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Review Article

HEAT SHOCK PROTEINS: KNOWLEDGE SO FAR AND ITS FUTURE PROSPECTS

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ABSTRACT

Heat shock proteins (HSPs) are one of the most versatile classes of molecules which regulate cellular homeostasis. In 1960, Ritossa accidentally raised the incubation temperature of *Drosophila* fly and found an increased gene transcription of certain unknown proteins, which he named HSPs. Further studies explored that HSPs, being expressed at low levels under normal conditions, act as molecular chaperones, which fold, assemble, localize, secrete, and translocate cellular proteins. Moreover, their expression is markedly induced in response to various stresses such as an exposure of cells to heavy metals, nitric oxide, ischemia, microbial infection, antibiotics, and hormones. The literature has been thoroughly investigated, and the present review summarizes the complex role of HSPs in gastric disorders, neurological disorders, apoptosis, cancer, etc. Expression of HSPs by cells has important physiological or pathological implications. HSPs can be used as novel molecular targets for both the pharmacological and therapeutic interventions to prevent and cure various diseases.

Keywords: Heat shock proteins, Apoptosis, Stress.

INTRODUCTION

Animals can adapt to the changes in environmental temperature (i.e., heat shock) and may acquire temperature tolerance. Heat shock response encompasses changes in stress physiology and reprograming of cellular activities to enable the organism's survival. The proteins, which are expressed during heat shock, are termed as heat shock proteins (HSPs). The major HSPs and their cognates have been presented in Table 1.

HSPs were reported for the first time, in 1960, by Ritossa, who observed a pattern of *Drosophila* salivary gland chromosome puffs that were induced in response to transient exposures to elevated temperatures. He accidentally raised the incubation temperature of *Drosophila* and found an increased gene transcription of certain proteins [1]. In the absence of stress, HSPs act as molecular chaperones by assisting in the folding, assembling, intracellular localization, secretion, regulation, translocation of cellular proteins, and even degradation of damaged proteins [2]. Following exposure to the stimulus (temperature, pesticides, heavy metals, solvents, and effluents), newly synthesized HSPs can:

1. Correct folding of nascent and stress induced misfolded proteins together with the ubiquitin-proteasome system [3,4],
2. Prevent formation of protein aggregates,
3. Promote selective degradation of denatured and misfolded proteins, and
4. Regulate apoptosis by interacting with mediators of apoptotic pathways (upstream and downstream) [4,5].

EXPRESSION OF HSP

HSPs may be either expressed constitutively or induced through the transcriptional activity of heat shock factor [6,7]. A number of stimuli can increase the expression of HSPs as represented in Table 2. Some of which are: Exposure of cells to amino acid analogs [8,9], protein kinase C stimulators [10], calcium increasing agents [10], hormones [11], Na_3AsO_4 [12] etc.

CLINICAL IMPLICATIONS OF HSPs

Gastrointestinal disorders

HSPs act as a double-edged sword, it either strengthens the gastric defense system or weakens (*Helicobacter pylori* or alcohol-associated gastritis) [6]. Exposure of microbial pathogens to gastric cells induces HSPs, causing modulation of the innate and adaptive immune responses, perpetuating gastric inflammation, or inducing autoimmune gastritis. *H. pylori* expresses the cytotoxin-associated gene-A that activates nuclear factor κB (NF-κB) inducing kinase which then cause phosphorylation and activation of IKK-α/β resulting in proteasomal degradation of the inhibitory subunit (IkB) of NF-κB [13]. As a result, translocation of p50 and p65 subunits takes place into the nucleus, where they bind to NF-κB binding motif in the promoter region of the interleukin-8 (IL-8) gene, producing IL-8 [14]. IL-8 production is regulated via RAS, RAF, MEK1/2, and extracellular signal-regulated kinases (ERK)1/2 (MAP kinase pathway). The activation of ERK1/2 causes phosphorylation of c-fos which together with c-jun forms the activation complex AP-1, regulating the expression of IL-8 gene (Fig. 1) [15]. Tang *et al.* [16] observed that increased expression of Hsp72 significantly inhibited phosphorylation of each kinase of mitogen-activated protein kinase pathway as well as IκB degradation, and nuclear translocation of p50 and p65 subunits.

Kawai *et al.* [17] reported that geranyl-geranyl-acetone (GGA), a non-toxic Hsp70 inducer, restores the heat shock response in gastric mucosa of protein-malnourished rats. GGA has also been found to confer protection to guinea pig gastric mucosal cells from necrosis induced by gastric stressors such as ethanol, H_2O_2, and HCl [18]. GGA also prevents non-steroidal anti-inflammatory drug-induced gastric lesions [19] and is therapeutically beneficial against inflammatory bowel disease-related colitis and lesions of the small intestine.

DISORDERS OF NERVOUS SYSTEM

Spinal and bulbar muscular atrophy (SBMA)

SBMA is an inherited motor neuron disease caused by the expansion of a polyglutamine tract within the androgen receptor (AR) [20]. Overexpression of Hsp70 and Hsp40 inhibits the accumulation of abnormal polyglutamine protein to toxic levels and also suppresses cell death in various cellular models of SBMA [21,22]. This preventive action is due to induction of proper refolding of abnormal pathogenic proteins [23]. It was seen that the oral administration of GGA upregulated the expression of Hsp70, Hsp90, and Hsp105 in the CNS of SBMA-transgenic mice and inhibited the accumulation of pathogenic AR in the nucleus [22]. Moreover, Hsp90 inhibitors, such as 17-AAG,

Table 1: Major HSPs with their expression, structure, and role

HSPs/Isoforms	Expression	Structure	Functions
Hsp27	C/I	Two compact domains composed of β sheets	• Thermotolerance • Apoptotic signaling • Prevent actin fragmentation • Cell differentiation
Hsp60		Three domains:	• Folding of proteins for matrix
Hsp60/Hsp10-cyt	C/I	• Apical domain	• Transport of proteins across membrane of mitochondria
Hsp60/Hsp10-mito	C	• Equatorial domain containing binding site for ATP	• Regulate apoptosis
		• Intermediate domain joins both the domain	
Hsp70		Two domains:	• Transport of proteins across cellular membrane
Hsc7	C/I	• A peptide binding domain	• Folding of newly synthesized polypeptide
Hsp70.1	C/I	• Amino-terminal ATPase domain	• Assembly of multi-protein complex
Hsp70.2	C		• Apoptosis
Hsp70.3	C		
Hsp70	C/I		
Grp75	C		
Grp78	C/I		
Hsp105	C		
Hsp90		Four domains:	• Assist in folding
Hsp90-α	C/I	• N-terminal domain	• Intracellular transport
Hsp90-β	C/I	• Middle domain involved in protein binding	• Maintenance and degradation of protein
Hsp90-N	C/I	• Charged linker region joins N-terminus with middle domain	• Cell signaling
Hsp75/TRAP-1	C/I		• Angiogenesis
		• C-terminal domain containing ATP-binding site	• Metastasis

C: Constitutive; I: Inducible, HSPs: Heat shock proteins

Table 2: Different inducers of HSPs

Physiological stimuli	Pathological stimuli	Environmental stimuli
Cycle of cell division	Microbial infection	Heat shock
Growth factors	Oxidant injury	Heavy metals
Cell differentiation	Autoimmunity	Metabolic inhibitors
Tissue development	Fever	Chemicals
Hormonal stimulation	Inflammation	Antibiotics
	Malignancy	Radiation

HSPs: Heat shock proteins

17-DMAG, have been found to promote the clearance of misfolded mutant AR through ubiquitin-proteasome system [22]. Some other Hsp90 inhibitors, such as insulin-like growth factor 1 and ASC-J9, have also shown efficacy in mouse models [24].

Neurodegenerative disorders (Alzheimer's and Parkinson's disease [AD and PD])

The accumulation of aggregated proteins has been remarkably found in diseases such as AD and PD. The pathophysiological feature behind AD is the aggregation of β-amyloid, hyperphosphorylation, and subsequent tangle formation of tau protein. The cause of PD remains vague; however, there is a strong evidence of association of α-synuclein in early steps of pathogenesis [25,26]. Many recent research activities have confirmed the protective role of HSPs in neurodegenerative disorders by folding of proteins or delivering misfolded proteins to ubiquitin-proteasome system for degradation [26]. The heat shock response genes are mainly regulated by the heat shock transcription factor (HSF-1) which is restrained in an inactivated monomer state by forming complex with HSP90 [3]. Stress, heat shock, or inhibition of Hsp90 releases the HSF-1 from Hsp90 complex. This is manifested by the subsequent production of Hsp70 and Hsp40, which promote desegregation and protein degradation [20,27]. In various animal studies, overexpression of Hsp70 and Hsp40, due to inhibition of Hsp90, has been found to suppress neurotoxicity induced by abnormally folded proteins [26]. Duo *et al*. [28] found that geldanamycin increased the expression of Hsp70 and reduced the amount of insoluble tau in an AD cell model and in rat primary cortical neurons [28]. 17-AAG has also been found to be effective against neurodegeneration in different animal models [20].

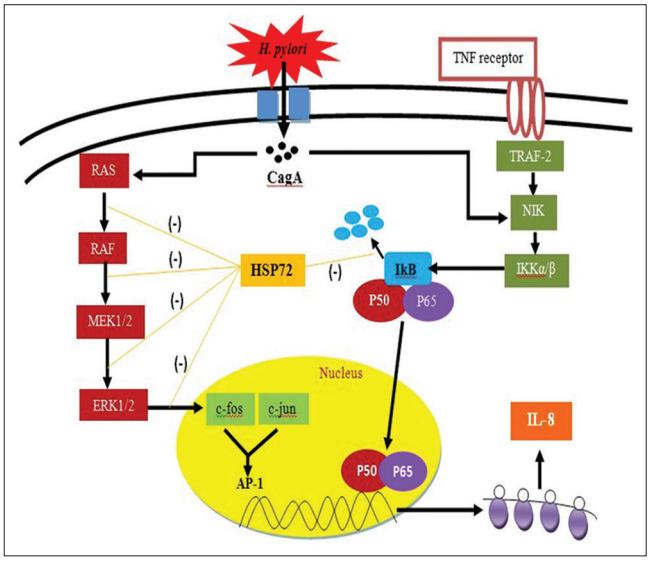

Fig. 1: The mechanism of *Helicobacter pylori* induced interleukin-8 (IL-8) production and role of Hsp72 in its inhibition. *H. pylori* expresses the cytotoxin-associated gene-A, which activates nuclear factor κB leading to IL-8 production. Hsp72 prevent IκB degradation and nuclear translocation of p50 and p65 subunits of NF-κB. Moreover, it also inhibits the phosphorylation of each kinase of mitogen-activated protein kinase pathway

CARDIOVASCULAR DISORDERS

Myocardial ischemia

Currie *et al*. [29] established the association between HSPs and myocardial protection by elevating the body temperature of rats from 37°C to 42°C for 15 minutes, which increased the cardiac inducible as well as catalase activity after 24 hrs. Hsp70 has been found to be associated with enhanced post-ischemic myocardial recovery in rat hearts [30]. It either prevents adverse conformational changes or promotes reassembly of denatured proteins, hence preventing myocardial infarction and reperfusion injury [31]. Hsp70 synthesis

also increases in cardiac tissue on exposure to stressful stimuli such as elevated temperature, hypoxia, volume or pressure overload and exposure to certain drugs (isoproterenol, vasopressin, or angiotensin), which protect the heart from further damage.

Atherosclerosis

The arterial wall undergoes continuous remodeling in response to various endothelial stressors, such as hypercholesterolemia, local injury, smoke, and toxins, causing overexpression of the HSPs [32], which are processed by macrophage and presented to T- and B-lymphocyte producing autoimmunity (Fig. 2).

Moreover, HSPs also serves as danger signals to activate the innate immunity system, causing the production of cytokines such as tumor necrosis factor alpha (TNF-α), IL-12, and IL-15. The overall effect is atherogenesis [33]. In this regard, Madrigal-Matute *et al.* (2010) [34] found that Hsp90 inhibitors (17-AAG and 17-DMAG) reduced inflammatory responses in atherosclerosis.

AUTOIMMUNE DISORDERS

Rheumatoid arthritis (RA)

It has been investigated that T-cells and antibodies from arthritic animals and RA patients are directed against HSPs [35]. The expression of Hsp96 is found to be increased in the synovial fluid of RA patients [35,36] which acts as an endogenous ligand for toll-like receptors (TLRs), mainly TLR-2 and TLR-4 (Fig. 3).

Ligand binding promotes dimerization of TLRs resulting in the recruitment of the TIR domain containing adaptor molecule (MyD88) intracellularly. The downstream signaling involves the formation of a complex containing IL-1 receptor-associated kinase-1, IL-1 receptor-associated kinase-4, TNF receptor-associated factor-6, and transforming growth factor beta-activated kinase-1 (TAK-1). The activated TAK-1 activates the IKK-β which then phosphorylates and degrades inhibitory IκB-subunit of NF-κB resulting into the translocation of active p50 and p65 subunits into the nucleus. Simultaneously, TAK-1 also activates AP-1 via MAPK cascade. In addition to MyD88, TLR-4 can interact with TIR-domain-containing adapter-inducing interferon-β (INF-β) that recruits TNF receptor-associated factor-3 and TANK-binding kinase-1, which in turn, activates IRF-3. Upon activation, IRF-3 forms a dimer and translocates into the nucleus. All these transcription factors (NF-κB, AP-1, and IRF) induce expression of pro-inflammatory genes leading to the synthesis of IL, TNF, INF, etc. [37,38].

Rice *et al*. [39] found that Hsp90 inhibitor (SNX-7081) has therapeutic benefit in rat arthritis models by blocking nuclear translocation of NF-κB. In another study, administration of EC144, a synthetic Hsp90 inhibitor, blocked disease development in rat collagen-induced arthritis by suppressing the inflammatory response [40].

Systemic lupus erythematosus (SLE)

SLE is a chronic inflammatory disease of autoimmune origin with complex immunological manifestations. In SLE, there is reduced immune tolerance and abnormal activation of T and B cells, which leads to the production of auto-antibodies mainly against protein-nucleic acid complexes such as chromatin and ribonucleoprotein [41]. It has been studied that TLRs play a role in the innate immunity by activating inflammatory pathways and regulating defense against pathogens. However, inappropriate activation of TLRs by exogenous or endogenous ligands (HSPs, fibrinogens, etc.) may lead to SLE [42].

Binding of ligand to TLRs, expressed on the surface of B cells, lead to the formation of antibodies and their immune complex with the ribonucleoproteins. The uptake of immune complex by dendritic cells (DCs) via Fc receptor and by B cells via B cell receptor lead to the IFN-α production. Moreover, activation of TLRs which are expressed on DCs upregulate the cell-surface expression of co-stimulatory (CD80 and CD86) molecules and also induces expression of cytokines such as IL-12 and other chemokines. Induction of CD80 and CD86 on DCs results

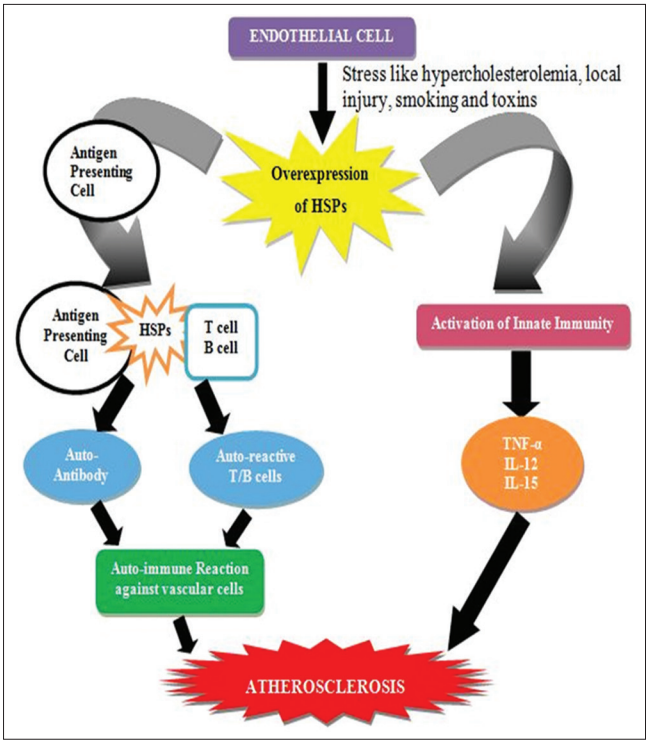

Fig. 2: Schematic representation of role of Hsp60 in the pathogenesis of atherosclerosis. Heat shock proteins (HSPs) are processed by macrophage and presented to T- and B-lymphocyte leading to activation of autoimmunity. Moreover, HSPs also activate the innate immunity system causing production of cytokines

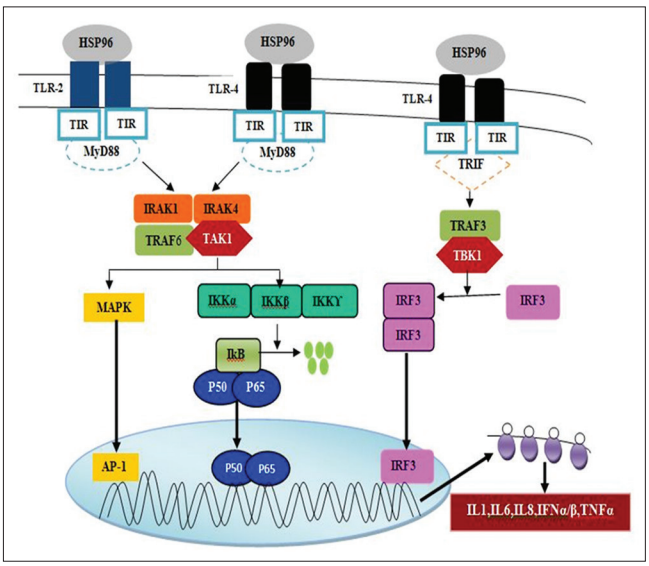

Fig. 3: The role of Hsp96 in signal transduction of toll-like receptors (TLRs). Hsp96 activate TLRs resulting into the translocation of active p50 and p65 subunits of nuclear factor κB into the nucleus along with activation of AP-1 and interferon regulatory factor-3. This leads to the synthesis of interleukin, tumor necrosis factor, interferons, etc.

in the activation of T cells (Fig. 4) [42,43]. In many studies, elevated level of Hsp90 has been correlated with increased expression of IL-6 in SLE; therefore, its pharmacological inhibition has increasingly become the focus of research on SLE [44]. In this regard, 17-DMAG has been reported to produce therapeutic effect in mouse model of SLE by

inhibiting Hsp90 [45]. In another study, ganetespib therapy was found to be effective in improving multiple disease parameters, including suppression of autoantibody production and the preservation of renal tissue integrity and function in MRL/lpr autoimmune mouse model [46].

Diabetes mellitus

Since a characteristic feature of diabetes is uncontrolled oxidative stress, HSPs, being antioxidant, should prove to be helpful in fighting diabetic complications [47]. The following are some proposed mechanisms by which diabetes may impair HSPs response.

Reduction in translational elongation-factors

Insulin regulates the initiation and elongation phases of translation by modulating the initiation-factors (eIF2, eIF2B, eIF3, eIF4B, eIF4E, and eIF4G) and elongation-factors (eEF1 and eEF2). In an experimental diabetic rat model, the rate of peptide chain elongation was found to be reduced due to a marked reduction of EF2. It was evident that the insulin therapy restored protein synthesis and also the level of EF2 in diabetic rats [48].

Impaired HSF-1 activation

In diabetes, the glycogen synthase kinase-3 (GSK-3) has been found to be upregulated. GSK-3 is an enzyme which was initially known to regulate the metabolism of glycogen, but now, it has been found to be involved in the phosphorylation and subsequent suppression of HSF-1 activity. Overexpression of GSK-3 impairs heat shock-induced activation of HSF-1 [49,50].

Reduction in membrane fluidity

For increased HSPs expression, membrane fluidity is a vital factor. Diabetes is associated with glycation, oxidative stress, and insulin deficiencies, which reduce the membrane fluidity and make it stiffer as a result of which cellular HSPs response is reduced [51].

A decreased expression of Hsp72 mRNA is observed in patients with type-2 diabetes [52]. Moreover, in diabetic rodents, pharmacological induction of Hsp72 expression improves the insulin sensitivity [47]. In the absence of Hsp72, c-Jun N-terminal kinases (JNK) and IKK phosphorylates IRS-1 on Ser-307, rendering it a poor substrate for the activated insulin-receptor which results in inhibition of insulin signal transduction via Akt [53]. Hsp72, by preventing phosphorylation of JNK and IKK, cause activation of Akt, which plays two principal roles in the metabolism of glucose regulated by insulin (Fig. 5) [54]:

1. It induces translocation of glucose transporter type 4 transporters from the cytoplasm to the plasma membrane and,
2. It promotes glycogen synthesis by inactivation of GSK-3 via serine phosphorylation,
3. Similarly, inhibition of Hsp90, by AUY922 administration in mice, led to inhibition of JNK-1 phosphorylation, cytoprotection, and improved insulin signaling in cells [55].

OTHER IMPLICATIONS

Apoptosis

Apoptosis refers to an energy dependent asynchronous, genetically controlled process in which the activated apoptotic genes cause self-destruction of damaged cells. The balance between cell survival and death is under genetic control. Apoptosis is a process of cell suicide, the mechanism of which is encoded in the chromosomes of all nucleated cells [56]. HSPs inhibit apoptosis (Fig. 6). The antiapoptotic action of Hsp27 is to:

1. Promote the antioxidant defense by decreasing reactive oxygen species [57],
2. Chelate cytochrome-c released from mitochondria to prevent the formation of apoptosome with subsequent activation of caspases [58,59], and
3. Inhibit Fas-mediated apoptotic pathway by interacting with death-associated protein 6 (Daxx) [59].

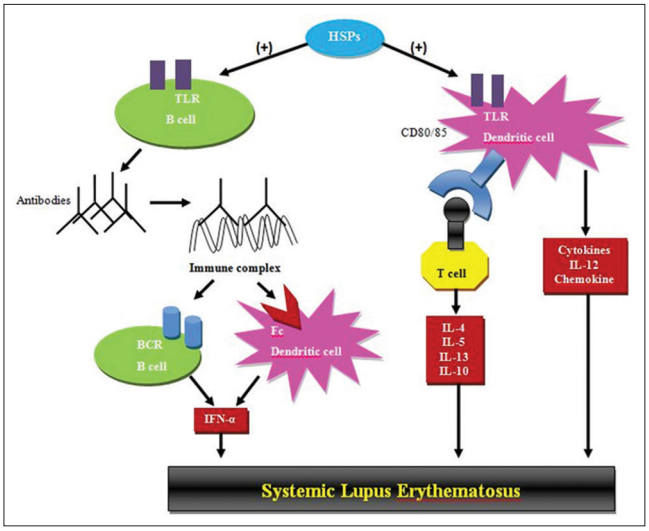

Fig. 4: Toll-like receptors (TLRs) signaling: The role of heat shock proteins (HSPs) in systemic lupus erythematosus. HSPs activate TLRs which lead to formation of immune complex along with activation of T-cells. This induces the expression of cytokines and other chemokines

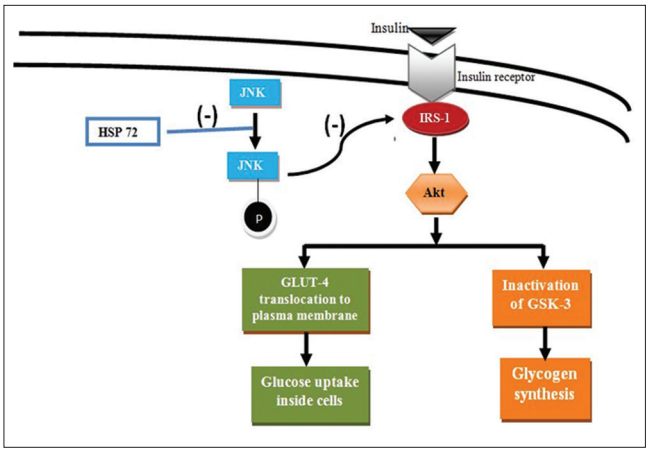

Fig. 5: The protective role of Hsp72 in type 2 diabetes mellitus via Akt signaling pathway. Hsp72 prevent phosphorylation of c-Jun N-terminal kinases and cause activation of Akt. That leads to glucose uptake as well as formation of glycogen

The antiapoptotic action of Hsp70 is to:

1. Inhibit apoptosis signal-regulating kinase-1 and interact with peptide binding domain of the JNK [59],
2. Bind with Apaf-1 to prevent caspase activation, and
3. Inhibit caspase-independent cell death by binding to apoptosis-inducing factor [57].

Hsp90 prevents cell death by forming a cytosolic complex with Apaf-1 and inhibiting the formation of apoptosome [60]. It also prevents degradation of RIP-1 kinase which connects death receptor to NF-κB activation. In the absence of Hsp90, RIP-1 gets degraded and NF-kb is inhibited, sensitizing the cells to apoptosis [57]. Hsp90 binds with phosphorylated Akt (serine/threonine kinase) inhibiting dephosphorylation and activation of Akt by PP2A. In the absence of Hsp90, Akt gets activated and cause phosphorylation of B-cell lymphoma-2 (BCL2) related pro-apoptotic protein [60-63]. Consequently, HSPs are ubiquitous and highly conserved class of proteins whose expression is induced in response to a wide variety of physiological and environmental insults [57].

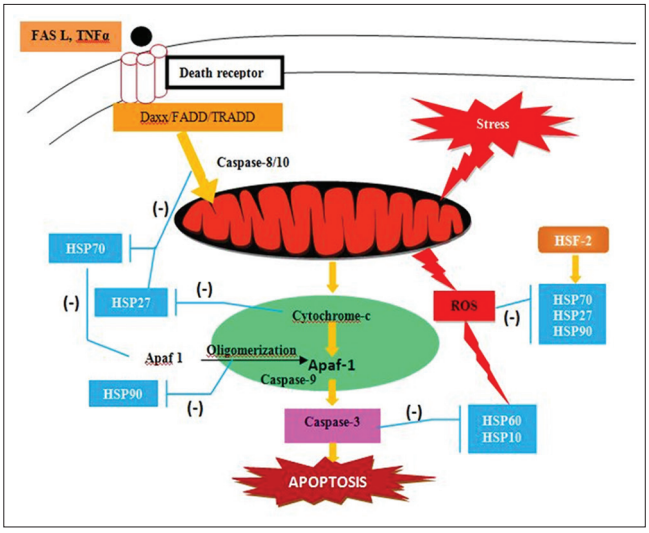

Fig. 6: The role of heat shock proteins (HSPs) in apoptosis. HSP27 decreases reactive oxygen species, chelate cytochrome-c, and inhibit Fas-mediated apoptotic pathway by interacting with death-associated protein 6. HSP70 mainly prevent oligomerization of apoptotic protease activating factor-1 (Apaf-1). HSP90 form a cytosolic complex with Apaf-1 and inhibit the activation of caspases

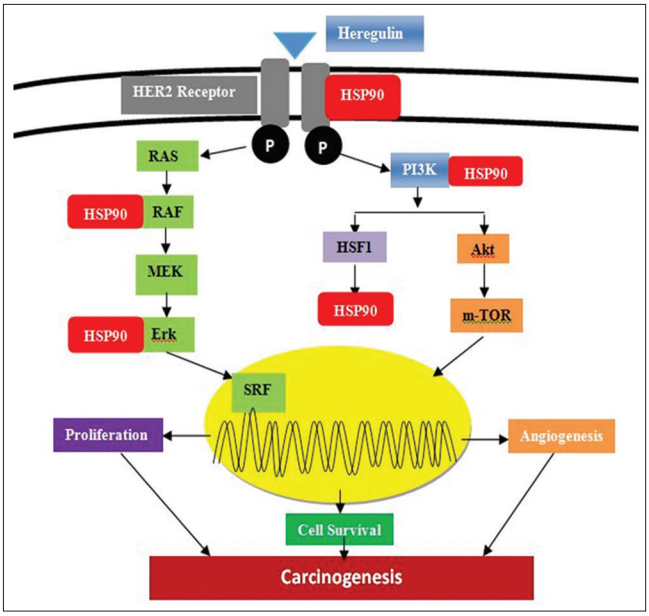

Fig. 7: The role of Hsp90 in the human epidermal growth factor receptor-2 (HER-2) signaling pathway. Hsp90 is essential for the activity of HER2 itself as well as its downstream signaling proteins. Activation of HER2 receptor by heregulin promotes cellular proliferation and prevents apoptosis leading to carcinogenesis

Cancer

Among all types of diseases, the cancer attrition rate is the worst: Only 5% of cancer drugs entering clinical trials actually reach marketing approval. HSP targeting drugs are now emerging as a potential anticancer agent because HSPs play a key role in the cytoprotection. Their constitutive expression makes the cancerous cells survive [64]. The proposed cytoprotective mechanisms of HSPs are:

1. Catalysis of proper folding of misfolded proteins and prevention of their aggregation [65],
2. Inhibition of caspase-dependent and caspase-independent cell death pathways [66], and
3. Stabilization or proteasomal degradation of proteins providing cellular survival [67].

Hsp27 exhibits the acquired resistance of tumor cells and its level increases in cancer of prostate [68-70], breast [70], uterus and ovary [70,71], head and neck, gastrointestinal tract [72], Hodgkin's disease [73], nervous system (meningiomas, astrocytomas, and neuroblastomas), and bladders [74].

Cancer cells abundantly express Hsp70 at different stages of tumorigenesis and during anticancer treatment to resist various insults. In this context, Wen *et al.* [75] reported that VER-155008 significantly inhibits non-small-cell lung cancer (NSCLC) proliferation and cell cycle progression by abolishing Hsp70 overexpression. Li *et al.* [76] reported that MKT-077 analogs have antiproliferative activity against cancer cell lines through their ability to inhibit members of the Hsp70 family.

Leu *et al.* [77] determined that 2-phenylethynesulfonamide (PES) interacts selectively with Hsp70 and promotes death of cultured tumor cells. In animal models of spontaneous BCL, administration of PES significantly protected mice from BCL development without any sign of organ toxicity [77,78].

Tran *et al.* [79] demonstrated that epigallocatechin-3-gallate inhibited the expression of Hsp70 and Hsp90 and thereby decreased cell proliferation and colony formation of MCF-7 human breast cancer cells.

Hsp90 acts in the cellular carcinogenesis via human epidermal growth factor receptor-2 (HER2) signaling pathway (Fig. 7). It is essential for the activity of HER2 itself as well as its downstream signaling proteins, e.g., Akt, RAF-1, ERK, etc. [80]. In normal cells, HER2 plays important roles in all stages of cell development. However, the mutation or overexpression of HER2 could directly lead to tumorigenesis as well as metastasis [81]. The activation of HER2 receptor by heregulin ligand leads to the phosphorylation of the tyrosine residues of the receptor which trigger downstream signaling pathways (PI3K and MAPK) promoting cellular proliferation and preventing apoptosis [81].

Many Hsp90 inhibitors (e.g., benzoquinone, ansamycins, herbimycin-A, and geldanamycin) block the binding of ATP to Hsp90 leading to destabilization of Hsp90 complex which results in proteasomal degradation of the RAF, Akt, and mutant p53 and inhibition of tumor growth with activation of apoptosis [15,80,82].

Geldanamycin downregulates Akt in Epstein-Barr virus-positive NK/T-cell lymphoma and thereby induces apoptotic cell death [83]. In another study, ganetespib (STA-9090), a non-geldanamycin Hsp90 inhibitor, caused inhibition of proliferation and induction of apoptosis in NSCLC cell lines [84]. Jensen *et al.* [85] reported that NVP-AUY922, a novel small molecule Hsp90 inhibitor, potently inhibits the proliferation of human breast cancer cell lines. Georgakis *et al.* [86] found that 17-allylamino-17-demethoxy-geldanamycin (17-AAG), a Hsp90 inhibitor, induced cell cycle arrest and cell death in a dose- and time-dependent manner in mantle cell lymphoma cell lines. Exposure of NSCLC cell line with IPI-504 causes degradation of echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase fusion protein, an oncogenic driver in NSCLC, which leads to a potent inhibition of downstream signaling pathways and to the induction of growth arrest and apoptosis in cancer cells [87]. Several other Hsp90 inhibitors have been reported in clinical settings, including AT13387, CH5164840, CUDC-305, MPC3100, PU-H71, SNX-2112, and XL888 [88].

Consequently, an interesting strategy for anticancer drug could be to combine Hsp90 and Hsp70 inhibitors [89].

Protein triage

One of the major physiological roles of HSPs is in the protein homeostasis [90]. Sometimes, abnormal protein synthesis, denaturation

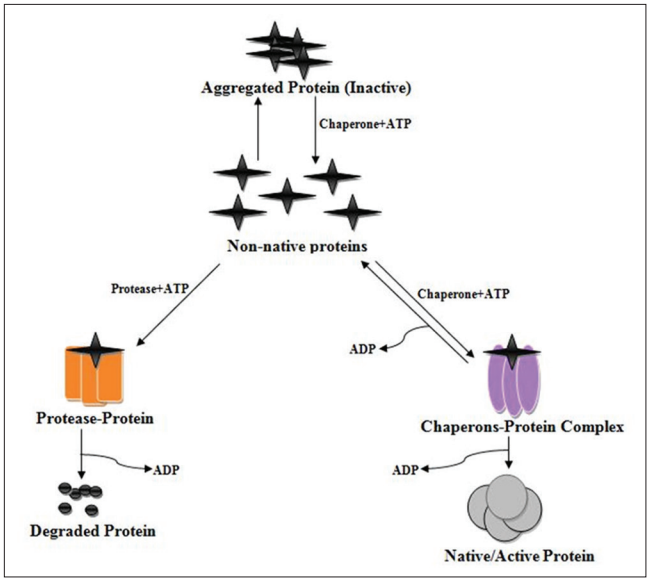

Fig. 8: Protein triage process: Involvement of chaperones and proteases. Heat shock proteins (HSPs) convert the non-native polypeptides into active or properly folded native protein. If the misfolded protein cannot be renatured, the proteasome favors its destruction. Moreover, HSPs also cause disaggregation of the aggregated non-native protein

of proteins by heat or chemicals, etc., leads to the formation of misfolded or non-native polypeptides. The peril of these inactive polypeptides is controlled by either of the two pathways [67]:

1. Refolding by chaperones or HSPs and
2. Degradation by ubiquitin-proteasome system.

There exists a balanced coordination between these two separate pathways. HSPs bind to the non-native polypeptides and cause release of the active or properly folded native protein (Fig. 8). If the misfolded protein cannot be refolded, the proteasome favors its destruction by promoting their ubiquitination [67]. In some cases, the non-native protein may aggregate, which can again be desegregated with the help of HSPs [91]. The ability of HSPs to restore or destruct damaged proteins confers on them a key role in protein quality control and in the regulation of the protein triage [67]. The decision of HSPs to direct "folding versus degradation" remains poorly understood, but it probably depends on the type and intensity of the stress stimuli (external or physiological).

CONCLUSION

The recent evidence indicates the connections between HSPs and the cellular machinery in the different diseased states. Collectively, the studies suggest that HSPs can be used as novel molecular targets for both the pharmacological and therapeutic interventions to prevent various diseases. With the effort of dedicated laboratories, there should be optimism about the rapid development of novel chemical therapies for unfolding/misfolding diseases based on the function of the core domain of HSPs. An understanding of different sites for subunit-subunit interaction, target substrate protein binding, phosphorylation and interaction with cytoskeletal elements, small metabolites, pharmaceuticals, and nucleotides need to be characterized chemically. Furthermore, continued research is needed to define the physiological and biological function of nearly all HSPs identified to date.

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