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Review: Stress Protein and Their Biomedical Implication

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Abstract: Animals and bacteria have different mechanisms to with stand stress conditions detrimental to them. Stress (Heat shock) proteins are one of these mechanisms commonly known. These proteins are present in cells under normal conditions but are expressed at high levels when exposed to sudden temperature jump or other stress. Normally, HSPs are found inside the cell but they are also found secreted into the extracellular milieu and displayed onto the cell surface to represent different cellular conditions. While present on the cell surface they also carry processed peptides of the respective cell. Heat shock protein help to cell survival at normal and stress condition for both eukaryotes and prokaryotes. Even if there are many types of heat shock protein families. HSP90 and HSP70 families are among the most highly conserved and well studied stress protein. This review highlights the basic mechanism of production and bio medical implication of these proteins.

Key words: Cytoprotective · Heat Shock Protein · Stress · Thermo Tolerance

INTRODUCTION

Prokaryotes and eukaryotes respond to development cues or cellular challenges by directing their protein synthetic apparatus toward the production of stress protein. Mammalian stress proteins appear to have been derived from prokaryotic ancestors that evolved to solve problems in protein folding [1]. The heat shock response was first discovered by FeruccioRitossa [2] who observed an enlargement of special sections of *Drosophila melanogaster* chromosomes (Heat shock puffs) after heat treatment of the flies. Ritossa first observed that either shifting the temperature from 20°C to37°C or treatment with sodium salicylate or dinitrophenol produced new chromosome puffing patterns. Ten years later it has been shown that heat shock induced the production of unique set of protein [3]. Thus it soon become evident that puffs observed at light microscopic level in Drosophila were exuberant RNA transcription and that the exposure of cells from wide verities of species of to heat challenges produced enhanced synthesis of several unique proteins that were designated as heat shock proteins(HSP). In spite of the expression of these protein following chemical treatment first describedin1962, this phenomenon has been called heat shock response [4].

All the cells that have tested; cells from animals, plants and yeast down to simplest prokaryotes when submitted to a stress such as mild increase in temperature, temporarily turn down their usual protein synthesis and turn up the synthesis of heat shock proteins. Because the response can be induced by virtually any type of stressing agent the term stress protein also used [5]. Animal life is mainly limited to narrow range of temperature from anew degrees below the freezing point of water to approximately 50°C. Animals nevertheless differ in the range of temperature that they tolerate. Temperature tolerance however change with time and certain degree of adaptation is possible. The limits for temperature tolerance forgiven animal are not fixed.

This particular response to heat as attracted considerable attention from molecular biologist over the last decade, hitch has resulted in rapid accumulation of data providing considerable insight , not only in to the molecular basis of a quailed thermotolerance, but into stress physiology in general. Heat shock response is now known to occur in bacteria and in plants as wells in animals [5].

Several types of heat shock protein have been identified including high molecular weight stress protein, low molecular weight and extracellular stress proteins [4]. Proteins with molecular weight of 100kd or greater describe as high molecular weight stress protein while those that have molecular weight ranging from 15-40kd are grouped under low molecular weight stress protein.

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More over stress protein can also as highly conserved which can be exemplified HSP90 and 70 families, less conserved including HSP58, 47and extracellular stress protein [4].

There for the objectives of this review were

- To have an overview, on current status of the biomedical implication of heat shock proteins, the role and association between heat shock protein
- To highlight the their expiration during normal development and disease

Heat Shock Protiens

Definition: Heat shock proteins are proteins synthesized by cells in response to many different physiological stresses [6]. Cells from virtually all organisms respond to varieties of stress by the rapid *synthesis* of highly conserved set of poly peptide termed heat shock proteins (HSPs) [7]. Heat shock response is about as ancient as it could be and genes that code for its proteins have changed little in there billion years [4]. For example if amino acid sequence of equivalent heat shock proteins from prokaryotes and eukaryotes are compared they are about 50% homologous and many of the other residues are similar. Heat shock or stress proteins are presently designated by HSP followed by the molecular mass in kilo Dalton s(KD). These proteins are ubiquitous, occurring in all organisms from bacteria and yeast to humans. Based on the molecular weight and biological functions, HSPs is classified as HSP 110, HSP100, HSP90, HSP70, HSP60, HSP40, HSP10and small HSP families, of which thermo-tolerance development is mainly correlated with HSP70 and HSP90 in livestock species [8]. HSP70 namely, HSP70-1 and HSP70-2is reported to be the most abundant and temperature sensitive [9]. In farm animals, elevation in HSP70 and HSP90 was observed in sheep, buffalo, cattle, broilers and goats [10].

Class of Heat Shock Protein

Highly Conserved and High Molecular Weight Heat Shock Protein

Heat Shock Protein 90 (HSP90): Members of the Hsp90 family are highly conserved and present in most prokaryotic and eukaryotic cells. Hsp90 is an abundant eukaryotic cytosolic protein contributing 1-2% of cellular proteins under physiological conditions. It is highly conserved and expressed in a variety of different organisms from bacteria to mammals including prokaryotic analogue htpG (High temperature protein G) [11]. It has been identified in the cytosol, nucleus and endoplasmic reticulum and is reported to exist in many tissues [12]. There are two isoform of HSP90 in mammalian cells SP90α and HSP90β. Recently, a membrane associated variant of cytosolic HSP90, lacking an ATP binding site, has been identified and was named asHSP90N. It consists of four structural domains [13]. Highly conserved N-terminal domain in which crystal structures are available [14]. A “Charged linker” region, that connects the N-terminus with the middle domain. A middle domain is involved in client protein binding. It also increases the ATPase activity of HSP90. The C-terminal domain possesses an alternative ATP-binding site, which become accessible when N-terminal Berger at pocket is occupied [1]. In unstressed cells, HSP90 plays a number of important roles, which include assisting in folding, 40 intracellular transport, maintenance and degradation of proteins as well as facilitating cell signaling [15]. It acts as a general protective chaperone [16]. HSP 90 also participates in many key processes in on cogenesis such as self-sufficiency in growth signals, stabilization of mutant proteins, angiogenesis and metastasis.

Heat Shock Protein 70 (HSP70): Heat Shock Protein 70 is a family of ubiquitously expressed heat shock proteins. There are at least four distinct proteins in the HSP70 group (HSP72, HSP73, HSP75 and HSP78), Proteins in the HSP70 group share common protein sequences but are synthesized in response to different stimuli [17]. When an HSP70 protein is ATP bound, the lid is open and peptides bind and release relatively rapidly. When HSP70 proteins are ADP bound, the lid is closed and peptides are tightly bound to the substrate binding domain. Under normal conditions, HSP70 functions as AT dependent molecular chaperon that assist the folding of newly synthesized polypeptides, the assembly of multi protein complexes and the transport of proteins across cellular membranes. Under stressful conditions, elevated HSP70 levels allow cells to cope with increased concentrations of unfolded or denatured proteins. It also inhibits apoptosis [18].

Less Conserved and Low Molecular Weight Heat Shock Protein: Heat shock protein 58 were first described in Tetrahymena as a normal cellular protein localized in mitochondria .synthesis of the protein in Tetrahymena is increased by heat shock for raised its level two to three times to normally present [19]. Heat shock protein 27 is a chaperone of the sHSP (Small heat shock protein) and was identified as a protein with high homology to the eye lens α-crystalline proteins [20]. For instance analysis of mouse

homologue, HSP25, showed that this protein has a compact two-domain structure, composed mainly of β-sheets that are similar to α-βcyrstallin HSP27 is constitutively expressed in several organs and tissues like eye, nervous system, heart, blood and blood vessels, lung, bladder, colon and stomach, as well as in estrogen responsive organs such as uterus, vagina, cervix and placenta. Lower levels were detected in other tissues including epithelial cells of the breast, testes and striated muscle. Elevated HSP27 levels have been detected in a range of different tumors including breast cancer, prostate cancer, gastric tumors, head and neck cancers, uterine and ovarian cancers as well as in cancers arising from urinary system (Bladder and kidney) and the nervous system (Meningioma's, astrocytoma's and neuroblastomas) [21].

Under stressful conditions such as following heat stress injury, HSP27 expression is increased at the transcriptional phosphorylation level and pre-existing and newly synthesized protein undergoes significant posttranslational phosphorylation at specific amino acid residues, which alters its functions in these cells. Such modifications result in the dissociation of larger HSP27complexes to form smaller complexes of the proteins (Tetramers, dimmers or monomers) which have distinct functions. HSP27 has homologous and highly conserved amino acid sequence, the so-called α-crystalline-domain at the Cterminus. These sequences consist of 80 to 100 residues with a homology between 20% and 60% and form β -sheets, which are important for the formation of stable dimmers [21]. HSP27 functions in thermo-tolerance. In vitro it acts as an ATP independent chaperone by inhibiting protein aggregation and by stabilizing partially denatured proteins. HSP27 is also involved in the apoptotic signaling pathway. HSP27 interacts with act in and intermediate filaments and protects act in filaments from fragmentation. It also preserves the focal contacts fixed at the cell membrane [22]. It is also involved in process of cell differentiation.

Extracellular Stress Protein: Different types of extracellular proteins have been expressed by heat shock, among these osteonectin and thrombospodin could be mentioned. Osteonectin is a32kda phosphor elate glycoprotein originally purified from bone tissue [23]. Latter these proteins have been identified in several tissues including placenta, platelets and fibroblast. Thrombospodin is trimetric extracellular matrix protein that binds to cell through membrane –associated heparin sulphate proteoglyacanes.

Expression of other protein like metalloproteinase, collagenase and streptolysine has been indicated. These proteins are expressed large quantity in rheumatic arthritis, diabetes. Periodontal disease and in connective tissue undergoing remodeling. Their production is as well regulated due to heat shock [4]. Heat shock proteins are normally found inside cells. When they are found outside the cell, it indicates that a cell has become so sick that it has died and spilled out all of its contents. This kind of messy, unplanned death is called necrosis and only occurs when something is very wrong with the cell. Extracellular HSPs are one of the most powerful ways of sending a 'danger signal' to the immune System in order to generate a response that can help to get rid of an infection or disease [24].

Role of Heat Shock Protein: Many functional role of heat shock protein are known. But the mechanism for these multiple functions not entirely under studs. It has been postulated that the determination of these mechanisms would permit the designs of more precise way to combat cellular stress in varieties of clinically relevant settings (Immunological, disease cancer, cardiovascular disease, aging [25]. HPS appear to play critical role in the development of thermotolerance and protection of cellular damage in associated with stress such as ischemia and associated tissue hypoxia and generation of ROS, cytokines, acidosis and energy depilation.

Heat shock protein through protection of transcription and translation of cell. These observations suggest that HSP play an important role in both normal cellular homeostasis and the stress response [26]. Several important cytoprotective functions have been attributed to HSPs and in particular the heat shock protein 70 family. These include: the folding of protein in various intracellular compartments, the maintenance of structural protein. The folding of misfolded protein, Translocation of protein across membrane and into various cellular compartments, the prevention of protein aggregation and the degradation of unstable protein [27]. HSP are also responsible for receptor regulation and cytoskeleton stabilization. In addition it has been noted that HSP play a role in apoptosis. HSP27, 70 and HSP 90 are predominantly apoptotic. Moreover it appears that these HSP function at multiple points in the apoptotic signaling path way of to elicit this response [28].

HSP accumulation with in a cell produce both transcriptional inhibition and decrease TNF-α and interleukin it has been demonstrated that conditioning

Table 1: Cellular location and function of mammalian heat shock protein families

HPS family	Cellular location	Function
HSP90	Cytosol, nuclease, endoplasmic reticulum (RE)	Regulation of steroid hormone receptor, protein trans location
HSP70	Cytosol, nuclease, ER, mitochondria	Anapoptotic protein folding, cytoprotection, molecular chaperon
HSP60	Mitochondria	Re folds protein and prevents aggregation of denature proteins apoptotic
HSP 27	Cytosol, nuclease	Microfilamentstabilization, Antipanoptic

Source: Kregle and Moseley [7]

and the resultant increase intracellular HSP70 levels protected animals from un endotoxin does that was lethal in unconditioned rates. These more ever this paradigm was associated with decrease serum TNF-α level after administration of endotoxin in the heat conditioned animals [29]. These result suggest that intracellular HSP accumulation may contribute to the redaction of inflammatory cytokines production with cellular phalange.

Conversely when HSPs Are present on the surface of cells or released in to the local extracellular environment during conditions such as necrotic cell death or viral infection. These proteins have unimmune stimulating response. These situation involving cell necrosis quite relevant to conditions of physiological challenge such as heat stress .Where wide spread cellular injury and necrotic cell death have been noted [26]. HSP is also known to facilitate antigen presentation in cells such as macrophages and dendrite cells. When hsp70 is applied to the environment external to cells Macrophages and lymphocytes produced inflammatory cytokines.

Studies have demonstrated the presence of HSP70 on the surface of tumor cells potentially functioning as recognition molecules fir natural killer (NK) cells. These observations demonstrate that HSP are important modulators of antigen presentation T-lymphocyte activation cytokine production and NK cell killing. Placing them in a unique position of contributing to physiological stress. In general cellular locations and proposed functions of the different families or heat shock proteins are listed below:

Bacterial Stress Protein: Pathogenic bacteria must withstand diverse host environments during infection. Environmental signals, such as pH, temperature, nutrient limitation, etc., not only trigger adaptive responses within bacteria to these specific stress conditions but also direct the expression of virulence genes at an appropriate time and place. An appreciation of stress responses and their regulation is therefore essential for an understanding of bacterial pathogenesis. Bacteria experience stress from their initial moment of contact with the host. For most pathogens, this entails a change in temperature. For bacteria transmitted by arthropod vectors, this also involves a transition from the insect gut to mammalian subcutaneous tissue or the bloodstream [30]. Respiratory pathogens must cope with an array of host-derived antimicrobial mediators, including bactericidal peptides produced by epithelial cells [31] and may also be required to adapt to nitrosative stress hyperosmolarity [32] and oxygen limitation [33]. In contrast, enteric pathogens are ingested and must survive the hostile environment of the stomach, which is notable for a strongly acidic pH and the presence of reactive nitrogen species generated from dietary nitrate.

Within the intestinal lumen, enteric pathogens encounter membrane-active antimicrobial peptides [34] bile salts, free fatty acids, enhanced osmolarity and changing oxygen tensions [6] Host inflammatory responses recruit phagocytic cells, subjecting pathogens to oxidative and nitrosative stress [35]. Host sequestration of essential metals and other nutrients creates additional challenges as intracellular pathogens such as *Francisella* and S*almonella* respond to distinctive cytoplasmicor phagosomal environments, respectively [37, 38].

Application of Heat Shock Protein

Bio Technical Application: Un understanding at molecular level of the result of thermal stress and of thermo tolerance may be of considerable biotechnical importance .Although heat shock will induced tolerance to further stress it also leads to increase in tolerance to other stresses .For example the application of heat stress to yeast greatly increase their subsequent tolerance of ethanol.

Researchers are also investigating the role of HSPs in conferring stress tolerance to hybridized plants, hoping to address drought and poor soil conditions for farming [39]. Various HSPs were shown to be differentially expressed in the leaf and root of drought-tolerant and drought-sensitive sorghum varieties in response to drought [40].

Clearly the ranges of stress protection remains to be fully expressed, but if plants could be genetically engineered to with stand heat as well as other stresses possibly through increased expression of HSPs, this

would be considerable economic importance. Animals cells capable of withstanding considerable stress will be required if high yields are to be achieved.

Clinical Applications: HSP trigger immune response through activities that occurs both inside the cell (Intracellular) and outside the cell (Extracellular). HSPs are normally found inside cells. Due to cell necrosis the cell contents spills out. The abnormal peptides so spilled out gives the 'danger signal' to the immune system to generate a response in order to prevent any infection or disease. Antigenic heat shock protein mechanism works by mimicking these 'danger signal' naturally triggered by extracellular HSPs. Depending on the abnormal peptides that have spilled out of the cell, the immune system can be activated to target different cancers and certain infectious agents [41]. The abnormal peptides found within diseased cells are different from cancer to cancer and from person to person. Therefore library of abnormal peptides is unique to each individual's disease and can be thought of as the cancer's fingerprint' [42]. Antigenic patient specific vaccine consists of HSP-peptide complexes that have been isolated from that patient's cancer cells. When the vaccine is injected into the body, the fingerprint of HSP-peptide complexes can directly encounter the immune system's cells, which is designed to stimulate the immune cells to target cancer cells bearing the fingerprint.

HSP end up binding virtually to every protein because of their normal functions of inside the cell (Such as helping proteins fold, preparing proteins for disposal, etc.). This means that at any given time, HSPs can be found inside the cell bound to a wide array of peptides that represent a'library' of all the proteins inside the cell. This library contains normal peptides that are found in all cells as well as abnormal peptides that are only found in sick cells [43]. Research suggests that inside the cell, the heat shock proteins take the peptides and hand them over to another group of molecules. These other molecules take the abnormal peptides that are found only in sick cells and move them from inside the cell to outside on the cell's surface. When these abnormal peptides called antigens are displayed in this way, they act as red flags, warning the immune system that the cell has become sick.

CONCLUSIONS AND RECOMMENDATIONS

Heat shock proteins are ubiquitous, occurring in all organisms from bacteria and yeast to humans. There is sebistantioal evidence that HSPs Play important physiological role in normal condition and situation involving both systemic and cellular stress. HSPs are synthesized in animals and humans in response to many relevant physiological (eg. heat stress, exercise), energy depilation and pathological (eg. viral infection, cytokine release) condition.

Researcher have subsequently demonstrated that HSPs have strong cytoprotective effect are involved in many regulatory path way, behave as molecular chaperones for other cellular proteins. Anti apoptotic, anti inflammatory and immune function are also described. HSPs come in various forms and are categorized into families on the basis of molecular weight.

There structure is well conserved among species high molecular weight stress protein with molecular weight of 100KDa or greater appear to stabilize ribosome while the more conserved highly conserved HSPs, belonging to the HSP90 family are involved in function steroid receptor HSP70family of protein are essential for cellular survival from heat stress and other type of physiological challenges. There is also cellular stress protein, which appear to play key role in preparing in preparing cells for migratory events or for cell division. As such these proteins are strongly suggested to be involved in normal development and important role in dysmorphology. Extracellular stress protein like thrombospodin and osteonectin are implied in the later stage of inflammation and repair. Recent developments in Hsp90-related pharmacology and the establishment of several clinical methods which utilize the role of chaperones in peptide presentation make this field an exciting area for future clinical studies.

Based on the above conclusion the following points are recommended.

A key issue to be elicited is whether induced proteins perform the same, function as the constitutively expressed proteins.

The mechanism for the various mechanism of cellular protection in association with an increase HSP level to be delineated.

Finally it is still uncertain whether HSPs can be utilized in therapeutic setting. Although gene therapy program have made impressive advances in recent years, thus the answer too many of these questions await further study.

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