of current interest. Many of the apparently singular Hsps of previous years, often detected by one-dimensional electrophoresis and autoradiography, are now known to represent entire families of Hsps.

Key words: Biological Systemic expression, heat shock proteins, Chaperones, evolutionary variation.

INTRODUCTION:

When studying the genetic basis of animal development in the early 1960s, much of the attention was focused on the fruit fly called *Drosophila melanogaster*. It has an unusual genetic feature: its salivary gland cells contain four chromosomes in which DNA has been replicated thousands of times. During development, certain bands along these polytene chromosomes enlarge[1]. Each puff results from a specific change in gene expression and can be seen through a light microscope. In 1962, F.M. Ritossa noticed a new pattern of chromosomal puffing after exposure of isolated salivary glands to temperatures slightly above the optimal for the fly's normal growth. Ten years later, it was demonstrated that these puffs represented specific transcription sites for the synthesis of a unique set of heat shock proteins (Hsp). By the end of the 1970s, it was evident that the heat shock response was a universal property of all cells and of all organisms.

Heat shock proteins (HSPs), also known as "stress proteins." They are a family of proteins that are produced by cells in response to exposure to stressful conditions. Many members of this group perform chaperone function by stabilizing new proteins to ensure correct folding or by helping to refold proteins that were damaged by the cell stress. This increase in expression is transcriptional regulated. Heat shock proteins (HSP) are members of the molecular chaperones, a group of proteins that play essential role in the folding of a large number of cellular proteins. They were firstly discovered as mediators of resistance to hyperthermia. Moreover, they participate directly in cell survival during hyperthermia by inhibiting programmed cell death and cell senescence. HSPs appear to be utilized in carcinogenesis in order for cells to escape the pathways of tumor suppression, to promote progression in more advanced stage, to become treatment-resistant, and to facilitate metastasis [2].

Heat Shock Proteins: HSP regulate the response to any detrimental factors, including temperature, radiation, hypoxia, toxins or infectious agents, by controlling the three-dimensional structure of the newly synthesized proteins, preventing their misfolding or degradation. Stress response may evoke the release of HSP outside the cell, as an effect of an active transport or cell disintegration due to the infection, damage, or necrosis. When a cell experiences environmental stress, it stops, or at least slows down most of its original functions, such as transport processes, DNA, RNA and protein synthesis. However, there is a peculiar set of proteins, called stress proteins, which are preferentially expressed under these, restrictive conditions. The archetypal of stress response is a sudden rise in the outside temperature, called heat shock [3].

Table No. 1 Types of Heat Shock Proteins:

Approximate molecular weight (kD)	Prokaryotic proteins	Eukaryotic proteins	Function
10 kD	GroES	HSP10	-
20-30 kDa	GrpE	The HSPB group of HSP. Eleven members in mammals including HSP27 or HSPB15	-
40 Kd	DnaJ	HSP40	Co-factor of HSP70
60 kD	Gro EL, 60 k Da antigen	HSP60	Involved in protein folding after its post translational import to the mitochondrion/chloroplast
70 kD	DnaK	The HSPA group of HSP including HSP71, HSP70, HSP72, Grp78 (BiP), Hsx70 Found only in primates.	Protein folding and unfolding provides thermo tolerance to cell on exposure to heat stress.
90 kD	HtpG, C62.5	The HSPC group of HSP including HSP90,	Grp94 Maintenance of steroid receptors and transcription factors.
100 kD	ClpB, ClpA, ClpX	HSP104, HSP110	Tolerance of extreme temperature

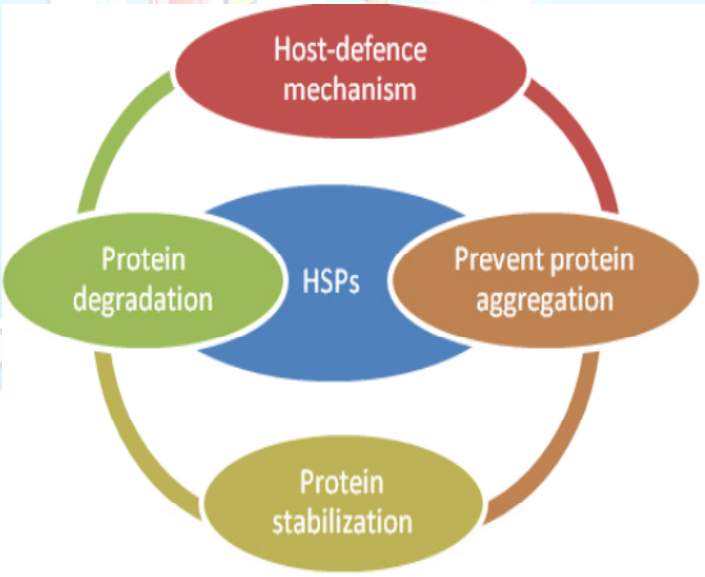

Figure-1: The function of HSPs under heat stress

Chaperones: When normal cells exposed to heat, the cells begin to intensively synthesize stress proteins, heat shock proteins (HSPs, heat-shock proteins) that have chaperone function. They are therefore called chaperones. Chaperones regulate changes in the protein arrangement through membranes during transport. They regulate conformation - arrangement of proteins at the slight damage. Later studies demonstrated the presence of molecular chaperones in the folding of new synthesized proteins they participate in their transport across membranes, as well as their integration into various organelles. Chaperones inhibit of change of proteins conformation at increased temperature to 42 °C in the cell [4]. The cell can adapt and range of this adaptation is limited and the cell is damaged by the intense stress. Molecular chaperones have important functions in maintaining cell homeostasis and the cellular response to stress. Specifically, the following various properties and functions:

•They prevent the proteins aggregation in folding and unfolding of protein,
•It has affect the production and kinetics in protein folding.
• They are involved in the transfer of cellular proteins between compartments.
• They have a regulatory function in signal transduction.

Stress proteins include molecular chaperones and proteins induced by high temperatures and also proteases, ubiquitin and dehydrins. Increase expression of HSPs is going in living organisms by sudden increase in ambient temperature above the optimum growth temperature. The presence of HSPs was demonstrated in all living organisms. It is synthesized as a response to other stress factors such as cold, UV radiation, bacterial and viral infections, heavy metals, pesticides and others.

Heat shock proteins as molecular chaperones: Molecular chaperones are defined as 'proteins that assist the correct non-covalent assembly of other protein-containing structures in vivo but are not permanent components of these structures when they are performing their normal biological functions. The precise nature of peptide binding and the factors involved appear to be chaperone dependent. Whereas ATP binding is important for the release of peptides from Hsp70, BiP (immunoglobulin heavy chain binding) and Hsp9, its role in peptide binding to and unloading from gp96, the endoplasmic reticulum prologue of Hsp 90.

Role as chaperone: Several heat shock proteins function as intra-cellular chaperones for other proteins. They play an important role in protein interactions such as folding and assisting in the establishment of proper protein conformation and prevention of unwanted protein aggregation. By helping to stabilize partially unfolded proteins, HSPs aid in transporting proteins across membranes within the cell [5].

Human heat shock proteins: Human heat shock proteins (HSPs) were originally identified as stress-responsive proteins required dealing with thermal and other proteotoxic stresses. It became clear shortly thereafter that all HSP families also encode constitutively expressed members like Hsc70 (HSPA8) in the HSP70 family. The heat shock genes (and the protein family members that they encode) that have been most extensively studied are those that are heat inducible, such as HSP70i (HSPA1A/B), HSP40 (DNAJB1), and HSP27HSPB1). With the sequencing of the human genome and the computational annotation of its genes, it became apparent that most HSP families contain additional members[6]. Moreover, gene duplication provides functional diversity for client specificity and/or processing. Since the annotation of the human genome, the names used for the human family members in the literature have become rather chaotic and up to ten different names can be found for the same gene product. In addition, almost identical names have been used to refer to different gene products. For example, HSPA1B has been called HSP70, where. This has greatly hampered studies that involve comparisons of regulation and function between these members. The first attempt to clarify the nomenclature of the HSPA family was published in 1996 but now requires modification and expansion.

Clinical significance: Heat Shock Factor 1 (HSF1) is a transcription factor that is involved in the general maintenance and up regulation of Hsp70 protein expression. Recently it was discovered that HSF1 is a powerful multifaceted modifier of carcinogenesis. HSF1 knockout mice show significantly decreased incidence of skin tumor after topical application of DMBA (**dim**ethyl**b**enz**a**nthracene), a mutagen. Moreover, HSF1 inhibition by a potent RNA aptamer attenuates mitogenic signaling and induces cancer cell apoptosis [7].

Types and Nomenclature: The principal heat-shock proteins that have chaperone activity belong to five conserved classes: HSP60, HSP70, HSP90, HSP100 and the small heat-shock proteins (sHSPs).

Structure and Biochemistry of HSP: Heat shock proteins are present in cells under normal conditions, but are expressed at high levels when exposed to a sudden temperature jump or other stress. Heat shock proteins stabilize

proteins and are involved in the folding of denatured proteins. High temperatures and other stresses, such as altered pH and oxygen deprivation, make it more difficult for proteins to form their proper structures and cause some already structured proteins to unfold. Most heat shock proteins are molecular chaperones. Chaperones aid in the transport of proteins throughout the cell's various compartments.

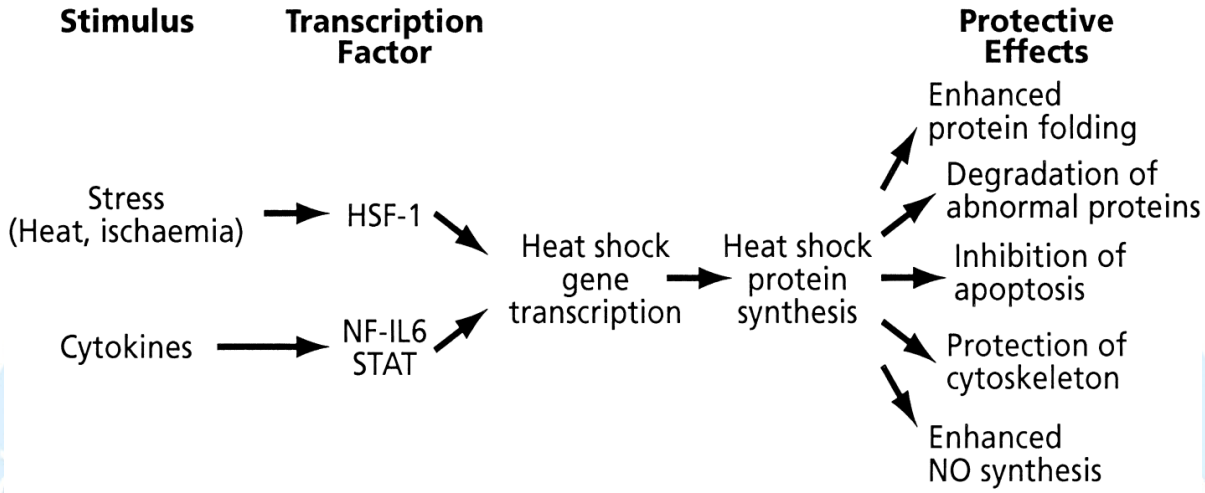

Figure- 2: Activation of the Hsps by specific stimuli and their protective effect.

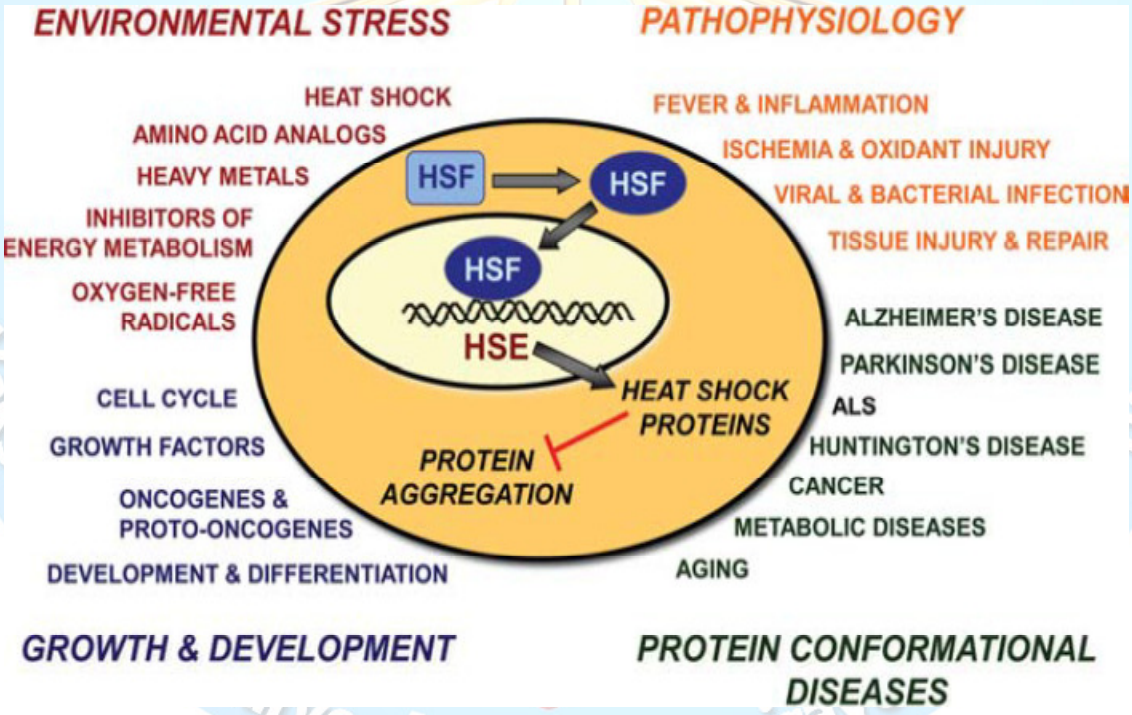

Figure- 3: Cell stress conditions that induce the heat shock response. Major categories of environmental and physiological stress inducers of the HSR.

Structural Biochemistry: Heat shock proteins or HSP are a class of proteins with related functions. Their expression increases when cells are exposed to elevated temperatures or other stress. Heat shock proteins help protect other proteins from heat stress. This response to heat stress can also be seen in heat-stressed animals and microorganisms. The dramatic up regulation or increase of cellular components, of heat shock proteins plays a key role in heat shock response and is induced primarily by heat shock factor. HSPs can be found in almost all living organisms, ranging from bacteria to humans[8].

Heat shock response: The heat shock response is one of the most highly conserved genetic systems known. In addition to heat, a wide variety of biological (infection, inflammation), physical (radiation, hypoxia) and chemical (alcohols, metals) stressors can induce the response. The response of HSP is controlled primarily at the transcription level by a heat shock factor. In unstressed cells, HSF is present in the cytoplasm and the nucleus in a monomeric form that has no DNA binding activity through its interactions with Hsp70. In response to stress, the monomeric forms combine into trimmers and accumulate within the nucleus.

Functions of HSP:

1.Physiological function of HSPs: HSPs have been called molecular chaperones. It is observed that HSPs prevents the cells from the damage effect caused by high temperature. The Formation and folding into three dimensional structures. Formation of three dimensional structures requires 50% of principle amino acids sequence [9].

2. Role of heat-shock proteins: The role of Hsps in the folding of other proteins is important. Hsps protect cells from injury and facilitate recovery and survival after a return to normal growth conditions. Unfolding of proteins is not the main effect and protection from damage could occur in an alternative way apart from ensuring the maintenance of correct protein structure.

3. Induction and regulation of heat shock protein expression: Regulation of transcription of heat shock protein genes is mediated by the interaction of heat shock factor transcription factors with heat shock elements in the heat shock protein gene promoter regions. In vertebrates, four HSFs have been identified, of which HSF1 and HSF2 are ubiquitously expressed and conserved.

4. Heat shock proteins as intercellular signaling molecules: The usual view of eukaryotic heat shock proteins is that they are intracellular molecules that are released from necrotic, but not apoptotic cells, and that their release into the extracellular environment indicates non-physiological tissue damage and therefore induces a range of proinflammatory responses [10].

5. Extracellular heat shock proteins: Heat shock proteins can be released from some viable (non-necrotic) mammalian cell types, including cultured rat embryo cells, human islet cells, rat glial cells and a human neuroblastoma cell line, and cultured vascular smooth muscle cells exposed to oxidative stress. These findings have profound implications for the perceived role of these proteins as exclusively proinflammatory intercellular signaling molecules and danger signals. Furthermore, Hsp60 and Hsp70 are present in the peripheral circulation of healthy individuals. Hsp60 is also present at high concentrations in people with early atherosclerosis, and Hsp70 concentrations are raised in patients with peripheral and renal vascular disease[11].

6. HSPs and Their Induction: Hsps or stress proteins are highly conserved molecules that fulfill a range of functions, including cytoprotection and the intracellular assembly, folding, and translocation of oligomeric proteins. Hsp gene transcription in response to stress is regulated by the interaction of heat shock factor transcription factors with heat shock elements in the hsp gene promoter regions[12].

7. HSP Expression and Hsp Reactivity in Vascular Disease: Although the precise influence of hsps on atherogenesis and atherosclerosis is unclear, an association between expression of and reactivity to hsps and induction of the inflammatory response that characterizes the development of atherosclerosis has arisen from a number of studies [13]. The intensity of hsp expression positively correlates with the severity of atherosclerosis; there is a localized enrichment of γ/δ T cells, which have a predisposition to respond to hsps, in the lesion; and immunization with recombinant mycobacterium hsp65 can induce atherosclerotic lesions in normocholesterolemic rabbits, normal C57BL/6J mice fed a high-fat diet, and LDL-receptor–deficient mice. Raised levels of anti-hsp antibodies have also been associated with the presence and progression of vascular disease.

8. Hsps as Inducers and Mediators of Vascular Disease: The potential nature and temporal involvement of hsps in the establishment and progression of the atherosclerotic lesion is complex. They may be involved in the initiation of atherosclerosis via nonspecific inflammatory events and/or its progression via the induction of adaptive immunity either to themselves or to homologous molecules derived from infective organisms.

9. Protective mechanisms: The clear protective effect of hsps in the heart is paralleled in a variety of other critical tissues and cell types such as the brain. This has led to a variety of investigations in different cell types aimed at elucidating the mechanisms mediating these protective effects. As well as simply indicating that hsps function by chaperoning the correct folding of other proteins, these studies have also identified specific biological processes, which are targeted by hsps as shown in Figure 2.

10. Therapeutic potential of Hsps in the cardio vascular diseases: The experiments described in earlier sections

clearly suggest that procedures which elevate hsp levels in the heart may be of significant benefit, for example, during reperfusion following a period of ischemia, during cardiac bypass or to preserve donor heart function prior to transplantation.

11. The extracellular HSP in the immune system: Although the presence of the circulating HSP and the antibodies against them has been known for more than a decade, there is still much controversy about the role of the extracellular forms of these proteins. HSP can also stimulate the production of cytokines by monocytes and macrophages, as well as the expression of the adhesion molecules on the endothelial cells [14]. HSP are also known as physiological adjuvant, strengthening the immune response by forming the complexes with antigens, also carcinogens, and ready to be transformed by APC.

Effect of HSP on different biological systems:

Life Cycles and Heat Shock Proteins: Organisms can encounter wide fluctuations in temperatures of their surrounding throughout their life cycle. For example the bacterium E. coli cycles between the 37°C of the mammalian gut and the <20°C of waste water. Dimorphic fungi (e.g., Histocapsulatum) and the parasitic protozoa Leishmaniamajor and Trypanosome brucei experience similar temperature changes between hosts. Not surprisingly, these organisms induce HSPs when they initially encounter the higher temperatures. Presumably the HSPs help the cell overcome temperature-induced damage in the same way they help other stressed cells whose life style shows less temperature variations. What is striking, however, and should be borne in mind when speculating about HSP function are the observations that several HSPs are induced during normal cellular development, in the absence of temperature stress (of course, there could be another kind of stress operating during these stages). During the sporulation of yeast, for example, genes for two of the major yeast HSPs are activated. The HSP70 gene itself is not activated under this condition but proteins for two HSPT0 family members are induced. An HSP70-1ike protein is one of the first proteins synthesized after zygote formation in mouse embryogenesis, and several HSPs are induced during cogenesis and pupation in Drosophila.

Virus Infection and HSP Synthesis: Bacteriophage lambda actually uses several of the E. coli HSPs for its replication. Several eukaryotic cell DNA viruses, i.e., adenovirus, herpes virus, simian virus, and polyoma viruses, activate synthesis ofHSP70 early in infection. Newcastle disease virus, an RNA virus, induces HSP70 and HsPg0 in infected chicken cells. As in the case of bacteriophage, the HSPs may be used by the virus replication system or their induction may simply reflect a stress from the infection [15]. The fact that the adenovirus E1A gene product is an inducer of cell HSP70 argues for a positive role of this protein in the virus life cycle.

Chaperones and the immune response: Molecular chaperones are one of the most conserved proteins in living organisms. Invading bacteria experience major changes in their environment when entering their host. These changes and the activation of defense mechanisms (depletion of nutrients, pH changes, osmotic changes, digestive enzymes, peroxides, superoxides and an increase in temperature) induce numerous heat shock proteins in bacteria, among which some are also expressed on the bacterial surface [16]. Because of their conservative structure, these bacterial heat shock proteins, especially the bacterial homologue of Hsp70 become a common recognition signal, and therefore provoke a general, high-capacity immune response. There are at least two dozen infectious diseases in which immune responses to heat shock porteins have been reported, including tuberculosis,leprosy, legionnaire's disease, Chagas's disease, lyme disease, chlamidyal infections and Q fever. In some unfortunate cases (such as in rheumatoid arthritis, in lupus erythematosus, in multiple sclerosis and in insulin dependent diabetes mellitus, IDDM) certain proteins of the host organism resemble some epitopes of these bacterial heat shock proteins.

Evolutionary Studies of HSP'S: The experimental tools for examining Hsps and the standards for such examinations have both advanced considerably. As a result, much of the earlier work on evolutionary and ecological physiology of Hsps regrettably either does not withstand current scrutiny or contributes little to issues of current interest. Several issues are obvious:

1. Many of the apparently singular Hsps of previous years, often detected by one-dimensional electrophoresis and autoradiography, are now known to represent entire families of Hsps, often with

(a) Discrete distributions within the cell (e.g. cytoplasmic-nuclear, mitochondrial, chloroplast, or endoplasmic reticulum),
(b) Different degrees of inducibility (constitutively expressed, constitutively expressed but increasing during or after stress, exclusively inducible),
(c) Differing kinetics of induction and removal from the cell,
(d) Differing tissue specificity. Representing this diversity as a single Hsp or two Hsps ("constitutive" and "inducible") through use of nonspecific probes or lysates of whole organisms and organs can obscure phenomena of

great significance.

1. This problem is sometimes remediable only with great difficulty. Often, highly specific probes are available only for standard model organisms, particularly at the level of proteins, and great care must be taken in applying these probes to non-standard organisms [16].

2. Inducible stress tolerance is increasingly understood to result from numerous molecular mechanisms, of which Hsps are collectively only one. Other mechanisms include synthesis of osmotic stress protectants such as polyols and trehalose, modifications of the saturation of cell membrane lipids (home viscous adaptation), compensatory expression of isozymes or allozymes of significant enzymes, metabolic arrest, radical scavengers (superoxide dismutase, glutathione system, cytochrome P450), and so on. Accordingly, the unambiguous attribution of stress tolerance to Hsps in general or to any specific Hsp requires more than correlative evidence. Increasingly, Proof resulting from genetic or direct experimental manipulation is becoming the standard for establishing the functional or evolutionary significance of Hsps. Again, this rising standard is often met only with great difficulty in ecological and evolutionary physiological studies, for many of the techniques for genetic and experimental manipulation are not readily applicable to the more ecologically and evolutionarily interesting species

The evolutionary history of hsps and the genes that encode them: Hsps are among the most ancient and highly conserved of all proteins. Homologues of Hsps occur in every species in which they have been sought, and in all kingdoms of living things. Thus, Hsps represent a remarkable example of molecular "descent with modification" at the levels of gene sequence, genomic organization, regulation of gene expression, and protein structure and function.

Micro evolutionary variation in HSPS: Hsps are routinely touted as adaptations that arose and are maintained via natural selection for stress resistance. Origin and maintenance of a trait by selection require that it vary within populations, and that this intra-population variation have a genetic basis and affect the Darwinian fitness of individuals. Here we ask whether Hsps, the genes that encode them and the factors that modify their expression display such patterns of variation and undergo stabilizing or directional selection in response to environmental stress.

For example, seasonal acclimatization and temperature acclimation in the laboratory can alter the minimum temperature at which Gillichthys, a gobiid fish, expresses an Hsp90 family member. Seasonal acclimatization likewise affects Hsp70 levels in mussels (Mytilus), and routine culture temperature affects the magnitude and temporal pattern of Hsp expression in HeLa cells. Such changes may stem from alterations in the cellular environment that modify the activation of HSF. These changes, however, are not universal; laboratory thermal acclimation does not alter the thermal sensitivity of Hsp expression in fish hepatocytes in culture, Drosophila larvae, and mussels [17].

Large-Scale Evolution of Hsp Genes: The extraordinarily conserved nature of hsp gene has facilitated their cloning, sequencing, and comparison in diverse organisms; their evolution is now becoming understood in detail. Gupta and colleagues have undertaken the most extensive surveys of hsp sequences, with a particular focus on organisms deemed critical to understanding the relationships of major taxes. The interpretations resulting from these comparisons relate to hypotheses about
(a) The origin of eukaryotic cells, the eukaryotic nucleus, and endoplasmic reticulum;
(b) Polyphyletic versus monophyletic origin of the major bacterial groups ;
(c) The validity of the three-domain (Archaea, bacteria, and eukaryotes) dogma.

Applications:

Cancer vaccine adjuvant: Given their role in antigen presentation, HSPs are useful as immunologic adjuvant in boosting the response to a vaccine. Furthermore, some researchers speculate that HSPs may be involved in binding protein fragments from dead malignant cells and presenting them to the immune system. Therefore HSPs may be useful for increasing the effectiveness of cancer vaccines.

Anticancer therapeutics: Intracellular heat shock proteins are highly expressed in cancerous cells and are essential to the survival of these cell types. Hence small molecule inhibitors of HSPs, especially Hsp90 show promise as anticancer agents [17]. The potent Hsp90 inhibitor 17-AAG is currently in clinical trials for the treatment of several types of cancer. HSPgp96 also shows promise as an anticancer treatment and is currently in clinical trials against non-small cell lung cancer.

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Conclusion: Though HSPs are so many but retro transcription and horizontal exchange of genome technology promises to advance in newer drug development and identification of disease state. On a less grand scale, hsp gene families represent superb case studies of how one or

a small number of primitive genes can diversify to encode a suite of compartment- and function-specific proteins. One of many examples is dank, a single gene in Archaea and bacteria that has become the complex multi gene hsp70 families of Saccharomyces, Drosophila, and Homo. Another example concerns the small Hsps, which evolution recruited to become a major component of the lens of the eye: alpha crystalline. A growing body of work examines the discrete evolutionary events by which these changes may have occurred, including gene duplication/conversion events, retro transposition, horizontal exchange of genomes, and others. New technologies promise to advance this work exponentially.

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