Role of HSP in the Pathogenesis of Age-Related Inflammatory Diseases

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Abstract

Introduction Heat shock proteins (HSP) are pivotal players in the normal cellular physiological processes and possess regulatory functions in pathogenesis of age-related disorders. HSP as chaperons are participating in protein folding, proper protein conformation, and prevention of undesired protein aggregation. In here, we provide the essential roles of HSP in inflammation with special focus on the ageing-related inflammatory diseases such as Alzheimer's disease, Parkinson's disease, diabetes, rheumatoid arthritis, and atherosclerosis.

Methods A literature based collection of articles in the available search engines (PubMed and Google Scholar).

Results We show the interrelation of HSP and inflammation-related ageing disorders such as Alzheimer's disease, Parkinson's disease, diabetes, rheumatoid arthritis, and atherosclerosis.

Conclusions Understanding the critical roles of HPS would help in designing and manufacturing therapeutics for ameliorating the symptoms associated with age-related diseases.

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Abbreviations

AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
Aβ	amyloid β peptides
CRP	C-reactive protein
HSF	heat shock factor
HSP	heat shock proteins
IL	interleukins
PD	Parkinson's disease
RA	Rheumatoid arthritis
ROS	reactive oxygen species
SOD	superoxide dismutase
TGFβ	transforming growth factor-β
TNF	tumor necrosis factor

1 Introduction

In 1962, Ritossa has been discovered Heat chock proteins (HSP). They are a family of highly conserved ubiquitous proteins. This family composed of group of different molecular weight proteins including HSP10, Hsp27, HSP40, Hsp60, Hsp70, Hsp90 and Hsp110 [25]. However, Hsp70 and 90 are the two major types that have the potential to bind to the unfolded protein helping them to folded and synthesized properly [25, 120]. Some types of this protein could express substantially, while the most of them expressed under stress conditions [166]. A variety of environmental or physiologic stress could lead to production and activation of HSP such as inflammation, hypoxia, chemotherapy, infections, as well as thermal injury [1, 86, 157–161]. In living systems, HSP have essential activities including polypeptides folding, proteins transportation, and formation of multiprotein complexes [62]. Moreover, they can prevent apoptosis, cleared aggregated proteins, and ameliorates the cytotoxic impact of toxic proteins.

During aging, declined HSP expression was reported in several tissues particularly muscle, liver, neurons, and vascular system [100, 133], with resultant protein aggregation, a commonly noted feature in neurodegenerative disorders [57, 64]. On the other hand, it is now well documented that, aging is related to presence of high concentration of pro-inflammatory cytokines such as interleukins (IL), IFNα, IFNβ, C-reactive protein (CRP), tumor necrosis factor (TNF), and transforming growth factor-β (TGFβ) [49, 55]. This inflammatory response becomes evolutionarily benefit during adulthood. However, during aging, it becomes detrimental due to inactive

natural selection [53]. Inflamm-ageing is a chronic inflammatory response associated to the physiologic aging. It is the primary risk factor for the common age-related pathologies including malignancy, dementia, and cardiovascular disorders. Moreover, it may be considered as generalized health indicator for mobility disability, impairment of daily activities, and premature death [105, 156, 162].

Recently, HSP proteins were reported for their anti-inflammatory and antiapoptotic effect. Therefore, they have the potential to modulate and reduce the responses against various inflammatory cytokines. Consequently, understanding for the essential role of HSP in pathogenesis of age-related chronic inflammatory diseases may be a promising target to block the establishment of those diseases [44]. The aim of the present work is to update knowledge concerning the key role of HSP in pathogenesis of age-related inflammatory diseases including neurodegenerative disorders (such as Alzheimer's disease and Parkinson's disease), vascular disorders (such as Atherosclerosis), diabetes, rheumatoid arthritis, and neoplastic changes.

1.1 History and Types of HSP

HSP are a collection of common and highly preserved proteins. According to their size, HSP have been categorized into two groups: small molecular weight HSP and high molecular weight HSP. The first group contains four families: Hsp60, Hsp70, Hsp90, and Hsp110. Some of these proteins have continuous expression whereas stressful conditions induce the expression of the others [166]. High molecular weight HSP are ATP-dependent chaperones and need cochaperones to modify their conformation and ATP binding. On the other hand, small molecular weight HSP are ATP independent chaperones. HSP are stimulated by many environmental and physiological factors, such as inflammation, hypoxia, temperature stress, anticancer chemotherapy, or infections [86].

1.2 Role of HSP in the Inflammatory Mechanism

The best biological stimulant to induce the innate immunity response is the invasion of a foreign molecule. Innate immune recognition receptors decide to respond or ignore that stimulus by activation of PAMP (pathogen-associated molecular patterns) molecules, i.e. factors linked with groups of pathogens (for example bacterial CpG DNA, lipopolysaccharides, etc.). Other pathway for the induction of innate immunity is 'danger theory' [119]. By this hypothesis, the innate immunity can be induced by endogenous substances produced by the stressed or damaged tissue. Based on this theory, stressed cells can transfer stress to other cells. The stress signals produced by cells can be the HSP stimulated in response to the damage, so they are possible candidates for signaling cellular stress or tissue damage. Some of

HSP such as Hsp70 and Hsp60 have been detected to be capable of signaling by TLR-4, TLR-2, and CD14 [8, 187]. Now, it is well established that Hsp70 is in charge of the stimulation of monocytes, macrophages, natural killer cells, dendritic cells, hepatocytes, etc. [26, 42, 58, 174]. Furthermore, extracellular HSP have been detected to work as powerful immunosuppressive or immunostimulatory molecules according to the various circumstances [124].

In addition to Hsp70, other HSP have been detected in the extracellular matrix, such as Hsp27 [108], Grp78/BIP [45, 99], Hsp90 [184], and Hsp60 [124]. The biological relation of these factors has been enhanced by the presence of Hsp70 in the serum of patients having myocardial infarction [47], chronic inflammation [135], coronary artery disease [212, 216], lung injury [59], infections [135], ischemia/reperfusion events [75], cancer [12], diabetes [137], hypertension during pregnancy [128], etc. HSP can also be detected at lower levels in the serum of healthy individuals [145]. Interestingly, the existence of Hsp70 in plasma is linked to enhanced survival of sever ill patients [217]. Other extracellular HSP such as Hsp90 [170], Hsp60 [211], and Hsp27 [108] have also been correlated with many diseases like coronary heart disease, pancreatic carcinoma, systemic lupus erythematosus or cancer metastasis.

Cytoprotection is the main role of HSP. Some investigations have revealed the number of cells surviving elevated when the temperature increased till 43 °C. This thermotolerance was attributed to the increased formation of HSP [104]. Some reports suggested the role of HSP in the suppression of stress-activated kinases. [56] revealed that preheating the human leukemic cells resulted in decreased cell death after heat shock, which was correlated with p38 activation and suppression of JNK. This influence might be made by HSP. This overexpression suppressed the stress kinase-activating influences of ultraviolet irradiation, H_2O_2 and heat. Park et al. indicated that Hsp72 inhibits the JNK signaling pathway by prohibition of JNK phosphorylation by its upstream kinase SEK1 [140]. Moreover, Hsp70 has been involved in the suppression of IKKγ and following synthesis of IKK complexes [163]. As for the impact of NfkB in inflammation, the suppression of its kinase, IKK, has specific therapeutic importance for inflammation. Furthermore, overexpression of Hsp70 prevents sepsis-induced lung injury in rats through suppression of the IKK complex [193].

1.3 Role of HSP in Aging-Related Diseases

The aggregation of oxidized proteins is an essential feature of the major neurological diseases, and many investigations have revealed that elevating HSP levels can have useful influences [101]. HSP have been detected to decrease the symptoms of Alzheimer's disease, a disease caused by the aggregation of β-amyloid in neurons [148]. The aggregation of β-amyloid was decreased after the over-expression of HSP

in primary neurons and neural blastoma cells [189]. In an in vitro study, Hsp70 was revealed to help in the digestion of amyloid plaques by enhancing microglia [90].

In Parkinson's disease, cytoplasmic protein aggregates (Lewy bodies) containing numerous proteins such as HSP, α-synuclein, ubiquitin and parkin are present in neurons [51]. Cells have increased levels of HSPB5 (αB crystalline) were detected to have a significantly decreased number of Lewy bodies [23]. Although, Amyotrophic lateral sclerosis (ALS) has no known cause, there is a powerful proof connecting this neurodegenerative disease with dysfunctional superoxide dismutase (SOD). It has been detected that Hsp70 interacts with ubiquitin to aim the degradation of dysfunctional SOD by proteasome [186]. Treatment of mice with HSP inducer, arimoclomol, lowered the progression of ALS [93]. ROS participate in the development of multiple sclerosis lesions, and an elevation in HSP expression with the beginning of multiple sclerosis has been detected [132]. Antioxidant therapies have a beneficial effect for multiple sclerosis [167], and an elevation in HSP is accompanied by the decrease of plaques in multiple sclerosis [152].

In addition to having a pivotal role in the treatment of age-related diseases, modification of HSP levels reveals a healthy lifespan and elevating longevity of humans. The function of HSR and HSP across species means that several influences observed in lower organisms could be utilized in humans. Many investigations on C. elegans have revealed marked elevations in life-span with the increased expression of HSP [191]. Moreover, enhanced longevity because of caloric restriction demanded a functional HSR pathway in C. elegans [175]. In Drosophila, HSP revealed the ability to elevate the lifespan of Drosophila, where overexpression of HSP22 was detected to enhance protection against stress and expand longevity [129]. Moreover, Murine models have assisted to reveal the mechanisms behind elevated life-span. Mouse embryonic fibroblasts were detected to reach replicative senescence far sooner at elevated levels of oxidative stress [142], and mice lacking the ubiquitin ligase/co-chaperone CHIP reveal a lowered lifespan with a quickly ageing phenotype [126]. A comparison between short-lived Mus musculus and long-lived Peromyscus leucopus, two closely related species of mice, revealed that the difference in life-span correlated with a variance in oxidative stress tolerance [37]. Moreover, caloric restriction, which is known to increase maximal life-span in murine models, was detected to keep levels of Hsp70 and Hsp60, which normally both decrease during ageing [35].

Exposure of human fibroblasts to frequent heat stress was detected to elevate the levels of Hsp70, Hsp27, HspA8 and Hsp90 and elevate tolerance to oxidative stress; however, no elevation in their Hayflick limit was detected [52]. Extracellular (secreted) HSP, in contrast to intracellular HSP, could have detrimental influences and be pro-inflammatory. Importantly, plasma levels of Hsp70, when compared to controls, were inversely correlated with longevity and significantly decreased in centenarian offspring [178].

1.4 Role of HSP in Alzheimer's Disease

Recently, Alzheimer's disease (AD) has a major effect on the international public health. AD characterized by the abnormal synthesis of Tau and amyloid-peptides (Aβ), resulting in the pathological creation of intracellular neurofibrillary tangles (NFTs) and extracellular senile plaques. Insoluble Aβ with a sequence between 38 and 42 amino acids created senile plaques in brains of AD patients [178]. According to the amyloid hypothesis, β-amyloid precursor protein (APP) which is a trans-membrane protein created Aβ peptides. Aβ42 is the main motif in amyloid plaques and creates the most toxic oligomers. Therefore, the increased synthesis of Aβ stimulates cell death, finally resulting in dementia [141]. Moreover, the pathological hyperphosphorylation of protein Tau and its misfolding and accumulation within the cytoplasm resulted in the intra-cellular NFT lesion [63].

The major cause of neuron's injury in AD is because of stress stimulated by the misfolding of Tau and Aβ peptides, inducing the synthesis of toxic oligomers and finally NFTs, the significant of the chaperones in AD has been proofed in the last two decades [113]. Among molecular chaperones, Heat Shock Proteins (HSP) are major constituent of the chaperone and Hsp90, Hsp70 and Hsp60 are deemed target of special superiority in AD [116] and as cancer [32].

Molecular chaperones modify protein activity, organize protein folding and target misfolded or accumulated proteins for degradation or for refolding. HSP are pivotal to ease the protein folding process [39]. They share in various mechanisms to guard the cells against stress-related mechanisms hurtful to the cell [39]. So, as detected in different neurodegenerative diseases, failure of these cellular mechanisms can lead to pathogenic lesions. Several data revealed that HSP organize protein misfolding in many neurodegenerative diseases, such as AD, showing preventative roles and/or working as pathogenic factors. Stress-induced proteins like chaperones have been reported to work as preventive molecules for cells of the nervous system [116]. Several proofs revealed that oxidative stress is a characteristic of PD and AD [208]. Abnormal aggregation of Tau and Aβ proteins and mitochondrial dysfunction can share in making the imbalance between antioxidant and oxidant mechanisms defining oxidative damage in AD patients [208]. In the brain, oxidative stress can make destruction that share in neuronal loss [2]. Reactive oxygen species (ROS) can aggregate inside cells and have negative influences on all biological molecules, determining, for instance, enzyme inactivation, nucleic acid breakage, lipid peroxidation and polysaccharide depolymerization. Under these stress circumstances, the expression of the genes encoding HSP was stimulated [2]. Furthermore, increased levels of ROS and mitochondrial dysfunction might synthesis a vicious circle sharing in AD progression and instauration [116].

Recently, several results were acquired from research on anti-cancer agents. Some compounds of therapeutic impacts were detected but clinical trials are not granted till now. So, acquisition further information is essential and several questions should be lighted, such as: (i) mode of action of HSP inhibitors; (ii) AD biochemical pathways related to HSP; (iii) sensing of client/HSP protein-protein

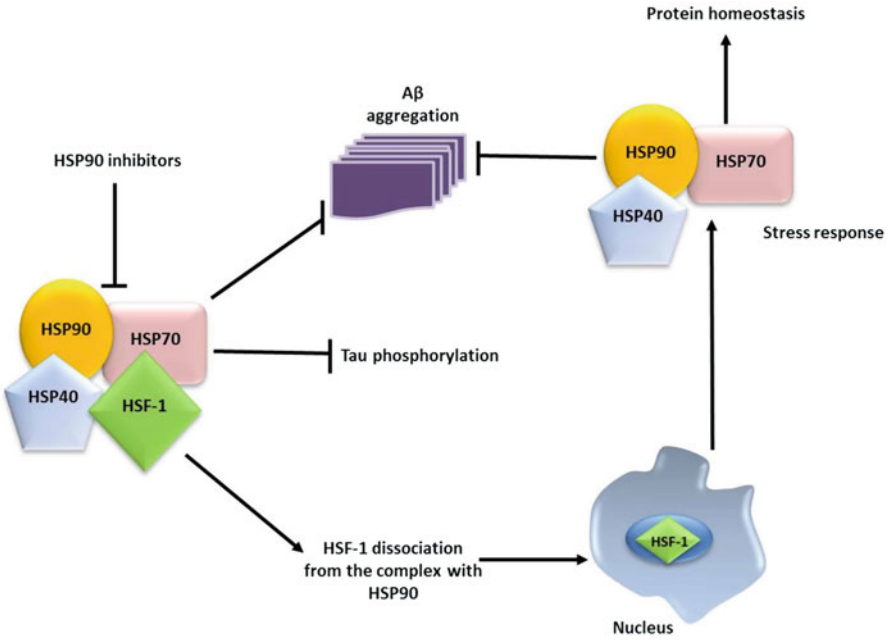

Fig. 1 Down-regulation of Hsp90 in Alzheimer's disease induce decline in aggregation and hyperphosphorylation of Tau protein. In cellular stress and Hsp90 inhibitors, Heat Shock Factor 1 (HSF-1) dissociates from the chaperone and induces the activation of heat shock genes within nucleus and stress response through production of Hsp90, Hsp70 and Hsp40, restoring protein homeostasis

interactions at the molecular level; (iv) selection of stress-induced versus constitutive HSP [138, 151]. In conclusion, HSP targeting might be the fundamental for potential drugs in the polypharmacological approach and multitargeted drug discovery and toward a complex disease such as AD. The role of HSP in the pathogenesis of Alzheimer's disease is illustrated in Fig. 1.

1.5 Role of HSP in Parkinson's Disease

Parkinson's disease (PD) is the second most popular neurodegenerative disorder influencing 1% of the population over 60 [41]. People having PD suffer from cardinal motor symptoms comprise muscular rigidity, bradykinesia, gait decay or rest tremor but often cause nonmotor symptoms, like psychiatric symptoms and cognitive sickness. Loss of the dopaminergic neurons of the *substantia nigra* (SN) *pars compacta* lead to most of symptoms accompanied by PD result from [91]. Recently, PD is handled surgically, by deep brain stimulation (DBS) and, pharmacologically, by supporting dopamine tone (e.g., dopamine replacement with

L-dopa) [91]. As the disease advances L-dopa remediation is accompanied by complications comprising dyskinesia and motor fluctuation. DBS is limited to a group of patients suffering from L-dopa-induced complications and L-dopa responsive motor symptoms, but without marked psychiatric disturbance or cognitive sickness. Interestingly, both interventions result in symptomatic cure and do not slow the progression of PD.

Thus, there is a requirement for a remedy targeting the main sources of the disease. By the pathological view, PD cause the existence of proteinaceous intracellular aggregates composed primarily of α-synuclein, called Lewy pathology (Lewy neurites and Lewy bodies). Multiplications and missense mutations of the SNCA gene, which encodes for α-synuclein, induce the tendency of α-synuclein to self-accumulate and cause heritable forms of PD and therefore involving α-synuclein accumulation in the pathogenesis of the disease [147, 172]. While there is suspicion concerning the specific form of accumulates ("species") that are neurotoxic, novel proof supposes that α- synuclein toxicity is granted by soluble oligomeric species [36, 92, 179]. Due to the pivotal role of α-synuclein accumulation in PD, researchers study about the nature and modification of the molecular pathways in charge of directing protein misfolding and folding, decreasing abnormal protein aggregation and keeping proper protein confirmation, gives a potential path for distinguishing a disease altering strategy.

Early proof involving molecular chaperones in the pathobiology of PD concluded from the detection by Auluck et al. [11] that Hsp70 overexpression alleviate α-synuclein-mediated dopaminergic neurodegeneration in a Drosophila model. This indicates that Hsp70 can have a neuroprotective role in PD. Posteriorly, McLean et al. [122] reported that the overexpression of Hsp70 and Hsp40 family members decreases the synthesis of α-synuclein accumulates in vitro and that Lewy bodies colocalize with multiple chaperone proteins. Molecular chaperones were involved in the pathobiology of PD by the detection of mutations within the promoter region upstream of both inducible and expressed Hsp70 family members elevate the danger of PD [201]. Moreover, mutations in the HspA9 (mortalin), Hsp70, were indicated to enhance the progress of PD [43]; on the other hand, other groups indicate mutations in HspA9 are not a common reason of early-onset PD as they are also detected in patient controls [54].

The ability of Hsp70 overexpression to improve α-synuclein toxicity has been well studied in yeast by autonomous groups which have revealed that Hsp70 overexpression can reduce α-synuclein in mediated cell death [50] and decrease high molecular weight aggregates in rodent models of PD [102, 127]. Hsp70 overexpression was detected to be preventive against cell death caused by the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), mitochondrial complex I inhibitor, both in vivo [46] and in vitro [149]. α-synuclein aggregation is not characteristic to the toxin model, but α-synuclein is necessary for MPTP-induced cell death as revealed by the opposition of α-synuclein null mice to MPTP [40]. On the other hand, mitochondrial HspA9 may play a pivotal role in the mitochondrial flaws inspired by the pathological A53T mutant α-synuclein as HspA9 knockdown

prevents against the mitochondrial fragmentation and elevated tendency to the complex I inhibitor, rotenone, stimulated by A53T overexpression [111].

The mechanism, Hsp70 decreases α-synuclein toxicity, appears to be dependent mechanism on both its function in protein degradation and its refolding activity by the ALP and UPS. Mutations which change the ATPase function of Hsp70 (K71S) cancel its preventive influence on α-synuclein toxicity, suggesting that Hsp70 folding activity is essential for its preventive function [102]. Importantly, this mutation has no influence on the ability of Hsp70 to inhibit α-synuclein accumulation [102], indicating that Hsp70 utilizes clear mechanisms to decrease the aggregation and toxicity and of α-synuclein. Moreover, Hsp70 can ease disassemble of preformed α-synuclein aggregates [134]. Gao et al. [60] revealed that an Hsp70 machine composed of HspH2, DNAJB1, and HspA8 could efficiently disaggregate created α-synuclein fibrils in vitro.

Many studies have indicated that CMA may play a pivotal role in alleviating α-synuclein toxicity [204]. Promoted α-synuclein expression in both paraquat and transgenic models of PD leads to the enhancement of HspA8 and LAMP2A expression and a larger movement of α-synuclein into the lysosomes [115]. Furthermore, both HspA8 and LAMP2A have decreased expression in the SN of PD patients [3], and a novel investigation revealed a link between the α-synuclein aggregation and loss of LAMP2A in postmortem PD brains [131]. Importantly, the detected reduction in HspA8 and LAMP2A expression anatomically overlaps with an elevation in miRNAs able to translationally suppress both HspA8 and LAMP2A [4], and implicate miRNAs in PD-associated chaperone dysregulation. In conclusion, the ability of Hsp70 and its cochaperones to disaggregate, refold, and aim for destruction of toxic α-synuclein species indicates that molecular chaperones can have a pivotal role in the pathobiology of PD. The role of HSP in the pathogenesis of Parkinson disease is illustrated in Fig. 2.

1.6 Role of HSP in Diabetes

Diabetes is a condition implicated a chronic elevation of blood glucose levels (hyperglycemia). This disease is classified into 2 types: type 1, which is accompanied by the demolition of pancreatic beta cells leading to scanty insulin production; and type 2, which embraces a range of disorders that finally result in hyperglycemia [196]. Both types of diabetes elevate the potential for the development of microvascular disorders, such as neuropathy, retinopathy and nephropathy, and for macrovascular disorders [10].

It has been mentioned that these HSP chaperones are accompanied by several clinical disorders, containing diabetes. HSP have been involved in the sources of type 1 diabetes and in the cure of the obesity and insulin resistance implicated in type 2 diabetes [34]. Reduced expression of Hsp70 and suppression of heat shock factor-1 (HSF-1) have been reported in different tissues of rats with type 1 diabetes. Inhibition of HSP 70 levels by diabetes is accompanied by elevation in tissue

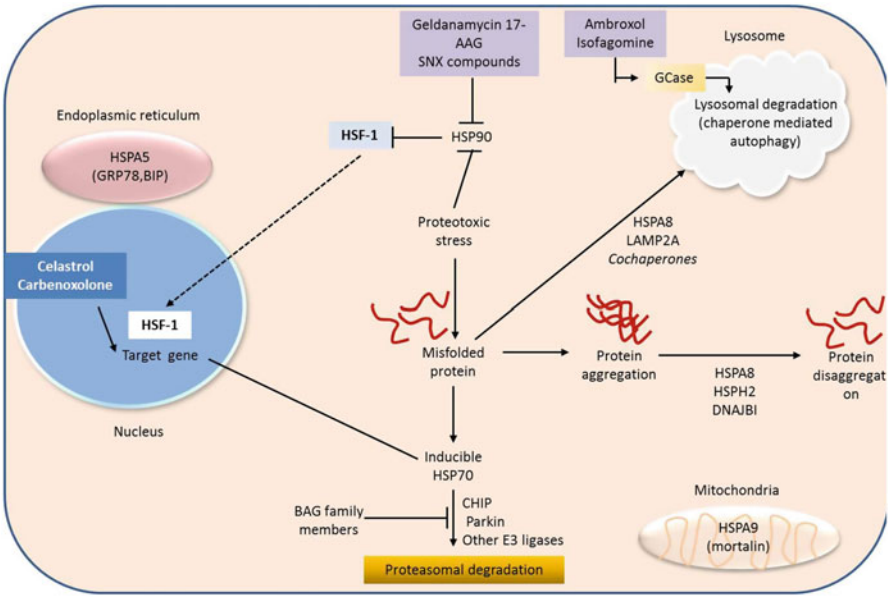

Fig. 2 Proposed role of molecular and small molecule chaperones in proteostasis in Parkinson disease. At normal state, Hsp90 bind to HSF-1 and block its activity. However, in presence of Hsp90 inhibitors (such as SNX compounds, geldanamycin, 17-AAG) or proteotoxic stress, active HSF-1 separated from Hsp90 and translocates to the nucleus where it stimulates the expression of Hsp70. Members of inducible Hsp70 family induce proteasomal degradation via a pathway activated by E3 ligases, CHIP, and Parkin. This degradation is prevented by members of BAG family and enhanced by celastrol and carbenoxolone (small molecule HSF-1 activators). In Proteotoxic stress, the misfolded proteins directed for degradation via the interactions of autophagy-lysosome system with various chaperone-mediated autophagy. Chaperone/cochaperone complexes can play a role in disaggregation of already formed protein aggregates. Also, the pharmacologic chaperones such as isofagomine and ambroxol can activate glucocerebrosidase (GCase) in the lysosome to further stimulation for chaperone-mediated autophagy. In the endoplasmic reticulum and mitochondria, chaperone are regulated by specific members of the Hsp70 family, HspA5 and HspA9, respectively

inflammation. Moreover, the same authors mentioned that normal Hsp70 and HSF-1 stimulation by endurance exercise has been prevented by diabetes [185].

Many investigations have revealed reduced expression of HSP in patients with type 1 and 2 diabetes. It appears that the decrease in chaperon activity in diabetic patients is one of the major causes for beginnings of diabetic problems. So, researchers are seeking to use various techniques, inclusive pharmaceutical and chemical compounds, thermotherapy and exercise, to stimulate the expression of HSP [81]. Former investigations suggest that an elevation in protein stability and a decrease in protein glycation can markedly reduce the complications of diabetes [85].

Diabetes is a disorder including elevated glycation, oxidation and inflammation; therefore, it would have been foretold that levels of HSP could be highly preventive in persons suffering from diabetes. However, results of investigations in humans and animals with diabetes detected reduced HSP expression. Therefore, the paradoxically reduced levels of HSP confirm the destruction caused by diabetes lesions. Intracellular HSP, through blocking nuclear factor-*k*B (NF-*k*B) activation, have anti-inflammatory influences on cells. Protein kinase C activation by NF-*k*B is a primary pathway resulting in diabetes-induced cytokine gene expression. Therefore, reduced levels of HSP in cases of diabetes will elevate the activity of NF-*k*B and confirm inflammation [80].

Type 2 diabetes mellitus is age related; it can lower longevity and fast several traits accompanied by aging. HSP are factors which have a pivotal role in aging and longevity [81]. Patients with type 2 diabetes have elevated incidence of neurodegenerative diseases, such as Parkinson and Alzheimer diseases. In Parkinson and Alzheimer diseases, amyloid precursor aggregation may result in a common loss of insulin signaling in the pancreatic beta cells and in the brain. Moreover, loss of insulin signaling results in reduced HSP in beta cells or neurons, which leads to abnormal protein aggregation and function. It has been mentioned that administration of Hsp70 and insulin can lower amyloid aggregation in the brain [81].

Bimoclomol is a drug that can elevate the fluidity of membrane and expands the activity of HSF-1, therefore can elevate the levels of Hsp70. It has been mentioned that bimoclomol lowers tissue damage, enhances wound healing, ameliorates insulin sensitivity in animal models of diabetes and decreases diabetes complications [74]. Lipoic acid administration in patients with neuropathy and type-1 diabetes was accompanied by normalization of the low level of Hsp72. This Influence was attributed to clinical amelioration in the neuropathy in these patients. It has been mentioned that thiazolidinediones, carvedilol and exercise elevate HSP. The anti-inflammatory action of on the pancreatic beta cells could be linked to the elevation of Hsp70 levels by this drug. Nitric oxide is a powerful inducer of HSP expression. Drugs that retrieve the secretion of nitric oxide from blood vessels, such as angiotensin-converting enzyme inhibitors, beta-adrenergic blockers, thiazolidinediones and HMG-CoA reductase inhibitors, are correlated to outstanding results in clinical trials of diabetes. Near-infrared light therapy releases nitric oxide from endothelium and, thus, treat diabetic neuropathy.

Finally, the oral or intravenous administration of HSP is impractical due to the intracellular position of HSP. On the other hand, it has been mentioned that liposomal delivery of Hsp72 into renal tubular cells blocks induction of NF-*k*B tumor necrosis factor and, so, blocks ischemia-induced apoptosis. It is an important finding that several drugs or conditions that may elevate HSP levels and also block NF-kB (i.e. statins [76], exercise [150], pentoxifyllin and carvedilol [79].

1.7 Role of HSP in Atherosclerosis

Atherosclerosis is an old disease slowly progressing disease that becomes manifested in the middle age or later, even if it begins in childhood [155]. In past, atherothrombosis is considered as the first killer of the aging people in the developed countries; however, dramatic increase in its incidence in the developing countries was recently reported. Currently, around 39% of death cases reported in the U.K. is concerning to atherosclerosis, however about 12 million of American citizens suffered atherosclerosis-related diseases [13]. This disease is characterized by lipids deposition, especially of low-density lipoproteins (LDLs), on the endothelial layer of medium- sized and large arteries, together with remodeling of arterial walls and severe infiltration of immune cells, forming the characteristic plaques called atheroma. Although the signs of disease have been discovered in Egyptian mummies more than 4000 years old [180], the lipid composition of atheroma and the combined mononuclear infiltration were first described about two centuries ago [121]. However, the scientists have reached to the inflammatory hallmarks in progress and pathogenesis of atherosclerosis over the past 30–40 years [73]. Recently, several researches proved that inflammation is the first steps of atherosclerosis [109]. They concluded that the expression of adhesion molecule on the endothelial cells, such as vascular adhesion molecule-1, intercellular adhesion molecule-1, and E-selectin, beside the activation of macrophages, T lymphocytes, mast cells, and several cytokines suggesting involvement of inflammatory and immune processes in the pathogenic progress of atherosclerosis [67, 72].

From another sight of view, the key role played by the immune reactivity in the pathogenesis of atherosclerosis confirmed the essential contribution of inflammatory process. Many investigators induced experimental atherosclerosis in rabbits by high fat diet, and examined the therapeutic activities of immunosuppressive drugs, authors concluded marked prevention for plaque formation and inflammatory infiltration in the aorta; they outlined the relationship between the declined production of local inflammatory and immune cells and the reduction in cholesterol content in the arterial walls [68, 190].

Normally, cells subjected to stress stimuli, such as oxidized LDL, heat shock, infectious, surgical, mechanical stress, or cytokine activation, will respond by production of increased levels of HSP to protect themselves from stress stimuli [16]. Accordingly, it was described that HSP could expressed in high levels in cardiovascular tissues to initiate the inflammatory process, and that they may be expressed during the progress of atherosclerosis as an autoantigen [143].

In 1990, Berberian et al. reported for the first time the increased expression of Hsp70 in arteries of human and rabbits. Authors concluded that the distribution of HSP in arteries was correlated to necrosis, lipid accumulation, and macrophages infiltration in human atheroma. Interestingly, Hsp70 was found to be concentrated mainly in the central thickened portions of atheroma around the accumulated lipid and sites of tissue necrosis [88]. On contrary, some of the most complex plaques contained foci of smooth muscle cells without obvious relation to necrosis or

increased expression of HSP [87]; where Hsp70 was produced in arterial wall cells even in dendritic cells [20]. Authors concluded that HSP production was increased within the depth of plate, particularly in macrophages and associated to necrotic tissue.

Consistently, Xu et al. [207] indicated that Hsp70 is overexpressed in the advanced atherosclerotic lesions. Authors found that Hsp70 ameliorates the NFκB activation, suggesting its anti-inflammatory potential. In another studies, authors declared that the levels of Hsp70 in plasma have a direct [203] and inverse [119] relation to atherosclerosis severity. Additional investigations concluded that administration of Hsp70 promoted the production of pro-inflammatory (such as IL-6) [9] and anti-inflammatory (such as Treg) cytokines [194]. Interestingly, Hsp70 could be considered as a favor factor for progression of atherosclerosis as well as mononuclear inflammatory infiltration. This theory confirmed in study designed by Xie et al. [203]; authors concluded that feeding diet with high-cholesterol level led to increased levels of Hsp70 in plasma. Additionally, the exogenous supplementation of Hsp70 promotes production of adhesion molecules within mononuclear cells in peripheral blood. In contrast, Madrigal-Matute et al. [114] observed that overexpression of Hsp70 was associated with declined oxidative stress and inflammatory response in the walls of arteries; suggesting its protective potential. Therefore, the promoting and inhibition effect Hsp70 against atherosclerosis are still a debate matter [18].

On the other hand, several investigations focused on the role of Hsp90 in atherogenesis. It was observed that the overexpression of Hsp90 is related to instability of atheroma. As well, the inhibition of Hsp90 led to declined production of inflammatory cells and oxidative stress due to reduced activation of transcription factors (such as the activators of transcription and NFκB signal transducers). Interestingly, the suppression of Hsp90 activity could be benefit in promoting the overexpression of Hsp70, with subsequent inhibition of the proinflammatory response and atherogenesis [114].

Recently, a growing body of evidence suggested the direct atherogenic potential for Hsp60; where increased expression of Hsp60 usually precedes the growth of atherosclerotic plaque [95]. In humans, the increased level of circulating Hsp60 and anti-Hsp60 are correlated to thickness of carotid artery wall [202], atherosclerotic lesions [146], and atherosclerosis-associated morbidity and mortality [205]. Furthermore, early atherosclerotic lesion was induced by transfer of Hsp60 reactive T cells [197]; where specific immunity of T-cell to Hsp60 is induced (Knoflach et al. 2007). In addition, administration of Hsp60 might induce or suppress atherogenesis, based on administration route, and the involved co-stimulatory molecules. Administration of Hsp60 parenterally activate infiltration of Hsp60-specific T cells, with subsequent secretion for anti-Hsp60 antibodies, pro-inflammatory cytokines, accumulations of macrophages and lipid, and atheroma formation. However, administration of Hsp60 via oral or nasal route reduced the atherosclerotic lesions, due to induction of Tregs and anti-inflammatory mediators including interleukin-10 (IL-10) and transforming growth factor beta (TGF-β) [197]. In human atherosclerosis, Kleindienst and colleagues indicated that Hsp60 was identified on smooth muscle cells, mononuclear

inflammatory cells, and endothelial cells of aorta and carotid artery compared to the small blood vessels that had no sclerotic lesions. The positive correlation between the severity of atherosclerosis and the produced Hsp60 was also confirmed by Hammerer-Lercher et al. [70]. In another investigation, the expressions of Hsp60 and Hsp70 in the aortic tree showed positive correlation with the progress of atherosclerosis in apoE-deficient mice [95]. The main expression sites for both HSP were within macrophages, smooth muscle cells, endothelium, and CD3 T lymphocytes [95].

Interestingly, results from another study revealed that Hsp47 might be also involved in atherogenesis [198]. Strong expression of Hsp47 was proved locally in atherosclerotic arteries (particularly in the collagenous areas) but not in normal artery. HSP47 was expressed mainly in cells produce type I procollagen [154]. Results from this study suggested the role of Hsp47 in atheroma formation in human coronary. In addition, authors concluded the upregulation of Hsp47 as a response to stress; this conclusion might indicate the possible role of Hsp47 in plaque stability.

Hsp27 is an intracellular chaperone that possesses an important role in stabilization of RNA, beside its role in the antioxidant and antiapoptotic responses [14]. In atherosclerosis, extracellular production of Hsp27 from atheroma was evident; may be due to cellular damage or as a co-secretion with exosomes or lysosomes. After secretion, in the extracellular space, Hsp27 able to binds with several receptors on cell membrane of inflammatory immune cells and endothelial cells, such as CD14, CD36, CD40, CD91, scavenger receptor A (SR-A), and toll like receptors (TLRs) as TLR2, TLR3, and TLR4 [19]. Interestingly, data from available research concluded the ameliorative role played by Hsp27 during atherogenesis. On the same line, the definition of Hsp27 as an estrogen receptor-associated protein could explain the ameliorative role played by estrogens during atherogenesis [153]. Consistent with that, several studies demonstrated that atheroma has low content of Hsp27 [117], and therefore, low circulating levels of Hsp27 indicates more severe atherosclerotic lesions [169]. On contrary, overexpression of Hsp27 may protect against atherogenesis [38]. The protective potential of Hsp27 against atherosclerotic disease may attribute to its suppressive activity for NFκB activation [14], involvement in lipid homeostasis via competing with LDL in binding to SR-A, with subsequent formation of foam cell [14], and declined the cholesterol content in atheroma the serum [38]. The role of HSP in the pathogenesis of atherosclerosis is illustrated in Fig. 3.

1.8 Role of HSP in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a widely known chronic inflammatory disease that particularly affects the aging population. It occurs due to damage of the synovial membranes of joints via infiltration of mononuclear and/or polynuclear inflammatory cells including macrophages, lymphocytes, and neutrophils [69, 123]. Usually, during the course of RA, patient developed severe pain due to progressive injury or

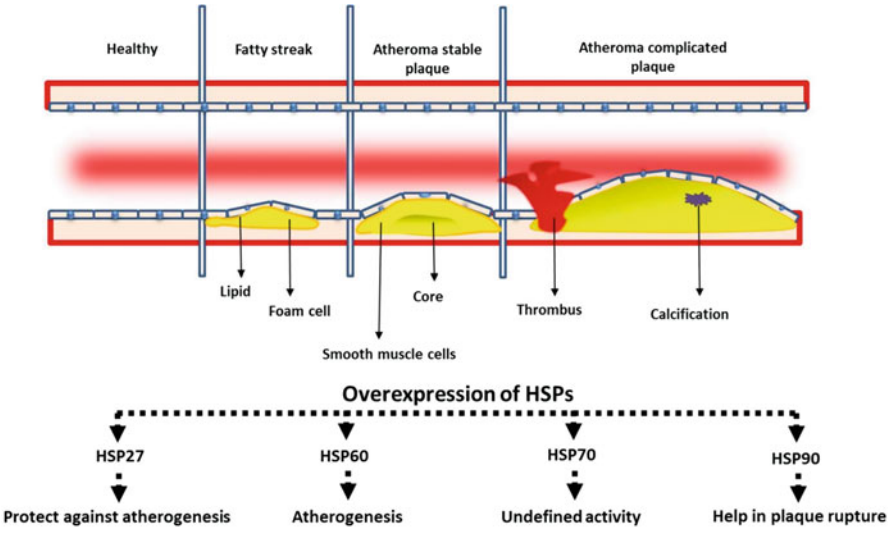

Fig. 3 The role of HSP in the pathogenesis of atherosclerosis. Overexpression of Hsp27 is protects against atherogenesis; however, overexpression of Hsp60 help in atherogenesis. In addition, Hsp90 aggravates atheroma by help plaque rupture

even complete loss of bone and cartilage around the inflamed joint. Generally, the pathogenesis of this disease is complicated; however, the pathologic events associated to RA suggesting an autoimmune cause in form of T-cell-mediated chronic inflammatory response [209].

On the other hand, it has been observed that overexpression of HSP family might be involved in RA pathogenesis; where increased expression can regulate the progress of disease [83]. The inflammatory events and other stress factors occur in synovial membrane are able to increase HSP expression. In RA, the hypoxia and reperfusion injury of the rheumatoid joint, lead to production of high levels of reactive oxygen species (ROS) [77]. Subsequently, this increased production of ROS and the high synovial content of inflammatory mediators (such as tumor necrosis factor (TNF)- a and interleukin (IL-l) will act as stress factors [199]. Consistently, Schett et al. [165] concluded that, in RA but not osteoarthritic, heat shock transcription factor 1 (HSFl) was activated and undergo hyper-phosphorylation and nuclear translocation that could lead to regulation of Hsp70 transcription. In another investigation, authors used cultured RA SM synovial fibroblasts to study the expression of Hsp70 in AR, they observed that the proinflammatory mediators including IL-l0 and TNF-α were able to upregulate expression of Hsp70 in cultured fibroblasts (Luo et al. 2008). In another research groups, authors declared that several types of HSP and chaperones were overexpressed in RA such as human Hsp27, Hsp90α, Hsp60 [168], and Hsp65 [83]. On contrary, Worthington et al. [200] concluded that human Hsp65 was expressed equally in RA and control non-inflamed synovia.

Moreover, Hsp60 was expressed equally in mitochondria of RA and osteoarthritis, as assessed by immunohistology [22].

Karlsson-Parra et al. [96] observed that human Hsp65 (huHsp65) was overexpressed at the cartilage-pannus junction; they concluded that the eroding front possessed the maximum expression compared to SM itself. Interestingly, the same authors identified the expression of huHSP65 in rheumatoid nodules; where rheumatoid nodules are the pathognomonic histologic and clinical feature of RA. This expression could be attributed to the presence of non-caseated hypoxic center, where hypoxia act as stress factor lead to increased expression of HSP.

Lewthwaite et al. [106] observed the correlation between huHsp60 circulating in plasma and the psychosocial and physiologic stress. Consistent with this finding, the increased levels of circulating huHsp60 was correlated to carotid atherosclerotic plaque [202]. Generally, in osteoarthritis, HSP are produced mainly from the chondrocytes [171]. However, in RA patient, they synthesized mainly in synovial intimal cells [112]. Therefore, it could be concluded that the inflammatory signaling in this tissue are able to initiate the production of HSP; with subsequent protection for the host cells.

In another theory, RA may define as autoimmune-inflammatory disease; where the immune system attacks the synovial fluid-membranes exist in different joints. Neglect treatment of RA could result in severe inflammatory response [173]. This inflammation has the potential to attract several immune components such as immune chemokine, cytokines, and lymphocytes to the infection area [84]. As a response to RA infection, the synthesis of HSP particularly Hsp70 is increased. It is now well documented that Hsp70 possess an anti-apoptotic property through inhibition of proinflammatory and proapoptotic factors such as Caspases and JNK (Jun N-terminal) signaling, cytochrome c release, and apoptosome formation [66]. Therefore, the overexpression of Hsp70 in synovial membrane during the infection with rheumatoid arthritis fibroblast-like synoviocyte (RA-FLSs) is not surprisingly. Herein, Hsp70 acts to control the inflammatory process through blocking of pro-inflammatory signaling, and to regulate the effect of T-cells [165].

In another study, Kang et al. [94] observed repression of Hsp70 produced in RA fibroblast-like synoviocytes (FLSs) after treatment with sodium nitroprusside (SNP) in an in vitro experiment. Authors reported that Hsp70 downregulated cells showed better survive compared to control cells. It was concluded that downregulation of Hsp70 protects RA FLSs against apoptosis induced via nitric oxide production through activation of the Akt signaling pathway. However, the real in vivo function of Hsp70 in the RA is still not fully clear. By considering these findings, we can conclude that inhibition of Hsp70 in RA may be used as a therapeutic approach to control the severe inflammatory response occurs in RA. Additionally, van Roon et al. [188] noted that T-cells collected from patients suffered RA have the potential to react with huHsp60 to suppress the activation of the pro-inflammatory mediator (TNF-α) via induction of Th2 cytokine regulator. However, this regulation is not reported for Hsp65 isolated from Mycobacterium tuberculosis [144]. Consistently, several investigators attributed this response of T-cell to self-Hsp70 and Hsp60 to production of the regulatory mediators (interleukin-4 and interleukin-10), with

subsequent prevention of arthritic diseases [6, 97, 144]. Taken together, it is may conclude that huHsp60 and mycobacterial Hsp60 might be considered as promising potential vaccines against autoimmune inflammatory diseases.

1.9 Role of HSP in Cancer

The progressive loss of physiologic and immunologic potency is a characteristic feature for the elderly [33]. Growing body of evidences has proved cancer augmentation by aging, which may be due to age- associated immune dysregulation [182], with subsequent poor prognosis [98]. Interestingly, around 50% of malignancies are diagnosed in aging patient over than 65 years old [78]. Several investigations concluded the anti-apoptotic activities of HSP. Therefore, it is not surprising that the high levels of HSP may have the potential to protect malignant cells against therapy-induced apoptosis [89]. The apoptotic process may occur in either intrinsic or extrinsic pathways. Whatever pathway, the final event is induction of caspases proteases, which is cleaved enzymatically leading to activation of the apoptotic stimulus [28]. In the intrinsic pathway, apoptosome is formed by mitochondria; where cytochrome c released from mitochondria to the cytosol, and then interact with pro-caspase-9 and cytosolic apoptosis protease activating factor-1 (APAF-1) forming apoptosome. Apoptosome is responsible for initiation of apoptotic cascade via activation of pro-caspase-3 [177].

Currently, it has been well known that Hsp27 and Hsp70 have the potential to inhibit the formation of apoptosome, with in turn inhibition of apoptosis. Another theory for inhibition of apoptosis by Hsp27 is direct binding to APAF-1, which subsequently led to inhibition of apoptosome formation [61]. Additionally, Hsp90 suppress pro-caspase-9 activation by cytochrome c [139]. On the other hand, the extrinsic apoptotic pathway work via binding to the respective ligands of death receptors (TNF receptor 1, TNF receptor superfamily, apoptosis antigen-1), leading to their activation and formation of death inducing complex at the plasma membrane. This complex activates the pro-caspase-8, which in turn induce direct or indirect activation of caspases [21].

In another research group, authors cleared that phosphorylated dimers of Hsp27 can bind to Daxx protein competitively with FAS; lead to subsequent interference with FAS-mediated apoptotic pathway [31]. Additionally, Bruey et al. [24] investigate the interaction between Hsp27 and cytochrome *c*. Authors concluded that Hsp27 can block Caspase activation via its binding to cytochrome c and inhibition for interaction with procaspase-9 and apoptotic protease activating factor-1 (APAF-1). In CD133 + colorectal cancer stem cells, activation of Hsp27 inhibits the cleavage of caspase-3 and -9 in the apoptosis pathway. However, its inhibition promotes apoptotic cascade in CD133+ cells [110]. Additionally, inhibition of Hsp27 activation up-regulated the activity of caspase-3 in glioblastoma cells [107].

Moreover, the anti-apoptotic activity of Hsp90 could be discussed by its ability to bind to the anti-apoptotic protein (such as AKT1) and suppress its activation, which

in turn enhanced cell surviving [62]. In contrast, several investigators concluded the pro- apoptotic activities of Hsp60 in in vitro experiment [164]. In addition to the antiapoptotic and proapoptotic activities of HSP members, some members such as Hsp27 are essential also in regulation, progression, and metastasis of tumor cells. Interestingly, blocking of Hsp27 led to decline in matrix metalloproteinase (MMP), epithelial-to-mesenchymal transition, migration, and metastasis of neoplastic cells [65]. In addition, in human prostatic malignancy, Hsp27 has the potential to up-regulates MMP2 activity stimulated by transforming growth factor b (TGF-b), lead to promoting cell invasion [206]. Additionally, Hsp27 reported to enhance the neoplastic migration in bladder malignancy [210], and promote metastasis of epithelial ovarian cancer to peritoneum [215].

Thuringer et al. [181] studied effect of Hsp27 on progression and metastasis of breast cancer. They concluded that Hsp27 has a direct role in enhancement of angiogenic activity and neoplastic migration via upregulating gene transcription of vascular endothelial growth factor (VEGF) and activated VEGF receptor type 2. In another study, [136] found that Hsp27 inhibit p53-induced activation of p21 in neoplastic cells, with in turn regulation of p53 signaling. Moreover, proliferation of lung cancer cells could be enhanced by Hsp27-induced activation of activator protein-1 [214]. However, in gastric adenocarcinoma, cancer progression could be enhanced by the C-X-C chemokine receptor type 1 (CXCR1); CXCR1 has the potential to decrease Hsp27 expression, indicating the relationship between cancer progress, Hsp27, and CXCR1 [82].

It has been reported that Hsp90AA1 is involved in enhancement of invasiveness and mobility of cancer cells [195], where it is required for the invasion of fibrosarcoma cells [48]. On these bases, Hsp90AA1 found to enhance the in vitro invasion of breast cancer and melanoma, with in turn increment of the metastatic activities. Also, serum Hsp90AA1 increased in breast, liver, pancreas, and lung cancer in correlation to degree of malignancy [192]. However, inhibition of Hsp90AA1 suppresses the metastatic invasion in mouse melanoma [176]. This enhancement of HSP against tumor invasion potential may attribute to their binding to the extracellular receptors activating ERK1/2 and PI3K-Akt pathways [71]. Additionally, Tsuneki et al. [183] reported that HspA9 is released from oral squamous carcinoma cells, and then interact with podoplanin; that is an adhesion molecule responsible for the invasion potential of tumor. Moreover, HspB6 has a role in angiogenesis, progression, and migration. For example, overexpression of HspB6 led to increase density of heart capillaries in mice [213].

In recent years, many researchers studied the extracellular and intracellular localization of HSP in tumor cells. In normal cells, it is uncommon to localized Hsp60 on the cell membrane. However, this localization is frequent in malignant cells [27, 29]. In addition, it was reported that Hsp60 is exist in exosomes released from malignant cells in human [125]. The extracellular HSP have several functions; one of them is immune modulation. For instance, TNFα and IL-6 were produced in mast cells under stimulation of HspA1A via activation of toll-like receptors 2 and 4 (TLR4, TLR2) [130] and interleukin 12 (IL-12) [15]. Additionally, treatment with HspA1A led to activation of macrophage and production of TNFα [5]. Recently, in vitro studies were performed on murine leukemia monocytes and hepatocellular

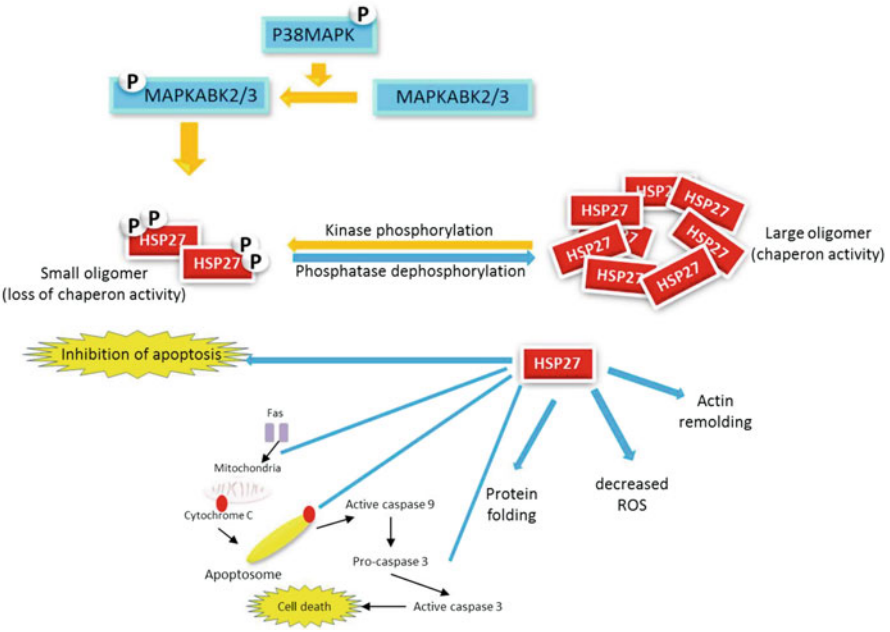

Fig. 4 Schematic representation for the role of Hsp27 in carcinogenesis. Hsp27 suppressed apoptosis with subsequent enhancement for tumorigenesis. Unphosphorylated Hsp27 present as large oligomers and possess chaperonage activities. Phosphorylated Hsp27 switches to smaller oligomers and lose their chaperonage activities and initiate their pro-oncogenic activities. Hyperactivation of Hsp27 induces inhibition of apoptosis

carcinoma cell line, author concluded release of HspA1A, Hsp90AA1, and HSPD1 from exosomes, which enhancing the activity of macrophages, natural killer, and mononuclear cells [103]. In contrast, Chalmin et al. [30] described the immunosuppressive role of HspA1A released from exosome; HspA1A is reported to suppress tumor immune surveillance via activation of myeloid-derived suppressor cells. In addition, in colorectal carcinoma, secretion of HspH1 led to differentiation of macrophage, with in turn anti-inflammatory profile and pro-tumor effect [17]. However, in primary breast tumor cells, released HspB1 led to monocytes differentiate into proangiogenic macrophages [7]. The role of HSP in the pathogenesis of cancer is summarized in Fig. 4.

2 Conclusions

HSP are the cornerstone for repairing damaged proteins resulted exposure of cells to different stresses including the age-related disorders. Hence, enhancing and modulation of HSP functions would help the human welfare through promoting healthy lifespan and elevating the longevity of humans.

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Ethical Approval for Studies Involving Humans This article does not contain any studies with human participants performed by any of the authors.

Ethical Approval for Studies Involving Animals This article does not contain any studies with animals performed by any of the authors.

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